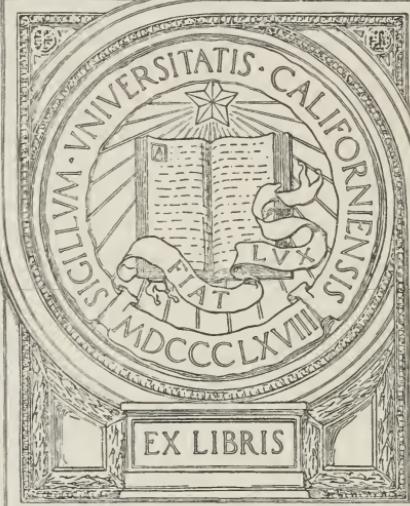


MARY G. RITCHIEY, M.D.
SEPTEMBER 1948

UNIVERSITY OF CALIFORNIA
SAN FRANCISCO MEDICAL CENTER
LIBRARY



Gift of

Dr. Mary R. Wicks

~~Thaddeus Szwedzki~~

A TEXT-BOOK
of
PATHOLOGY

By

W. G. MACCALLUM

Professor of Pathology and Bacteriology
The Johns Hopkins University
Baltimore

Sixth Edition, Entirely Reset

R B III
M 12
1937

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1937

203886

Copyright, 1916, 1920, 1924, 1928, and 1932, by W. B. Saunders Company

Copyright, 1936, by W. B. Saunders Company

All Rights Reserved

This book is protected by copyright. No part of it
may be duplicated or reproduced in any manner
without written permission from the publisher

MADE IN U. S. A.

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

To
G. A. MacCallum, M.D.
My Father
And My Best Friend



Digitized by the Internet Archive
in 2012

PREFACE TO THE SIXTH EDITION

THIS book, which was first published in 1916, has undergone many changes in later editions and has now been thoroughly revised with reference to our own experience and to the literature up to the present time. This was found more than ever necessary because of the extraordinary advances reflected in the literature of the last few years, especially in the fields of endocrine disturbances, vitamin deficiencies and virus infections.

Although most text-books take up each organ separately and describe the pathological alterations which can affect it, it has seemed more reasonable to begin with the cause of a disease and describe its effects throughout the body. For this reason, too, we have discarded a museum of isolated specimens and for teaching preserve all the organs from each case so that such cases may be grouped in rooms which are reserved for the diseases which they represent.

While many topics are included which were omitted before, the general plan of this book remains the same. Naturally, in many diseases the cause is still unknown and these must be dealt with in chapters arranged as logically as possible.

Beginning, then, with the idea that all departures from normal health are brought about by some harmful or disturbing agency, the endeavor has been made to trace these changes back to their cause, and then to describe not only the anatomical alterations but the disturbances of function and the reaction which tends to restore the body to a normal state and even to establish a protection against a recurrence of the same injury. If this, with some mention of symptoms, makes the book seem like a treatise on clinical medicine, it is only because pathology and clinical medicine are, after all, the same thing viewed from slightly different angles.

References to the literature given with each chapter have been chosen, as far as possible, to direct the student to readable and comprehensive papers which review the subject and give further and more complete references.

The illustrations are almost entirely from material which we have studied in the laboratory. The drawings with very few exceptions have been made by Mr. Alfred Feinberg. Photographs were made by Milton Kouglof and microscopical preparations by Miss Lyons, while Miss Finley has given great assistance in preparing the text.

W. G. MacCALLUM.

THE JOHNS HOPKINS HOSPITAL,

August, 1936.

CONTENTS

CHAPTER I

	PAGE
DISTURBANCES OF THE FLUIDS OF THE BODY.....	1
Relation of Fluids to Tissues; Blood, Lymph, Tissue Fluids. The Blood: Variations in Quality and Quantity. Readjustment. Plethora and Oligæmia. Clotting. Thrombosis.	

CHAPTER II

LOCAL DISTURBANCES IN THE CIRCULATION OF THE BLOOD.....	16
Hyperæmia; Anæmia. Postmortem Changes in Distribution. Active and Passive Hyperæmia. Local Anæmia. Embolism. Infarction. Gangrene.	

CHAPTER III

DISTURBANCES OF INTERCELLULAR FLUIDS AND LYMPH.....	47
Their Movement, Character, and Excessive Accumulation. Oedema, Ascites.	

CHAPTER IV

THE STRUCTURE AND METABOLISM OF CELLS.....	53
Cellular Doctrine; Ultimate Unit of Life. Nucleus and Cytoplasm. Mitochondria, Plasmosomes, Paraplastic Substances, Intercellular Substances. Tissues and Motile Cells. Variations in the Appearance of Cells. Necrosis, Coagulation, and Autolysis. Death.	

CHAPTER V

DISTURBANCES IN THE NUTRITION AND METABOLISM OF CELLS.....	65
Course of Metabolism. Disturbances Resulting in Accumulation of Various Substances. Degenerations. Atrophy: Its Causes. Hypertrophy and Hyperplasia.	

CHAPTER VI

DISTURBANCES OF FAT METABOLISM.....	78
Neutral Fats and Lipoids. Their Source, Absorption, Distribution and Functions. Pathological Disturbances.	

CHAPTER VII

DISTURBANCES OF PROTEIN AND CARBOHYDRATE METABOLISM.....	94
General Character of Protein Metabolism. The Purine Bodies. Gout. Cloudy Swelling. Hyaline Metamorphosis. Amyloid Infiltration. Carbohydrate Metabolism. Glycogen.	

CHAPTER VIII

DISTURBANCES OF MINERAL AND PIGMENT METABOLISM.....	113
Calcium: Its Source, Distribution, Deposition in Necrotic and Other Tissues; Its Relation to Various Functions of the Body. Iron: Its Distribution and Functional Importance. Disturbance in Its Quantitative Relations. Chlorosis. Haemochromatosis. Pigment: Function and Distribution. Endogenous and Exogenous Pigmentation. Jaundice. Dust Diseases. Silicosis.	

CHAPTER IX

DEFENCES OF THE BODY AGAINST INJURY.....	PAGE 139
--	-------------

Immediate and Late Reactions to Injury. Inflammation, Fever, Immunity Production, and Repair. Inflammation an Elaborate Mechanism to Combat Injury. Details of Vascular and Phagocytic Phenomena. The Wandering Cells.

CHAPTER X

DEFENCES OF THE BODY (CONTINUED).....	164
---------------------------------------	-----

Fever. General Nature of the Reaction. Its Chemical Characters and Relation to Immunity. *Immunity.* Nature of Injurious Agents. Types of Resistance. Artificial Immunity. Anaphylaxis; Allergy. Asthma.

CHAPTER XI

DEFENCES OF THE BODY (CONTINUED).....	176
---------------------------------------	-----

New-growth of Tissue. General Characters. Influences of Various Agencies on Growth. Growth Stimuli.

CHAPTER XII

DEFENCES OF THE BODY (CONTINUED).....	190
---------------------------------------	-----

Repair. Established Character of Tissues. Their Early Differentiation. Metaplasia. Regeneration as Exemplified in the New Formation of Various Tissues.

CHAPTER XIII

DEFENCES OF THE BODY (CONTINUED).....	206
---------------------------------------	-----

Transplantation of Tissues and Organs, Its Limitations. Healing of Wounds —by Direct Union, Under a Crust, by Granulation Tissue, etc. Healing of an Open Ulcer, of Inflamed Wounds and Abscesses. Healing of Special Tissues.

CHAPTER XIV

ILLUSTRATIVE EXAMPLES OF INFLAMMATORY PROCESSES.....	224
--	-----

Catarrhal Inflammation. Serofibrinous and Fibrinopurulent Pericarditis, Pleuritis, Peritonitis, Appendicitis, Endocarditis, Lobular Pneumonia, Puerperal Infection. Pyæmia, Abscess Formation, Diphtheritic Inflammation.

CHAPTER XV

INJURY WITH INFLAMMATORY REACTION AND ATTEMPTED REPAIR.....	261
---	-----

Nephritis: General Nature. Relation of Anatomical Changes to Functional Disturbances. Nephrosis. Acute and Subacute Nephritis. Acute Interstitial Nephritis. Tubular Nephritis. Chronic Glomerulonephritis. Chronic Arteriolosclerotic Nephritis. Functional Derangements Resulting from These.

CHAPTER XVI

INJURY WITH INFLAMMATORY REACTION AND ATTEMPTED REPAIR (CONTINUED).	
---	--

—INJURY AND REPAIR OF THE LIVER.....

293

Structure of the Liver in Relation to Disease. Direct Injury to Liver-cells. Extreme Necrosis of Liver. Eclampsia, and Infections. Repair and Compensatory Hyperplasia. Cirrhosis: Its Various Types. The Alterations in Architecture Involved. Obstruction of Portal Circulation. Collateral Circulation. Biliary and Hypertrophic Cirrhosis. Wilson's Disease.

CHAPTER XVII

	PAGE
FURTHER ILLUSTRATIVE EXAMPLES OF DESTRUCTIVE AND REPARATIVE PROCESSES.	318

Structure of Arteries. Arteriosclerosis. Anatomical Changes in Arteriosclerosis in Aorta and Other Vessels. Pathogenesis and Aetiology. Sclerosis of Peripheral Arteries: Thrombo-angiitis Obliterans. Arteriolosclerosis. Mechanical and Infectious Injuries to Arteries. Cerebral Haemorrhage. Effects.

CHAPTER XVIII

TYPES OF INJURY: PHYSICAL AND MECHANICAL INJURIES.....	349
--	-----

Mechanical Injuries: Pressure, Direct Violence Affecting Bones, Central Nervous System, etc. Gunshot and Other Wounds. Secondary Effects: Complication with Infection. Shock. Experimental Study and Various Theories. Effects of Heat: Burns, Heat-stroke, Insolation. Effects of Cold: Freezing. Effects of Light-rays and Radiant Energy on Skin, Blood-forming Organs, etc. Electricity: Effects of Strong Currents.

CHAPTER XIX

TYPES OF INJURY (CONTINUED).—CHEMICAL INJURIES.....	375
---	-----

Nature of Poisons: Their Varying Effects. Reaction of Organism; Elimination, Detoxication, Resistance. Auto-intoxication. Poisoning by Illuminating Gas, Corrosive Substances, Cyanides, Chloroform, Alcohol, Metallic Poisons, etc.

CHAPTER XX

TYPES OF INJURY (CONTINUED).—EFFECTS OF OBSTRUCTION OF THE FLOW OF CONTENTS OF HOLLOW ORGANS. OBSTRUCTION IN THE ALIMENTARY TRACT.	388
--	-----

Salivary Ducts. Bile-ducts (Gall-stones, Cholecystitis, Jaundice). Pancreatic Ducts (Pancreatic Cirrhosis, Acute Pancreatitis). Obstruction of Digestive Tract: Oesophagus, Stomach (Gastric Ulcer). Intestine; Varying Mechanism of Obstruction (Hernias, Intussusception, Volvulus, Compression or Kinking by Adhesions, Paralysis, Stenosis). Diverticula of Intestine.

CHAPTER XXI

TYPES OF INJURY.—OBSTRUCTION (CONTINUED).—OBSTRUCTION OF RESPIRATORY TRACT.....	414
---	-----

Nose (Coryza, Adenoids, etc.). Larynx (Edema, Diphtheria, Foreign Bodies, Compression Stenosis). Bronchi (Foreign Bodies, Stenosis). Atelectasis: Its Causes. Mechanism of Bronchial Dilatation. Bronchiectasis. Emphysema.

CHAPTER XXII

TYPES OF INJURY.—OBSTRUCTION (CONTINUED).—OBSTRUCTION OF THE URINARY TRACT.....	424
---	-----

Urethral Stricture. Prostatic Obstruction; Hypertrophy of Prostate. Cystitis. Urinary Calculi. Hydronephrosis. Renal Calculi. Ascending Renal Infection; Pyelonephritis.

CHAPTER XXIII

TYPES OF INJURY.—OBSTRUCTION (CONTINUED).—GENERAL DISTURBANCES OF CIRCULATION.....	444
--	-----

Mechanism of Circulatory Organs, Arteries, Capillaries, Arterial Hypertension. Pathological Obstructions. Pericardial and Pleural Effusions. Emphysema. Chemical Influences. Arterial and Myocardial Disease. Coronary Obstruction. Valvular Lesions and Their Effects. Congenital Malformations of the Heart. Cardiac Hypertrophy and Dilatation. Decompensation. Disturbances in Conduction of Impulses in the Heart. Chronic Passive Congestion.

CHAPTER XXIV

TYPES OF INJURY (CONTINUED).—OBSTRUCTION OF THE CEREBROSPINAL FLUID: HYDROCEPHALUS.....	<small>PAGE</small>
	483

CHAPTER XXV

TYPES OF INJURY (CONTINUED).—BACTERIAL DISEASE.—STREPTOCOCCAL INFEC- TIONS.....	488
--	-----

General Character of Bacterial Infection: Nature of Bacterial Action. Pyogenic Micrococci. Streptococcus Infections—of the Respiratory Tract, the Middle Ear, the Digestive Tract. Streptococcus Wound Infection, Erysipelas, Pneumonia, Endocarditis. General Septicæmia (Acute Splenic Tumor).

CHAPTER XXVI

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—STAPHYLOCOCCUS IN- FECTIONS.....	514
---	-----

General Character. Furunculosis. Paronychia, Impetigo, etc. General Septicæmia, Pyæmia, Suppurative Nephritis, Endocarditis, Lobular Pneumonia, Osteomyelitis.

CHAPTER XXVII

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—PNEUMOCOCCUS INFEC- TIONS.....	523
---	-----

Character of Organism. Lobar Pneumonia. Consolidation. Resolution. Organization, etc. Septicæmia. Endocarditis. Meningitis.

CHAPTER XXVIII

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—MENINGOCOCCUS AND GONOCOCCUS INFECTIONS.....	538
---	-----

Menigococcus Infections: Epidemic Cerebrospinal Meningitis. Endocarditis. Gonococcus Infections: Urethritis and Sequelæ. Salpingitis and Sequelæ. Arthritis. Ophthalmia. Dermatitis, Endocarditis, Vulvovaginitis in Children.

CHAPTER XXIX

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—DIPHTHERIA. TETANUS. 552	
--	--

Diphtherial Infection: Diphtheria of Respiratory Tract. General Effects upon the Heart, Kidneys, etc. Paralysis. Immunization. Tetanus Infection: Mode of Occurrence and Mechanism of Distribution of Toxin. Botulism.

CHAPTER XXX

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—CHOLERA. PLAGUE. GLANDERS. ANTHRAX. UNDULANT FEVER. TULARÆMIA.....	561
---	-----

Asiatic Cholera: Intestinal Lesions. General Intoxication. Bubonic Plague: Transmission. Bubonic Type. Pneumonic Type. Glanders: Acute and Chronic Forms. Anthrax: Infection through Skin, Digestive Tract, Lungs. Undulant Fever. Tularæmia.

CHAPTER XXXI

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—TYPHOID AND PARA- TYPHOID INFECTIONS.....	576
--	-----

Typhoid Infection: General Relations. Intestinal, Lymphatic, Splenic, and Other Lesions. Necrosis in Various Organs. Affections of Circulatory, Respiratory, and Nervous System. Salmonella (Paratyphoid) Infection: Relation to Typhoid and Enteritis Infection. Acute Gastro-enteritis, Accessory Lesions. Dysentery: Various Organisms Concerned. Intestinal Lesions. Pyocyanus Infections, Localization of Neoseroses.

CHAPTER XXXII

	PAGE
TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—LEPROSY	599
Leprosy: Nodular and Anaesthetic Forms. The Bacillus and Transmission. Lesions of the Internal Organs. Affections of Nerves and Their Sequelæ.	

CHAPTER XXXIII

TYPES OF INJURY.—BACTERIAL DISEASE (CONTINUED).—TUBERCULOSIS	608
Tuberculosis: <i>Ætiology, Distribution and Transportation of Bacilli. Modes of Infection. Effects of the Tubercle Bacillus on the Tissues. Virulence, Immunity, Allergy, and Dosage in Relation to the Form of Lesions. Distribution of Bacilli in the Body. Acute Miliary Tuberculosis.</i>	

CHAPTER XXXIV

TYPES OF INJURY.—BACTERIAL DISEASE.—TUBERCULOSIS (CONTINUED)	631
Tuberculosis of Lungs in Children and Adults. Tuberculosis of Pleura and Pericardium, Digestive Tract, Heart and Arteries, Serous Surfaces, Lymph-nodes, Genito-urinary Tract, Nervous System, Ductless Glands, Skin, Bones, and Joints.	

CHAPTER XXXV

TYPES OF INJURY.—DISEASES DUE TO FUNGUS INFECTION	669
General Scope. Yeast-like Fungi. Torula. Meningeal Infection. Thrush. Blastomycosis or Coccidioidal Granuloma. Sporotrichosis. Actinomycosis. General Character; Mode of Infection. Ringworm. Favus.	

CHAPTER XXXVI

TYPES OF INJURY.—SPIROCHÆTAL INFECTION.—SYPHILIS	677
Syphilis: History, <i>Ætiology, Course of the Disease, Immunity. Experimental Syphilis in Animals. Congenital Syphilis. General Considerations. Acquired Syphilis, Primary Stage, Secondary Lesions, Tertiary Stage.</i>	

CHAPTER XXXVII

TYPES OF INJURY.—SPIROCHÆTAL INFECTION.—SYPHILIS (CONTINUED)	695
Syphilitic Lesions of Circulatory System, Heart, Arteries, Aneurysms. Syphilitic Lesions of Lymph-nodes, Blood-forming Organs, Alimentary Tract, Respiratory Tract, Bones and Joints, Genital Organs.	

CHAPTER XXXVIII

TYPES OF INJURY.—SPIROCHÆTAL INFECTION (CONTINUED)	723
Syphilitic Lesions of Central Nervous System: Meningo-encephalitis, Tabes Dorsalis, Dementia Paralytica. Congenital Syphilis: Anatomical Lesions. Other Spirochætal Infections: Yaws, Spirochaetosis Icterohæmorrhagica. Vincent's Angina or Trench Mouth.	

CHAPTER XXXIX

TYPES OF INJURY.—RICKETTSIA INFECTIONS	749
Typhus. History. Interrelation of Various Diseases Caused by Rickettsia. Character of Typhus Fever. Lesions; Experimental Studies of Transmission.	

CHAPTER XL

	PAGE
TYPES OF INJURY.—VIRUS DISEASES.....	752

General Conception of Viruses. Specific Relations. Immunity Production. Herpes Simplex, Herpes Zoster. Poliomyelitis. Infectious Nature, Transmission. Lesions of Nervous System. Epidemic Encephalitis, Various Types, Lesions and General Effects. Parkinson's Disease. Multiple Sclerosis; Schilder's Disease.

CHAPTER XLI

TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES.....	764
---	------------

Influenza. History, Mode of Occurrence, Symptoms, Complications and Sequelæ. Demonstration and Cultivation of the Virus. Common Colds, Cultivation of the Virus. Stimulation of Associated Pathogenic Bacteria. Rheumatism. General Character, Course and Symptoms. Cardiac Involvement. Specific Lesions. Search for Aëtiological Agent.

CHAPTER XLII

TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES.....	780
---	------------

Yellow Fever: Course, Transmission by Mosquitoes, Aëtiology, Anatomical Lesions. Dengue: Symptoms, Transmission. Psittacosis: Distribution, Transmission, Aëtiological Studies.

CHAPTER XLIII

TYPES OF INJURY.—INFECTIONS APPARENTLY CAUSED BY FILTRABLE VIRUSES..	784
---	------------

Rabies or Hydrophobia: Aëtiology, Symptoms. Pasteur's Virus for Preventive Inoculation, Lesions. Landry's Paralysis. Mumps: Symptoms and Lesions; Aëtiology. Lymphogranuloma Inguinale: Distribution, Lesions, Virus Origin, Frei Test. Periarteritis Nodosa: Vascular Changes and Aëtiology.

CHAPTER XLIV

TYPES OF INJURY.—INFECTIONS CAUSED BY FILTRABLE VIRUSES.....	790
---	------------

Exanthematic Diseases: General Character. Measles: Occurrence, Transmission, Aëtiology, Secondary Infections, Pathological Anatomy, Neurological Symptoms. Scarlet Fever: Aëtiology, Course, Pathological Anatomy. Smallpox: Occurrence, Relation to Vaccinia, Alastrim, Chickenpox. Aëtiology, Symptoms, Pathological Anatomy; Relation of Encephalitis Following Vaccination.

CHAPTER XLV

TYPES OF INJURY.—DISEASES DUE TO ANIMAL PARASITES.....	805
---	------------

Introduction. General Relation of Parasites to Host. Table of Main Zoological Divisions. Amoebic Infections: Types of Parasites and Life-history; Intestinal Infection; Abscess of Liver; Abscess of Lung. Pyorrhœa Alveolaris. Malaria: Types and Life-history of Parasites; Symptoms and Pathological Anatomy; Blackwater Fever. Leishmaniasis; Kala-azar. Trypanosome Infections: Biology; Sleeping Sickness.

CHAPTER XLVI

TYPES OF INJURY.—DISEASES DUE TO ANIMAL PARASITES (CONTINUED).....	822
---	------------

Cestode Infections: *Tænia* and *Bothriocephalus*; *T. Echinococcus*; *Echinococcus* Cysts in Man. Trematode Infections: Bilharziosis; *Paragonimus* and *Clonorchis*. Nematode Infections: Trichiniasis. Biology of the Parasite, Symptomatology, Pathological Anatomy. Uncinariasis: Symptomatology; Life History of Parasite; Pathological Anatomy. Infections with *Ascaris*, *Oxyuris*, *Onchocerca*, *Trichocephalus*, and *Filaria*. Elephantiasis.

CHAPTER XLVII

THE EFFECTS OF INJURIES UPON THE BLOOD AND BLOOD-FORMING ORGANS	PAGE 839
---	-------------

Importance of Changes in Blood-forming Organs. The Bone-marrow, Its Regenerative Changes. The Spleen. The Lymphoid Tissues. Injuries to the Red Corpuscles and Erythrogenic Tissues. Polycythaemia. Anæmia or Oligocythaemia. Post-hæmorrhagic and Other Secondary Anæmias. Pernicious Anæmia: Recent Investigations. Sprue. Sickle-cell Anæmia. Osteosclerotic Anæmia. Splenic Anæmia. Hæmophilia. Purpura Hæmorrhagica. Hæmatoporphyrina. Hæmolytic Icterus.

CHAPTER XLVIII

EFFECTS OF INJURIES TO BLOOD AND BLOOD-FORMING ORGANS (CONTINUED)	869
---	-----

Leucocytosis; Leucopenia. Lymphocytosis; Eosinophilia. Agranulocytosis. Diseases of Blood-forming Organs with Corresponding Changes in Blood. General Characters; Attempt at Classification. Chronic and Acute Lymphoid Leukæmia. Mikulicz' Disease. Recent Studies of *Aëtiology*. Infectious Mononucleosis. Leucosarcoma and Chloroma. Lymphoid Myeloma. Lymphosarcoma.

CHAPTER XLIX

EFFECTS OF INJURIES TO THE BLOOD AND BLOOD-FORMING ORGANS (CONTINUED)	891
---	-----

Chronic Myeloid Leukæmia. Acute Myeloid or Myeloblastic Leukæmia. Monocytic Leukæmia, Myeloid Chloroma, Myeloid Myeloma.

CHAPTER L

HODGKIN'S DISEASE	902
-----------------------------	-----

History. General Character. Pathological Anatomy. Efforts to Discover Causative Agent.

CHAPTER LI

DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETIONS	910
---	-----

Survey of Relations of Endocrine Functions. Controlling Influence of Hypophysis.

CHAPTER LII

DISEASES DUE TO INJURY TO THE ORGANS OF INTERNAL SECRETION (CONTINUED)	915
--	-----

Effects of Disturbances in the Hypophysis. Structure, Relations with Central Nervous System. Distinctions Among Cell Constituents. Experimental Studies by Partial Extirpation, Implantations, Testing of Extracts, etc. Relation with Products of Other Endocrine Organs. Effects of Hyperactivity and Hypoactivity at Different Periods of Life. Gigantism, Acromegaly, Cushing's Disease, Dwarfism, Simmonds' Disease. Fröhlich's Syndrome. Diabetes Insipidus.

CHAPTER LIII

DISEASES DUE TO INJURY TO THE ORGANS OF INTERNAL SECRETION (CONTINUED)	928
--	-----

Diabetes Mellitus: General Character, Relation to Islands of Langerhans. Experimental Studies. Insulin. Relation to Action of Hypophysis. Carbohydrate Metabolism. Relation to Fat Metabolism. Pathological Anatomy. Symptoms. Metabolic Disturbances. Fat and Carbohydrate in Diet. Hyperinsulism. Von Gierke's Disease. Accumulation of Glycogen in Tissues.

CHAPTER LIV

DISEASES DUE TO INJURIES OF ORGANS OF INTERNAL SECRETION (CONTINUED)	945
--	-----

Disturbances of the Functions of the Thyroid Gland. Anatomy and Physiology. Chemical Studies of Secretion. Relation of Iodine. Relation to

Hypophysis. Effect of Loss of Thyroid Function. Myxoedema. Colloid Formation. Goitre, Various Forms, Aetiology, Relation to Iodine Consumption. Cretinism. Riedel's Ligneous Thyroiditis. Exophthalmic Goitre. Symptoms, Pathological Anatomy. Theories of Origin and Nature. Effect of Iodine.

CHAPTER LV

DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETION (CONTINUED) 964

The Parathyroid: Anatomy, Physiology. Tetany; Hyperexcitability of Nerves. Relation to Calcium Metabolism. Effect of Excessive Action by Parathyroid Tumors or by Renal Insufficiency. Osteitis Fibrosa. Thymus: Anatomy. Evolution and Involution. Effects of Extirpation. Hyperplasia. Thymus in Exophthalmic Goitre, in Myasthenia Gravis, in Status Thymicolumphanticus. Effect of Extracts upon Growth and Maturation.

CHAPTER LVI

DISEASES DUE TO INJURIES OF THE ORGANS OF INTERNAL SECRETION (CONTINUED) 975

The Adrenals: Anatomy, Functions of Medulla and Cortex. Extracts of Medulla, Adrenalin or Epinephrine. Extract of Cortex, Cortin. Influence upon Electrolytes. Addison's Disease. Tumors of Cortex. Effect upon Reproductive System. Aplasia in Anencephalic Monsters.

CHAPTER LVII

DISEASES RELATED TO SPECIFIC DIETARY DEFICIENCIES..... 982

Vitamins. Their Occurrence in Natural Food. Chemical and Physical Characters. Vitamin A: Relation to Xerophthalmia, Metaplasia of Mucosae. Vitamin B: Antineuritic. Beriberi. Pellagra. Vitamin C: Scurvy. Vitamin D: Rickets. Vitamin E: Fertility. Rickets: Pathological Anatomy. Effect of Sunlight, Irradiated Ergosterol, etc. Osteomalacia. Scurvy.

CHAPTER LVIII

DISTURBANCES OF LIPOID METABOLISM.—LIPOIDOSES..... 1000

Gaucher's Disease. Niemann-Pick's Disease. Lipoidosis, Schüller-Christian Type. Xanthoma or Xanthelasma.

CHAPTER LIX

CONDITIONS OF UNKNOWN AETIOLOGY AFFECTING CENTRAL NERVOUS SYSTEM OR MUSCLES..... 1003

Syringomyelia. Pathological Anatomy. Amaurotic Family Idiocy or Tay-Sachs' Disease; Eye Changes. Myasthenia Gravis, Muscular Infiltration, Thymus Tumor. Progressive Muscular Atrophy. Amyotonia Congenita. Amyotrophic Lateral Sclerosis. Progressive Muscular Dystrophy. Myotonia Congenita. Friedreich's Ataxia.

CHAPTER LX

DISEASES OF UNDETERMINED ORIGIN AFFECTING BONES..... 1007

Chondrodystrophy Foetalis. Osteogenesis Imperfecta. Osteopetrosis, Legg-Perthes' Disease. Osteitis Deformans (Paget's Disease).

CHAPTER LXI

ARTHRITIS DEFORMANS..... 1012

Confusion as to Classification; Infectious, Traumatic, Neuropathic, and Gouty Forms. Terminology: 1. Proliferative Arthritis Deformans or Progressive Polyarthritis: Clinical and Gross Pathological Characters; Histology. Spondylitis of Bechterew and Marie. 2. Degenerative Arthritis Deformans: Clinical and Gross Pathological Changes; Histology. Malum Coxa Senile; Spondylitis Deformans.

CHAPTER LXII

	PAGE
DISEASES AFFECTING TEETH AND RELATED STRUCTURES.....	1022
Formation and Structure of Teeth; Development. Influence of Metabolic Disturbances. Caries. Pyorrhœa Alveolaris. Periapical Abscesses. Relation to Distant Disturbances.	

CHAPTER LXIII

TUMORS.....	1025
General Nature of Tumors; Difficulty of Classification. Fibromata, Keloids, Lipomata. Chondromata. Osteomata. Xanthomata. Myomata; Leiomyomata, Adenomyomata, Rhabdomyomata.	

CHAPTER LXIV

TUMORS (CONTINUED).....	1043
Tumors Derived from Elements of the Nervous System: General Relations to Stages in Development. Neuroblastoma; Neurinoma, Ganglioneuroma, Paraganglioma. Tumors of the Brain, of the Glioma Type, Medulloblastomata, Spongioblastomata, Astrocytomata.	

CHAPTER LXV

TUMORS (CONTINUED).....	1055
Angiomata, Hæmangioma, Lymphangioma. Sarcomata: General Characters; Spindle-cell, Mixed, and Round-cell, and Alveolar Sarcomata. Giant-cell and Osteosarcomata. Myomata.	

CHAPTER LXVI

TUMORS (CONTINUED).....	1076
Pigmented Tumors: Nævi. Their Relation to Epithelium and Connective Tissue. Melanomata or Melanotic Sarcomata. Tumors of Adrenal Origin: Hypernephromata; Relation to Aberrant Adrenal Tissue. Endotheliomata: Difficulty of Establishing Their Relation to Endothelium. Endotheliomata from Lymphatic Endothelium. Cylindromata. Pleural and Peritoneal Tumors. Endotheliomata of the Meninges. Tumors Derived from Endothelium of the Blood-vessels.	

CHAPTER LXVII

TUMORS OF EPITHELIAL ORIGIN.....	1094
Relation of Epithelium to Stroma. Papillomata: Origin from Skin and Mucosæ, Papillomata of Antrum or Sinuses, of Bladder and Ovary. Adenomata: Origin from Skin, Salivary Glands, Gastric and Intestinal Mucosæ, Kidney, Liver, Adrenal, Hypophysis, and Prostate. Adamantinomata. Adenomata of the Breast; Intracanalicular Forms. Cystadenomata of Ovary; Their Origin and Form; Papillomatous Types. Adenomata of the Uterus.	

CHAPTER LXVIII

CARCINOMATA.....	1115
General Characters, Grouping. Flat-cell Carcinomata. Epitheliomata of Lip, Skin, etc. Mode of Growth and Metastasis. Epitheliomata of Tongue, Tonsils, Bronchi, Oesophagus, Gall-bladder, Urinary Bladder. Epitheliomata of the Vaginal Portion of the Cervix Uteri. Their Frequency and Importance. Basal-cell Carcinomata. Their Relatively Benign Character. Distribution, Peculiar Morphology. Relation to Nævi. Argentaffine Tumors of Intestine and Appendix.	

CHAPTER LXIX

CARCINOMATA (CONTINUED).....	1135
Adenocarcinomata: General Characters and Distribution. Carcinomata of the Stomach: Polypoid, Solid and Scirrhous Forms. Their Histology and Mode of Growth; Metastasis. Colloid Forms, Their Somewhat Different	

Mode of Growth. Carcinomata of the Gall-bladder and Ducts. Carcinomata of the Pancreas, of the Colon, of the Prostate. Metastasis of Prostatic Tumors in Bones. Adenocarcinomata of the Uterus and of the Ovary.	1156
CHAPTER LXX	
CARCINOMATA (CONTINUED).....	1156
Gland-cell Carcinomata. Carcinoma of the Breast. Carcinoma of the Ovary, of Thyroid. Primary Carcinoma of Liver with Cirrhosis. Ovarian Tumors with Endocrine Character. Disgerminoma, Brenner Tumor, Granulosa Cell Tumor, Arrhenoblastoma. Chorionic Tumors. Hydatidiform Mole. Chorionic Epithelioma. Histogenesis, Relation to Corpus Luteum.	1156
CHAPTER LXXI	
CONGENITAL MALFORMATIONS.....	1177
General Character: Repetition of Typical Forms. Defective Embryonic Development in Localized Areas of the Body. Medullary Groove, Face, Genito-urinary Apparatus, etc. Double Monsters. Twins.	1177
CHAPTER LXXII	
TERATOMATA: COMPOSITE TUMORS.....	1181
Chorionic Epithelium in Tumors of the Male and in Female Apart from Pregnancy. Teratomata, Their Composition. Theories of Origin; Inclusion of Blastomere, Parthenogenetic Development of Sex Cell. Experimental Production of Teratomata by Auto-implantation of Such a Cell. Character and Maturity of Tissues of Teratoma. Malignant Character. Teratomata of Testis. Dermoid Cysts. Mixed Tumors of Salivaries.	1181
CHAPTER LXXIII	
CLASSIFICATION OF TUMORS.....	1198
CHAPTER LXXIV	
GENERAL DISCUSSION OF TUMORS.....	1200
General Character of Tumors: Origin from Tissue of Host. Independence of Laws Governing Growth of Normal Tissue. Mode of Growth: Idea of Return to Embryonic State; Dependence upon Host for Nutrition. Implantation, Invasion, Metastasis, Recurrences. Predisposing and Actual Causes of Tumor Growth. Experimental Production in Normal Animals. Recent Work on Tar Derivatives. Parasites as Inciting Cause. Viruses in Production of Tumor Growth. Influence of Internal Secretions, Senility; Heredity.	1200
CHAPTER LXXV	
GENERAL DISCUSSION OF TUMORS (CONTINUED).....	1219
Resistance and Immunity. Theories as to the <i>Ætiology</i> of Tumors: Parasitic Origin; Effect of Irritants; Disturbance of Equilibrium of Tissues; Displacement of Embryonic Cells. Changes in Structure and Mitosis in Cells; Abnormal Metabolic Activities of Cells. Fundamental Changes in Cells Releasing Them from Laws of Normal Growth.	1219
<hr/>	
INDEX.....	1229

TEXT-BOOK OF PATHOLOGY

CHAPTER I

DISTURBANCES OF THE FLUIDS OF THE BODY

Relation of fluids to tissues; blood, lymph, tissue fluids. The blood: variations in quality and quantity. Readjustment. Plethora and oligemia. Clotting. Thrombosis.

Relation of Fluids to Tissues.—The cells of the tissues are, like other living beings, dependent for their life and activity upon a constant and abundant supply of food and oxygen and an equally adequate removal of their waste products. This service is rendered them by the circulation of the various fluids through every part, propelled by a mechanical arrangement, the perfection of which we shall have frequent occasion to admire. There are three main types into which we may divide these circulating fluids, the blood, the tissue fluids, and the lymph.

The blood is practically everywhere separated from actual contact with the cells of the tissues by a semi-permeable membrane composed of other cells, the endothelium. It flows through the whole body, giving off certain substances and withdrawing others, always through this membrane. Between the cells outside the blood-vessels there are spaces, or at least potential spaces, in which a small amount of fluid collects which directly bathes the cells and directly receives their waste. This tissue fluid is constantly being changed too, by interaction with the blood. But it also stands in exactly the same relation to the lymph, which, like the blood, flows inside channels with semi-permeable walls composed of endothelial cells and goes to empty into the vein. We do not believe now that there are open communication between the lymphatic channels and the tissue crevices. That idea, it seems, has been thoroughly disproved by the recent work which shows the completeness of the endothelial lining of these channels.*

Of course, a moment's thought will make it clear that everything, whether necessary to life or a waste product to be excreted, must take a rather roundabout course in the blood. All that is absorbed from the digestive tract by veins or lymphatics must go a long way to reach the arteries and be distributed to the tissues and the waste from every tissue must travel in veins or lymphatics to reach the arteries so as to be carried to the organs of excretion. The actual interchange must be continuous but only partial as the blood hurries by, whether in bringing nutriment or removing waste and everywhere the two processes go on simultaneously. Materials pass from the arterial side of the capillaries into the tissue spaces in immediate contact with the cells which absorb

* MacCallum: Archiv f. Anat. u. Physiol., Anat. Abth., 1902, 273. Bull. Johns Hopkins Hosp., 1903, xiv, 1, 195.

them and set free their own products, in some cases useful to other organs, in others merely waste, and these pass into the lymphatics or veins. It is obvious that, according to the character of the cells which make up the tissue, the nature of the lymph and of the venous blood produced in this way must vary greatly in different parts of the body. The portal blood is filled with materials which could not be found in any such quantities in the blood of the femoral vein, and the hepatic vein contains blood which is altogether changed by passing through the liver. The degree of activity of the organs plays a great part also, so that during digestion portal blood undoubtedly differs very greatly from the blood of the same vein at other times.

THE QUANTITY OF BLOOD IN THE BODY

Normally the quantity of blood bears a definite relation to the weight of the body, but until recently the efforts directed toward determining this quantity have led to very uncertain results. Now, however, it is realized that by allowing a person to inhale a certain amount of carbon monoxide and measuring it in a sample of blood, the quantity of haemoglobin containing corpuscles can be estimated. Similarly, by injecting a colloid dye, such as vital red, the amount of circulating plasma may be learned. Whipple and his associates found that in the dog the plasma volume is 48 c.c. per kilogramme of body weight, the red corpuscles 42 c.c., the total blood therefore 90 c.c. per kilogramme. Seyderhelm and Lampe in human beings find the plasma about 45, the total blood-volume about 83 c.c. per kilogramme of body weight; that is about one-twelfth of the body weight.

LITERATURE

Salvesen: Jour. Biol. Chem., 1919, xl, 109.

Seyderhelm and Lampe: Ergebn. d. inneren Med., 1925, xxvii, 245; Klinische Woch., 1927, vi, 1833.

Whipple and others: Amer. Jour. Physiol., 1921, 56, 313-360.

Experimental efforts to increase or decrease the amount of blood in proportion to the tissues fail except for very short periods, because the excess of fluid introduced is immediately excreted, and that which is removed from the blood-vessels by bleeding is quickly made up by the filtration of fluid from the tissues into the capillaries. Blood-pressure is scarcely changed by any such measures because the vasomotor mechanism immediately adapts the capacity of the stream-bed as nearly as possible to its new contents.

The adjustment is especially rapid and effective when an excess of fluid is introduced, and if it does not enter the veins too abruptly and rapidly the excretion by the kidneys keeps pace with it almost perfectly. In the other case, the removal of blood, there are naturally limits to the power of the tissues to give up fluid to restore its bulk. Even under the best circumstances this is a slower process than the removal of fluid by excretion. The terms *plethora* and *anaemia* or *oligæmia* have long been in use to imply an excess of blood, on the one hand, and a poverty of blood, on the other, but with this extraordinary compensatory power of

the body in view, it seems that we must use them with some caution. Nevertheless it is perfectly obvious at autopsy, if not during life, that in some persons the vessels are distended with an enormous quantity of blood, while in others not only do the vessels seem collapsed, but all the tissues are shrunken and dry looking. Especially is the latter true in old persons and those who have long suffered from a wasting disease.

Plethora.—Apparently the existence of actual changes in the amount of blood which last for any time is dependent chiefly upon qualitative changes in the blood itself and in the tissues. A true plethora, in which the blood is increased without change in its composition, probably occurs with defects in the action of the heart which then allows a part of the blood to remain practically stagnant in the veins and propels an abnormally small part of it into the arteries. The compensation for this diminution of the arterial circulation by introduction of more fluid may restore the normal amount in active circulation, but increases the total amount in the body. In one peculiar disease, polycythaemia vera, there is a great increase in blood volume due entirely to an increase in the number and size of the red corpuscles, while the plasma is rather decreased in amount. Hydræmic or serous plethora is spoken of as a condition in which the quantity of blood is increased by a relative increase in its watery part. As has been said, it is impossible to maintain this for any length of time experimentally because the kidneys promptly excrete the excess of water; even in renal disease it is rare to find any increase in the volume of the circulating blood and there is no relation between the amount of blood and the excessive blood-pressure which is so common with some disease of the kidney.

Oligæmia.—Practically the same things may be said of oligæmia or anæmia. The simplest type of general anæmia is undoubtedly that which is produced when a considerable amount of blood is lost through the opening of a blood-vessel. The person becomes blanched, makes forced respirations, and may become unconscious on account of the poor supply of nutrition to the brain. He becomes very weak and thirsty, and his pulse is low and scarcely perceptible, but often very rapid. The vessels contract so as to hold up the blood-pressure, and an immediate attempt is made by the tissues to pour back again into the vessels enough fluid to fill them, and consequently, for some time, on account of this adding of fluid both from the tissues and from water taken in by mouth, the blood becomes dilute. The proportion of red corpuscles, which can be determined by counting, sinks for two or three days, at which time the inflow of fluid ceases and the reproduction of corpuscles by the blood-forming organs begins to make itself evident. From that time onward there is a steady increase in the number of corpuscles to each cubic millimetre until the blood reaches its normal state. There seems to be also the other form of oligæmia in which the quantity is reduced by loss of water. Naturally this will be compensated as quickly as possible, too, but in such diseases as cholera the loss is so rapid that the tissues become desiccated as well. It is quite possible, therefore, that the decrease in the quantity of blood is merely proportional to the desiccation of all the tissues.

CLOTTING, THROMBOSIS, ETC.

Clotting.—We are not well informed as to the nature of the process through which an injury to a single cell or a unicellular animal is healed. The wound is closed very rapidly, and apparently by a process rather more complex than the mere flowing together of the protoplasm. We do know, however, that in such animals as the crustacea and in the higher types, where there is a circulation of blood and other body juices, these fluids possess the peculiar property of clotting, or coagulating as soon as they are exposed to contact with anything which has not the character of the living vessel-wall. It is through this property that the loss of blood from every trifling wound is checked, although otherwise it might well prove fatal. In this sense the clotting is distinctly a protective process, probably developed from the time of the first appearance of animal life as a factor indispensable to the preservation of the animal. The same process appears again and again under the greatest variety of circumstances in pathological conditions, but it will be seen that in all—in spite of many imperfections in the mechanism—it has a protective significance.

When blood and lymph are allowed to escape into a glass dish they clot, usually in a very short time. If the blood is continually stirred, the clot adheres to the stirring rod, leaving a permanently fluid blood (defibrinated blood). If it is not stirred, the clot forms uniformly throughout the whole quantity of blood, converting it into a solid, rather dry, firm mass, often so tenacious that the dish, if it be not too wide and shallow, may be inverted without spilling. Such a clot is of uniform dark-red color. If it be squeezed, a red fluid is forced out which is identical with defibrinated blood. If the spongy mass be washed in running water, all the red blood-corpuscles may be washed away, leaving a stringy, yellowish white, elastic mass of fibrin. If the fresh blood be kept very cold, or if it be received into an oiled dish, it will not clot so quickly, and since the red corpuscles are heavier than the plasma, there may be time for them to sink to the bottom in a very thick layer. The leucocytes are lighter and rest in a layer on top of the red corpuscles, while above there is some plasma almost free from cells, but containing abundant platelets which sink very slowly. By this time clotting occurs throughout, the clot differing from the uniform red one formed by rapid coagulation, in the presence of a grayish-yellow upper layer which contains most of the leucocytes and platelets. This was called the "buffy coat" by the old bloodletters, and its thickness was an index of the rapidity with which the blood clotted, although their deductions usually took various other turns.

This slow clotting, allowing time for the action of gravity, is seen very commonly in the heart at autopsy, for the intact endothelial lining of the heart keeps its contents a long time without clotting. There the deep-red portion of the clot ("cruor clot") is in the dependent part, while the tough, elastic, translucent, yellowish substance (chicken-fat or turtle-fat clot) occupies the uppermost part of the heart as the body lies on the table (Fig. 1). The homogeneous elasticity of this kind of clot and the fact that it is readily removed from the heart-wall,

leaving it unaltered, make it quite easy to distinguish it from the thrombus formed on injured areas of the heart-wall during life, although extraordinary mistakes have been made and the postmortem clot held to be the cause of death.

At first—and especially when it is rapidly formed—the clot is quite dry. Indeed, it is this which confers the dryness and firmness upon the lung in the early stages of pneumonia, where a fresh clot occupies each air-cell. Later, however, through its own elasticity, the clot contracts away from the wall of the glass and shrinks together. In this way it expresses from its meshes a clear fluid, the serum, in which it is finally bathed. If we examine the clot microscopically, we shall find it to be composed of a delicate network of fine fibrils, among which there are entangled the cells of the blood. In the rapidly formed clot these are perfectly homogeneously distributed in the proportions in which they

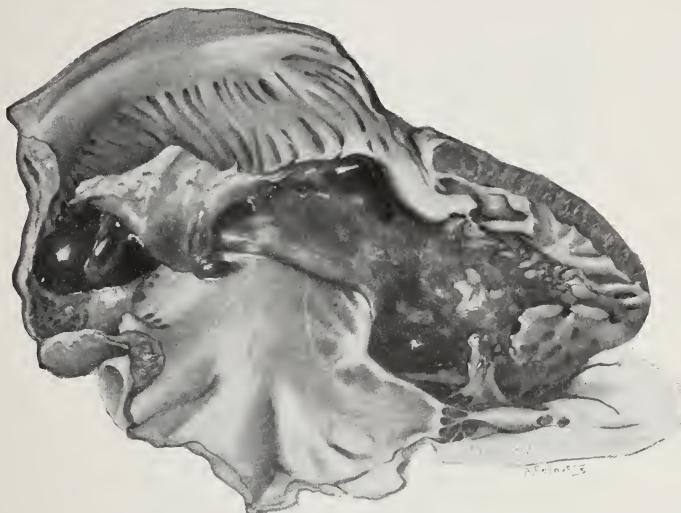


Fig. 1.—Postmortem clot in the cavity of the heart.

existed in the circulating blood, but in the layered clot which has slowly formed there are red corpuscles, but fewer leucocytes in the lower red part of the clot, while in the upper layer there are numerous leucocytes with platelets, but no red cells; there may even be a layer in which there are very few cells of any kind (Fig. 2).

Throughout the clot one may sometimes recognize minute centres about which the fibrin radiates, or if the corpuscles are not too much crowded, it may be possible to see star-like radiations of filaments of fibrin about single cells. One sometimes sees these radial arrangements of fibrin about bacteria in the blood, and this may be especially striking in cases of anthrax or other such infection in which the blood contains many foreign cells. Besides these, in clots which are formed after death in the heart or large blood-vessels, it is generally possible to find in sections pale, pink-staining clumps to which a number of leucocytes adhere,

buried deeply and irregularly among the red corpuscles. These have been described by Rost and others and seem to consist chiefly of groups of blood-platelets. Nevertheless, the distinctive character of the clot formed after death in the stagnant blood is its general homogeneity of structure, in which respect it differs so sharply from the clots formed during life in the streaming blood.

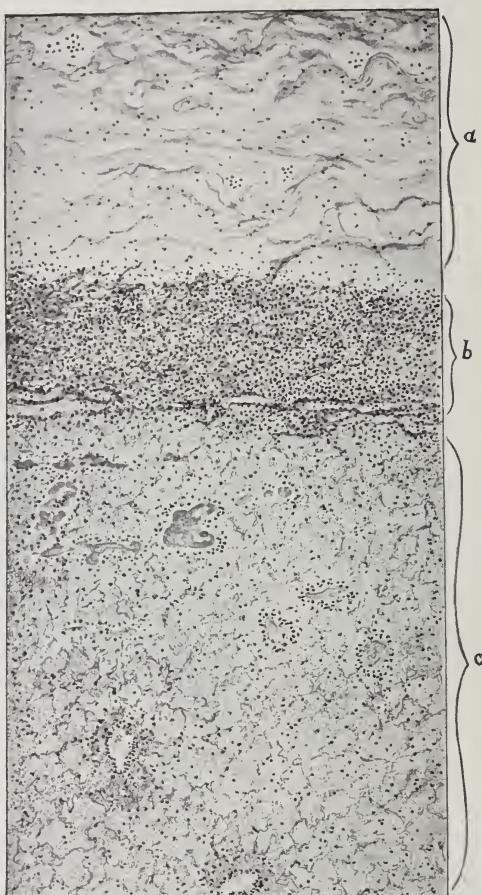


Fig. 2.—Postmortem clot: *a*, Fibrin; *b*, layer of leucocytes; *c*, cruor clot with red corpuscles and platelets in clumps.

A great deal of experimental and chemical work has been devoted to the attempt to explain the clotting of blood, and many theories have been proposed; all, however, are insecure and unsatisfactory, because the very substances involved are only imperfectly recognized or are being even now discovered, so that the nature of the physical and chemical reactions among them must be obscure.

Although there are some who would ignore the known chemical reactions and state the whole process of fibrin formation as a physical

change of fibrinogen into its hydrogel, most workers, as Howell points out, accept in general Alexander Schmidt's thrombin theory of clotting—namely, that soluble fibrinogen is converted into insoluble fibrin under the influence of thrombin which in some way is used in the process.

The greatest confusion and actual obstruction to comprehension of the problem arise from the multiplication of terms applied to substances, real or assumed to exist as factors in the process, and from this point on we shall use the terms employed by Howell.

It is clear that clotting will not occur if calcium be removed from the blood by precipitation or changed into some inactive form, by addition of oxalates or citrates. It does occur, however, if the calcium is restored to such blood. It is also known that thrombin is not found in the circulating blood nor in oxalated blood, and it follows that there must be an antecedent substance, known as prothrombin in the normal blood, which can be converted into thrombin only in the presence of calcium.

Then it was recognized that some substance derived from the corpuscles of the blood or tissue cells must also be present to start the process of clotting. This has been given many names, thrombokinase by Morawitz, thromboplastic substance by Nolf, accepted by Howell, and cytozyme by Fuld and Bordet. At first regarded as a lecithin-containing substance, it has been shown by Howell to be a compound of the phosphatid, cephalin.

Four factors in clotting are therefore agreed upon by most workers—three of these, prothrombin, fibrinogen and calcium, exist in the circulating blood. The fourth, the lipoid or phosphatid factor, is furnished by the cells and especially by the blood-platelets. Most workers have, therefore, thought of clotting as follows (to quote from Howell):

"When blood is shed, the disintegration of the platelets or contact with the tissues liberates some of the phosphatid factor. The phosphatid factor, the calcium and the prothrombin react to produce thrombin. The thrombin reacts with the fibrinogen of the plasma to form fibrin." This theory, suggested by Morawitz, assumes that the phosphatid (thrombokinase) acts as an enzyme or kinase together with calcium to convert prothrombin into thrombin. Bordet's theory which is complicated by the use of a quite different nomenclature is not really very different. Cytozyme (the phosphatid) unites with serozyme (prothrombin) in the presence of calcium to form thrombin. Contact effects are much emphasized, and it is necessary to assume a proserozyme to explain the absence of clotting in the vessels.

Howell has shown that there is no phosphorus in thrombin, which is a serious objection to such theories as assume a combination of the phosphatid with prothrombin. Howell's theory is rather radically different from the older ones in that he believes that calcium alone is sufficient to convert prothrombin into thrombin and would do so in the circulating blood, were it not for the presence of an inhibiting substance. The phosphatid factor brings about clotting by neutralizing this inhibitory substance—permitting the calcium to activate the prothrombin and form thrombin.

The nature of the inhibiting substance is then to be sought. It is known that leeches secrete in their mouth-glands a substance, hirudin, which will prevent coagulation by neutralizing fully formed thrombin. A similar substance occurs in the blood which is known as antithrombin and which will prevent the coagulation of a mixture of thrombin and fibrinogen. It is destroyed at temperatures of 60° to 70° C., and is developed in the blood in increased quantities when peptone is injected intravenously. Little else is known about it or about what function it can serve, for it is able to act only on the finished thrombin, but it is probably called into play to neutralize thrombin in unusual amounts in the daily destruction of cells.*

But Howell has discovered another anticoagulant which he has named heparin because it is obtained from the liver, although it is present in the circulating blood. This is a protein-free, non-crystallizable substance, stable at 100° C., and containing no phosphorus. It contains nitrogen and there is evidence of the presence of a carbohydrate grouping, and the purest sample so far obtained appears in the form of brownish scales. It is exceedingly powerful in preventing clotting of blood, but it has no effect on the reaction between thrombin and fibrinogen. When added to a solution of thrombin or incubated with it for hours it does not interfere with the coagulating effect of the thrombin on fibrinogen. Heparin is, therefore, not the same as antithrombin. It does, however, cause the development of an increased amount of blood antithrombin when added to blood. If the plasma or blood is first heated to 70° C., this does not take place so that there must be a thermolabile element in blood which reacts with heparin to form anti-thrombin.

But heparin does apparently react with prothrombin so as to prevent its activation to thrombin by the calcium. It inhibits coagulation in its initial stage and may therefore be spoken of as antiprothrombin.

It would seem, therefore, that the process of clotting as thought of by Howell at present might be stated in its simplest form as follows: Fibrinogen, prothrombin and calcium are present in the circulating blood—quite sufficient in themselves to form a clot by the activation of the prothrombin by the calcium to form thrombin, and the change of fibrinogen into fibrin through the agency of the thrombin—were it not for the presence of heparin which constantly interferes with the activation of prothrombin to thrombin, except when it in turn is neutralized by the thromboplastic substance, cephalin, which comes from injured platelets or tissue cells. Then the activation of prothrombin is possible and the resulting thrombin coagulates the fibrinogen.

Fuchs in still more recent studies denies the assertion of Howell that thrombin contains no phosphorus and maintains that the amount of phosphatid necessary to produce this combination is so small that it is beyond the reach of ordinary analytic methods. He finds that prothrombin is not free in circulating plasma but loosely combined with

* Howell: Pasteur Lecture on the Problem of Coagulation. Proceedings of the Institute of Medicine of Chicago, 1925; Amer. Jour. Physiol., 1926, lxxvii, 680; lxxviii, 500.

antiprothrombin (proserozyme of Bordet) from which it is liberated by the phosphatid (thromboplastic substance, or cytozyme) which combines with it in the presence of calcium to form thrombin. Incidentally he brings much evidence to show that prothrombin is identical with the complement of immune reactions or at least with its mid-piece. He thinks of coagulation in the body as a progressive phenomenon. The platelets contain prothrombin and cytozyme or thromboplastic substance, ready on the rupture of their cell membrane to unite in the presence of the calcium of the plasma to form thrombin. This is the most prompt form of coagulation. Tissue juices contain cytozyme but not much prothrombin. The prothrombin of the plasma must first be liberated from its association with antiprothrombin to be able to form thrombin.

Fuchs points out, also, the fact that the change in hydrogen-ion concentration produced by the excess of carbon dioxide in venous blood promotes clotting there as compared with arterial blood, since the anti-prothrombin is rendered reversibly inactive by the carbonic acid.

The clot itself has been watched in process of formation with the aid of the ultramicroscope. At first there is a clear field, but as the clotting begins, shining needle-shaped crystals appear in great numbers, dancing about, and later arranging themselves in strands, which are the fibrils of fibrin. Fibrin is thus one of the rare examples of crystalline gels.

The origin of the thromboplastic substance was long discussed, but it seems now to be a matter of less interest than the origin of the prothrombin, which Drinker has shown to depend largely on the integrity of the bone-marrow which has been generally regarded as the point of origin of the platelets. The recent work of Dr. Howell, which seems to show that platelets are formed in great numbers in the lung and possibly in other tissues, throws some light on this. There are some conditions, particularly such infectious processes as pneumonia, in which clotting occurs very rapidly, and shortly after death complete moulds of the vessel may be pulled out from the large vascular trunks. In such cases the clots are dry and uniformly deep red throughout. On the other hand, there are other conditions, such as haemophilia, icterus, etc., in which coagulation is greatly delayed, and serious haemorrhage may occur during and after the slightest surgical operation.

Howell finds in icterus no excess of antithrombin or of heparin in the blood. Haessler found that bile-salts interfere with the conversion of fibrinogen into fibrin, but the matter appears not to have been analyzed further. V. Falkenhausen and Sauer* find that coagulability of the blood is not delayed by the presence of bile or bile-salts in the blood-stream. Icterus following severe liver damage, according to them, results in slowing the coagulation from the increase in antithrombin or anticomplement. In haemophilia there is no deficiency of thrombin or excess of heparin, but the usual swelling and loss of outline of the disc-shaped platelets which occur when they furnish the thromboplastic substance do not occur in the blood of patients suffering from

* Ztschr. f. d. ges. exp. Med., 1927, lvii, 398.

haemophilia. This is seen also, according to Dr. Howell, in heparin or oxalate plasma, and might afford an explanation of the slow coagulation through lack of thromboplastic substance from the platelets, but it is difficult to understand the mechanism of the protection of the platelets. Dr. Howell's summary of the work of recent years makes it evident that although many new theories based largely on physical-chemical reasoning are put forward, so much is invalidated by the use of impure materials in experiments that the confusion and uncertainty is increased. It seems necessary, therefore, to rehearse the older theories until convincing new work is completed.

Thrombosis.—On the basis of either theory of clotting it is easy to understand that a coagulum might form about any mass of cells which,



Fig. 3.—Thrombus: coral-like laminae of platelets with marginal leucocytes and intervening red corpuscles and fibrin.

after suffering some injury, had become clumped together or agglutinated in the blood, and, indeed, Loeb and others have observed that an agglutination of formed elements always precedes the formation of the fibrin. The part played by the platelets is perhaps important in post-mortem or extracorporeal clotting, but it becomes especially prominent in the inception of thrombi, which are peculiar clots formed during life in the streaming blood.

The character of these thrombi is very different in some respects from that of the postmortem clots, although the principles connected in their formation are the same, except that the single mechanical factor of the streaming movement of the blood disturbs the ordinary process



Fig. 4.—Thrombus, laminæ of platelets with festoons of fibrin and marginal leucocytes.

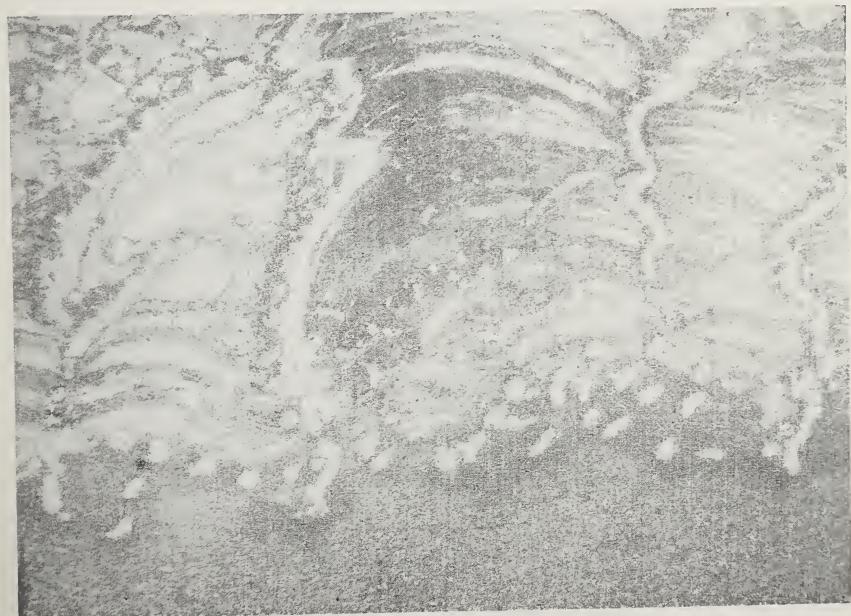


Fig. 5.—Thrombus: the strands of platelets form superficial corrugations.

of clotting and brings into prominence the feature of preliminary agglutination of the platelets.

A thrombus begins by the deposition, on the wall of the blood-channel, of a minute, pearly, translucent mass of platelets which grows by the adhesion of other platelets as they come by. These produce curious upstanding laminae or walls running transversely to the blood-stream and anastomosing freely with one another; the platelets are so welded together that their outlines can no longer be seen, and in section these laminae appear as faintly pink-staining, finely granular bands in the substance of the thrombus (Fig. 3). However, it must not be supposed that they arise alone and unsupported in the current. Instead of that, they quickly catch the passing leucocytes and hold them all along their surfaces (borders in the section), like flies on sheets of sticky fly-paper; and at the same time they seem to liberate thrombo-plastic substance, so that filaments of fibrin spread out from them on all sides, and meeting with filaments from the next lamella, hang in



Fig. 6.—Thrombus in auricular appendage.

festoons between them. In this way the branching and anastomosing lamellæ are guyed and braced together by fibrin, which, needless to say, entangles quantities of red corpuscles, so that finally the whole is a solid mass of peculiarly constructed clot. At first, of course, this thrombus is predominantly a red mass, although the grayish-white lamellæ of platelets can be seen in a cross-section forming a web all through the red. On the free surface of the thrombus these same lamellæ project slightly above the red part of the clot, and these corrugations are known as the "lines of Zahn" (Fig. 6). Red corpuscles, under such circumstances, soon die, lose their haemoglobin, and finally disappear into a formless débris which in time assumes a semitranslucent appearance. A thrombus, therefore, which is largely red at first, becomes yellowish gray after a time, and the contrasting color of the platelet sheets is lost in the homogeneous mass. Nevertheless, since a

thrombus continually tends to grow by accretion, the parts of different ages show differences in color. Indeed, when a thrombus forms in a vein, occluding it, there is left a perfectly stagnant column of blood reaching to the next affluent of the vein, and in this an ordinary homogeneous clot is formed, just as it would be in a test-tube—not exactly, however, for there is some motion communicated to this column of blood and clumps of platelets are formed. At the inflow of the next branch the clotting may stop or begin once more to assume the character of the thrombus. Thus, as Aschoff says, a thrombus has a head, and then, perhaps, extending both ways in the vein, a propagated part or tail, which differs from it, being like a postmortem clot.

Thrombi may be formed anywhere in the blood-stream, even on the walls of the aorta, where it might seem that the pulsating torrent of blood would allow no chance for the deposition of the pioneer platelets. But most commonly they appear in the veins or in the auricular appendages or intertrabecular spaces of the heart or upon the valves of the heart. In the veins they seem to start from the region of a valve, where the slight obstruction gives rise to eddies. In the heart (Fig. 6) they bulge forward from the recess as pinkish yellow, distinctly corrugated masses, generally coated with an adherent red clot—sometimes they are quite smooth and globular, and these, which seem to be old ones, are frequently found to be softened into a semifluid or fluid material in their central parts. In the veins (Fig. 7) the lumen is usually, though not always, obliterated, and at the lower end the vein is plugged for a long way with a soft red clot. The thrombus itself differs from a postmortem clot in being inelastic, friable, and granular, and in adhering to the wall of the vein so that when it is removed the lining of the vein is left roughened and dull looking. In the propagated clot one may find for some distance indications of the general characters of the thrombus, and such freshly formed thrombi are hard to tell from postmortem clots. Any part of the thrombus may break off and be swept along in the blood-stream to plug some distant vessel.

It may be difficult to avoid looking upon thrombosis as a process harmful to the body, since it causes the obstruction of blood-vessels, and through the dislocation of part of the material of the thrombus frequently gives rise to embolism of distant organs, with death of some part of their tissue or even death of the individual.

But it might be argued that this is only a form of the very useful and protective clotting of the blood, and that these inconveniences represent the usual imperfection in a mechanism of defense. Indeed, there are innumerable instances in which thrombosis has the character of a life-saving process. Even the final cessation of bleeding from a cut vessel is really due to a form of thrombosis, since the clot is produced in streaming blood. The covering of bacteria lodged on a heart valve or on any part of the wall of the circulatory system by a thrombus is a temporary protection inasmuch as it prevents the bacteria from being spread through the whole body. When thrombosis occurs in a blood-vessel on account of injury and weakening of its wall, either from within or from the advance of an infectious or other destructive process from

the outside, it prevents haemorrhage by obstructing the vessel and withdrawing it from the pressure of the blood. This is well illustrated in the blood-vessels about ulcerative processes of all sorts, whether in the intestinal walls, lungs, or elsewhere. It must be said, however, that thickening of the walls of the vessels usually plays a large part in shutting off the current of blood, especially when the erosion of tissue pro-



Fig. 7.—Thrombus in vena cava.

ceeds slowly, but it may be agreed that were it not for thrombosis more serious consequences might follow the injury of the walls of the blood-channels. Less can be said for the advantages conferred by embolism.

The question as to the cause of the formation of thrombi has been answered in various ways. The wall of the vessel underlying them is always injured, but whether by the presence of the thrombus or by something which in that way provoked the

formation of the thrombus is hard to say. Most of the older writers assumed a primary injury of the wall (Eberth and Schimmelbusch, Welch) which allowed the production of thrombokinase or thromboplastin. This seems especially true of those instances in which thrombi are formed in the aorta upon ragged, arteriosclerotic patches or in the venous sinus of the dura at a point where an abscess extending from the middle ear encroaches upon it. For a time there was great interest in the idea that thrombi occurring in general infections and after surgical operations were due to the presence of bacteria which injured the vessel wall. Perhaps this was going too far, but now the pendulum has swung the other way, and Aschoff and his colleagues contend that thrombi are essentially produced by some mechanical obstruction or slowing of the stream, and that the bacteria which are found in them are brought to the thrombus after it is well formed. Aschoff has made elaborate studies to show that, in a stream of water with obstructions of various forms, sawdust or sand carried on by the stream will accumulate according to definite laws in a certain relation to the obstructions, and especially where eddies are formed and where consequently the stream is slowed. The distribution of little sand-banks in the course of a crooked stream with many obstructions is familiar enough to every one, and it is easily credible that such mechanical factors are of great importance in determining where the thrombus shall start and how the deposition shall proceed.

More recent writers, such as Fischer-Wasels, separate those thrombi which stop the bleeding from cut vessels of small size, and those which are evidently due to profound injury of the vessel wall from the more common and perplexing form that occurs, usually after a surgical operation or serious contusion or fracture, in a distant vein which is in no way involved in the injury. These, because they are so frequently the cause of fatal embolism, have attracted much attention, but as yet no convincing explanation of their inception has been found. Some cling to the idea that bacteria lodge in the wall of the vein although frequently there is, as in a simple fracture, no reason to suppose that bacteria could be concerned. Others hold that the immobility of the muscles or the flexed position of the thighs, often maintained in the new adjustable beds, for a long time after an operation, may produce a certain venous stasis with its high carbon dioxide content of the blood, which might favor femoral vein thrombosis. Dietrich, from animal experiments, suggests a sort of allergic reaction with changes in the vascular endothelium. Heusser finds increased viscosity, changes in albumen content and altered rate of sedimentation of red corpuscles after operation which he thinks promotes thrombosis.

On the whole it is evident that we do not as yet understand the formation of thrombi in distant and apparently uninjured veins, and that all these theories are very unsatisfactory.

LITERATURE

- Aschoff, Beck, de la Camp, and Krönig: Beiträge zur Thrombosefrage, Leipzig, 1912.
 A. Dietrich and K. Schröder: Virch. Arch., 1930, cclxxiv, 425.
 Eberth and Schimmelbusch: Thrombose, Stuttgart, 1888.
 B. Fischer-Wasels: Dtsch. Med. Woch., 1929, Nr. 13 and 14.
 H. J. Fuchs: Ergebni. d. inn. Med., 1930, xxxviii, 173.
 H. Heusser: Dtsch. Ztschr. f. Chir., 1928, ccx, 132.
 Howell: Amer. Jour. Physiol., 1910, xxvi, 452; 1912, xxxi, 1; 1913, xxxii, 264; 1914, xxxv, 474; 1916, xl, 526; 1918, lvii, 328; 1926, lxxvii, 680. Arch. Int. Med., 1914, xiii, 76; Proc. Inst. of Med., Chicago, 1925. Bull. Johns Hopkins Hosp., 1928, xlii, 199. Harvey Lectures, 1916-17, 273.
 Howell's classical work on the coagulation of the blood is brought together in his Harvey Lecture. More recently he has summarised the literature up to the present time in his paper, "Theories of Blood Coagulation," Physiological Reviews, 1935, xv, 435.
 Morawitz: Ergebni. d. Physiol., 1905, iv, 368.
 Welch: Allbutt's System of Medicine, 1899, vi, 155.
 Wöhlsch: Ergebni. d. Physiol., 1929, xl, 121.

CHAPTER II

LOCAL DISTURBANCES IN THE CIRCULATION OF THE BLOOD

Hyperæmia; anaemia. Postmortem changes in distribution; active and passive hyperæmia. Local anaemia. Embolism. Infarction. Gangrene.

THE circulation through a tissue is modified by three main factors: the activity of the heart, the changes in the calibre of the blood-vessels, and the amount of blood. Of these, the changes in the calibre of the blood-vessels are of special importance as far as the local conditions are concerned. The muscular walls of the arteries, and to a less extent the veins, are controlled, as is well known, by the vasoconstrictor nerves, so that the amount of blood which passes through any given tissue depends largely on the activity of these nerves. Quite aside, therefore, from any pathological conditions, there are remarkable changes from time to time in the amount of blood which passes through the different tissues, the arterial blood-supply generally increasing with the activity of that particular tissue. The regulation of the arterial pressure has been ascribed more recently to the influence of an extraordinary mechanism described first by Hering, and related to the carotid sinus which stirs reflexly adrenalin secretion. Of this a detailed account will be given later.*

* **Postmortem Changes.**—During life the distribution of the blood in any organ or tissue is a very uniform one, as a rule, but on the cessation of the action of the heart numerous alterations take place, so that in the tissues, as observed in the dead body, the distribution of the blood is very much changed, and it is necessary to be familiar with these changes in order to appreciate those which are actually the results of pathological conditions which have existed during life. The contractility of the arterial walls is dependent not only upon their muscular structures, which aid, by a sort of peristaltic movement, the action of the heart, but also upon the large amount of elastic tissue which exists in their walls. The combined effect of the contraction of these two tissues, as soon as the heart stops beating, is to drive the blood out of the arterial side into the venous side of the circulation in each organ, in that way immediately producing a change in the appearance of the organ.

The liver, which is in life of a uniform red color, shows at once on cessation of the heart-beat the lobulation with its darker blood-filled central portion and paler periphery, a mottling being produced by the collection of blood in the central portion of each lobule, while the periphery is left pale. In the same way the great veins in the abdomen become filled with blood, whereas the arteries everywhere are found collapsed and nearly empty. This, indeed, was the origin of the name *artery* since from dissections of dead bodies they were thought to contain air.

Other influences are brought to bear also, and especially that of gravity, so that all dependent portions, as the body lies, become overfilled with blood and assume a dark purplish hue, while the upper portions are relatively pale. This is true even of the different parts of the internal organs, so that the loops of intestine which lie in the pelvis and in the lower part of the peritoneal cavity show a great distension of the veins, although the upper portions of the loops are pale. When the intestine is opened and stretched out, these areas appear as patches of congestion, the nature of which is not always recognized by the beginner.

The purplish discoloration of the skin of the back is not seen in those parts upon which the body has lain; thus, for example, the backs of the shoulders, the

An increase in the amount of blood to any part is spoken of as *hyperæmia*; and such hyperæmia may be active, when there is an actual increase in the amount of arterial blood, or passive when, through any obstruction, the outflow of venous blood is retarded. On the other hand, decrease of the supply of blood in any area is known as partial or complete *anæmia* and generally results from obstruction of the arterial flow.

HYPERTÆMIA

Active hyperæmia is usually the result of vasomotor effects upon the vessels, and is essentially a physiological process, being concerned so largely with the supply of increased nutritive fluid to tissues which are assuming for the time a heightened activity. It, however, appears in certain nervous disturbances, and also may be brought about by the direct application of heat and irritants, which cause the blood-vessels to dilate. It is probably in just this way that the irritant, which is sufficiently intense to bring about an inflammatory reaction, causes the active hyperæmia which forms so striking a feature of that process. The tissues through which such a rapid stream of arterial blood is passing are usually somewhat swollen and red and warmer than the surrounding tissue.

Passive hyperæmia is more commonly a pathological or abnormal process, inasmuch as it is the result of interference with the outflow of blood. It is usually a very widespread obstruction, due to some in-

buttocks, and heels usually appear quite white, because, owing to the pressure of the weight of the body, the blood has not been allowed to sink into them. Firm pressure of the fingers upon the purple area is sufficient to drive the blood out of those veins and to leave white marks. This overdistention of the veins through gravity is spoken of as *livor mortis*, and it must be distinguished from accumulations of blood in the tissue themselves—haemorrhage. This distinction is readily made because in *livor mortis* (hypostasis) the blood is still within the veins, while in haemorrhage it has escaped from the blood-vessels and can no longer be pressed away with the fingers.

If the body has lain for some time, and especially if the temperature of the surrounding air has been high, there may appear other discolorations which are due not particularly to the distribution of blood nor to its escape from the vessels, but to the disintegration of the red corpuscles by a physico-chemical process which we shall discuss later under the name of haemolysis. This sets free into the fluid the red staining matter of the blood (haemoglobin) which tinges diffusely all dead tissues with which it comes into contact; the lining of the aorta, for example, and of the heart itself may assume a dull red color which is in sharp contrast to the normal. Such blood staining of the tissues may appear with great rapidity in persons who have died from infection with one of those bacteria which have the property of destroying the red corpuscles rapidly by the poison which they produce. In such infections, notably the streptococcus infections, the blood in the vessels stains the surrounding tissues to such an extent that the course of the subcutaneous veins may be seen through the skin in the form of a network of purplish lines.

If the body has lain long after death, especially if it has been kept warm, evidences of decomposition may be found changing the color of tissues toward an opaque grayish-green, with marked softening. Further, if for any reason gastric juice has been regurgitated and aspirated into the lungs before death, there appear softened patches in the lungs which again are dull, grayish-green, in contrast with the red of the surrounding lung tissue. The cells in such areas no longer stain properly.

ability on the part of the heart which dams back blood into the whole venous tract, but occasionally it may be quite local. This is especially due to the fact that the veins are more easily compressed than the arteries, so that pressure from without which will occlude the veins can still allow the blood to be poured in from the more resistant arteries, congesting and distending the tissues with stagnant blood.

It is by no means uncommon to find a loop of intestine pushed through an aperture in the abdominal wall, thus constituting a hernia. Such a loop may, in most cases, be pushed back into the peritoneum; but sometimes, when it has escaped habitually through this newly formed aperture into the sac which is formed outside, it may become so enlarged by an increase of its contents that it can no longer be returned, and indeed so large that its blood-vessels, which, of course, stretch through the aperture, also become constricted there, and the circulation is brought to a full stop, not because blood cannot get in through the artery, but because it cannot escape through the more readily compressed vein. This is a condition which is known as "strangulated hernia."

A local congestion of not quite so extreme a degree may often be seen in the liver when a tumor nodule embedded in the liver substance presses on the efferent vein and causes that portion of the liver ordinarily drained by the vein to become congested. The process is put to therapeutic use in Bier's treatment of various local infections in which a stagnation of blood is produced for a time in the inflamed area by the application of a tight bandage which obstructs the veins and leaves the arteries open.

Ordinarily, the communications between veins are very abundant, so that the obstruction of any one vein is hardly likely to cause such congestion. Nevertheless, the surgeon must be careful in operating to leave the tissues not only with a sufficient arterial supply, but also with an adequate venous outflow if they are to remain alive; for the stoppage of the stream from the venous side is just as important as the obstruction of the arterial side. In the case of mesenteric renal veins, etc., ligation or occlusion may readily lead to the death of the tissue which they drain. In other places where anastomosis is free there may be no effect, but if the obstruction, as in the case of a long thrombus of the femoral vein, is extensive enough to plug the communicating branches, the accessory channels are also closed and the circulation is greatly disturbed. In such a case great pain is experienced, the leg becomes swollen and livid, or later pale, with purplish blotches, and, because of the malnutrition and oedema, it can scarcely be moved (milk-leg). Oedema or oozing of the fluid of the blood into the tissue-spaces is characteristic of all instances of marked passive hyperæmia, and in extreme cases, with great disturbance of the nutrition of tissues, haemorrhage may also occur.

In all these cases it is apparently the failure of the oxygen supply ordinarily brought by the moving blood which is very important. This local anoxæmia, so extreme when the blood is quite stagnant, may reach a considerable degree when through disease of the heart the movement

of the blood is incomplete, that is, when the stream bed is slowly and incompletely flushed out at each pulsation. It is probable that the retardation of the supply of nutritive substances and salts is equally important and that the failure of removal of waste products is directly injurious. Impoverishment of the blood in general, so that it fails to carry sufficient oxygen, does not depend upon this mechanical obstruction and will be discussed elsewhere.

Passive hyperæmia may be the effect also of nervous disturbances which render immobile for a long time the muscles of an extremity. The same result follows to a slight extent if disease of the joints with ankylosis makes them immovable. In both these cases the passive hyperæmia is relatively slight, and is essentially the effect of gravity. In this respect it resembles the condition which is found in the dependent portions of organs in persons who are constrained to lie in bed for a long time in one position. It is spoken of as *hypostasis*, and becomes particularly striking in the lungs, where it may so lower the nutrition, and consequently the power of resistance, of the tissues as to allow bacteria to take root there and produce the so-called hypostatic pneumonia.

LOCAL ANÆMIA

In a general anæmia, such as has been mentioned, each individual tissue may, of course, suffer somewhat, but the most intense effects of this type may be brought about locally without regard to the general condition of the circulation. Such local anæmia must always result from an obstruction opposed to the inflow of arterial blood. This may be an effect of the active contraction of the blood-vessels through the intermediation of the vasomotors, or it may be due to pressure on these vessels from without, or to thickening of the walls of the vessels with narrowing of their lumen, or, finally, and most commonly, to a complete obstruction or plugging of the artery by some foreign material which is lodged there. Combinations of all these things very commonly occur. The vasomotor narrowing of the vessel is ordinarily a normal process, aimed at the withholding of blood from a vessel which does not need it at that particular stage of its activity, but sometimes it may become pathological, as in the so-called Raynaud's disease, which consists in such a constriction of the vessels of the fingers and toes as to cause even the death of those tissues. Apparently the familiar chilblains depend upon such excessive narrowing of the vessels when the hands or feet are exposed to cold. That seems to happen in particularly susceptible persons, and probably especially in those whose habits are sedentary and in whom the circulation is ordinarily not very active.

Pressure from without might cause the closure of an artery if it were directly enough applied. It is difficult, however, to obstruct the arteries by pressure from without, because they are so protected by other tissues; and it is well known that a ligature tied tightly around an extremity will cause rather an increase of blood in the ligated part, because it obstructs the outflow through the veins long before it can

obstruct the artery. In order to render a limb bloodless for the purpose of carrying on an operation in a clean field, as in the method of Es-march, a rubber bandage must be applied with great force after much of the blood has been allowed to sink back into the body by holding the arm or leg high in the air.

The pressure of tumor-nodules and of aneurysms upon arteries may sometimes cause their obstruction in such a way as to cut off completely the supply of blood from the part. The pedicle of a tumor or the long mesentery of a loop of intestine may become twisted so as to shut the lumen of the artery and cause the death of the tissue supplied by it; but usually, as we have stated in speaking of strangulated hernia, this first results in the obstruction of the vein, so that the tissue becomes engorged with stagnant blood and the final effect of shutting off the artery masked.

The walls of the arteries themselves may undergo structural changes which finally lead to such narrowing of the lumen as to prevent the further flow of blood. This usually occurs when an organ has passed its stage of usefulness, and such an abundant blood-supply is no longer necessary. It is somewhat difficult to draw a line between this more or less physiological process of narrowing the artery and that which comes from actual disease of the artery wall. Still, in extreme cases, the pathological character of the process is very evident. There are various forms of disease of the artery wall, roughly classed under the general name of *arteriosclerosis*, which bring about this effect, and so completely may the vessel be obstructed that all the tissue ordinarily supplied by it dies. When, in the legs, for example, this extreme is not reached, the narrowing of the artery may be only sufficient so to cut down the blood-supply that the person is able to walk perfectly well for a short distance, when his muscles fail him solely on account of their insufficient nutrition. After a rest he is able to go on again for a time. This is often spoken of as intermittent claudication. Harmful in some cases, this shutting-off of the blood-stream by thickening of the vessel walls is useful in others—it is the physiological method by which the ductus Botalli is closed; it appears in organs such as the senile uterus and breast, which have outlived their usefulness, and it forms a safeguard against haemorrhage from the erosion of arteries in the lung by advancing tuberculosis: as the cavity extends and cuts across these arteries it finds them reduced to bloodless cords. Arteries thus narrowed by changes in their walls are very often finally and completely closed by the formation of a thrombus throughout the narrowed portion, and it seems probable that such scars as have been described in a kidney, the remaining tissue of which is normal, are really old healed infarctions the result of complete obstruction of certain vessels.

EMBOLISM

Local anaemia of extreme degree is produced most commonly by some sort of plug which obstructs the artery supplying blood to the part. Such a plug is known as an embolus, and embolism is defined

by W. H. Welch as the impaction in some part of the vascular system of any undissolved material brought there by the blood-current. Naturally, the number of kinds of material that can get into the blood-stream is limited, but there is, nevertheless, a surprising variety. The commonest are thrombi or fragments of thrombi, but tumor cells, tissue fragments, clumps of bacteria, protozoan and worm parasites, as well as oil-globules and gas-bubbles, may play the same rôle. Of these, only the thrombi are from the first within the blood-vessels: the others must gain access to the stream before they can act as emboli.

It has been shown that thrombi form most commonly on the venous side of the circulation, although they are occasionally found in the



Fig. 8.—Complete occlusion of both pulmonary arteries by a folded and twisted embolus formed as a thrombus in the femoral vein.

arteries, and are common enough upon the heart-valves. Their rather intimate adhesion to the underlying vessel-wall was mentioned, though not the fact that, after they remain in position for a time, they become firmly fixed to the wall by blood-vessels and connective-tissue cells which grow into them and ultimately replace them completely with fibrous tissue. Before this so-called organization begins they can be dislodged by violent movements or by manipulation, and then arises at once the condition which makes embolism of some distant part of the blood-channel inevitable. A loose mould of the vein or a fragment of

it caught in the current of the blood-stream must move along toward the heart because the vein becomes larger and larger. Sometimes the whole thrombus, with its long adherent propagated clot, is thus dislodged; sometimes only a fragment, the original situation of which might perhaps be recognized by fitting together the surfaces of fracture.

Such an embolus when formed from a part of an old thrombus can usually be recognized easily enough by its evident age, although in its new lodging-place it is almost at once surrounded by propagated clots.

When the crumbly thrombi which form on the heart-valves are the source of such emboli, the dislodged fragments may be large enough to plug the aorta, or at the other extreme sifted off as fine particles which go on to the smaller arterioles. It must be remembered that a long narrow thrombus may become folded and doubled on itself and thus occlude a much larger cavity than that in which it formed. This is the case when dislodged clots from the femoral vein are swept into the pulmonary artery, blocking it completely. This whole process may occupy only a few seconds after the loosening of the thrombus, and death may follow instantly. This should be emphasized because of its frequent occurrence and tragic results. Persons apparently completely recovered from the effects of an operation and ready to leave the hospital may suddenly experience a sharp pain in the chest and within two or three minutes are dead. At autopsy a coiled and entangled thrombus is found completely obstructing the pulmonary artery, and thus bringing the whole circulation to a standstill. It is not the cessation of the blood-supply to the coronary arteries of the heart, but rather that to the brain which must be responsible for the sudden death, for, since the whole circulation is stopped, what happens to the heart is a matter of indifference.

Seats of Embolism.—Given its size and its point of origin, the site at which the embolus will lodge may be foretold with some accuracy, although the actual distribution of multiple small emboli has been learned by experiment. It was found, for example, that the great majority of a large number of recognizable particles introduced into the blood-stream of the aorta were hurried past the mouths of arteries supplying the viscera into the vessels of the muscles of the legs. After that only came the embolism of the brain, liver, kidney, spleen, skin, etc.

Briefly, one may say that an embolus set free in any of the systemic veins, and caught in the current entering from the next branch above the part of the vein which had been completely occluded, is swept through the vena cava into the right side of the heart, and thence thrown violently into the pulmonary artery. Only the exceptional chance of its passing through a wide-open foramen ovale will allow it to reach the systemic arteries unless it is a particle so minute that it can pass through the capillaries of the lung. The same course is followed by a thrombus mass originating in the right auricle or in the intertrabecular spaces of the right ventricle, and obviously this holds true also for vegetations dislodged from the tricuspid or pulmonary

valves. Thrombi set free in any of the veins which go to form the portal trunk are caught in the branches of that channel in the liver. Those arising in the pulmonary veins, left auricle, or left ventricle, vegetations from the mitral and aortic valves or thrombi formed on the walls of the aorta, are hurried into the aorta and distributed as described above. Naturally a thrombus formed in any smaller artery and dislodged is merely pushed further into the branches of that artery. Since emboli are most easily traced by the effects they produce, the impression is likely to arise that they lodge most often in such organs as the brain, the kidneys, or the spleen, but from what has been said it will be clear that even though no effects become visible, the actual number is greatest for the lungs, the body musculature, and perhaps the liver, which is menaced through both the portal vein and the hepatic artery.

With regard to the size of the embolus, a few more words may be said. The mass travels until it comes to a pass too narrow to admit it, and there it lodges like a cork. Naturally, since the branches are smaller than the main trunk in a bifurcating vessel, the plug is often found riding or balanced upon the point of bifurcation. Still, most arteries become narrower as they advance, and the majority of emboli stick on this account. In a case of vegetative endocarditis seen at autopsy recently there were two masses of thrombus material successively lodged in the common iliac artery, and one much larger mass riding at the bifurcation of the aorta. Each was surrounded by a propagated clot formed in the blood rendered stagnant by its advent.

The other things which can act as emboli do so rarely and are of far less importance as emboli than are thrombi, although in their other effects they may be of great significance. Air-bubbles may act as emboli of a rather temporary character, because the gas is so readily dissolved in the circulating blood. If, however, a great amount of gas is introduced into the circulation at any one time, the obstruction may be sufficient to cause death either by passing into the vessels of the brain, or, much more commonly, by filling up the heart and yielding to its churning action, so as to exclude the inflow of blood. A considerable amount of air or other gas is necessary to produce this result—probably much more than is generally supposed. It is in operations and injuries which involve the accidental opening of the veins of the neck that this is likely to take place. The pressure in these veins is so lowered by the inspiratory enlargement of the chest that the air enters with a hissing sound, and the death of the individual may take place very rapidly. Probably its entrance into the coronary arteries is of great importance.

For a time the appearance of gas in bubbles in the organs of the body was regarded as evidence of air embolism, especially in the case of women who had died after childbirth when it was thought that the air had entered the large open sinuses in the uterine wall. Welch has pointed out that these were cases of infection with the *Bacillus aërogenes capsulatus*, which produced after death bubbles of hydrogen gas everywhere throughout the organs, so that they became distended like bread that is rising and full of holes. The liver assumes the appearance of a red rubber bath sponge, and on incision bubbles of gas appear which burn with a blue flame

when a match is applied. Similar cavities may be formed all through the brain, where they have somewhat the appearance of the holes in a Swiss cheese. In the intestine or stomach the mucosa may be lifted up into blebs.

At other times emboli may be constituted of droplets of fat which are set free into the blood-stream from the adipose tissue. Such globules lodge, as a rule, in the capillaries of the lung, and are pressed into a sausage shape by the blood of the pulmonary artery. They can be recognized in the frozen section of such a lung by their highly refractive character, and also by the fact that they readily stain with those stains which are soluble in fat, such as Sudan III. They produce no obvious change in the appearance of the lung, and indeed must be searched for in this way. They are commonly introduced by some mechanical injury to the bones, such as fracture; but even a severe blow seems sufficient to cause such a commotion in the marrow as to introduce some of the abundant fat into the venous channels. Fat embolism also occurs in a number of convulsive diseases, and particularly in such conditions as delirium tremens, in which probably the violent exertions of the individual play a part in the process.

Injury or crushing of the tissues of cellular organs sometimes introduces fragments or groups of cells into the blood-stream, where they act as emboli. Most commonly this is observed in connection with the cells of the bone-marrow and the syncytial structures which arise in pregnancy. There is little evidence, however, of their producing any mechanical effect where they lodge in the capillaries.

Bacteria may enter the blood-stream by growing through the walls of capillaries or lymphatics, or by being discharged from infected thrombi, and can, as is well known, circulate with the corpuscles of the blood through any capillaries. That they often lodge and grow into colonies which produce characteristic effects on the surrounding tissue is shown in cases of generalized miliary tuberculosis and in general pyæmia, but they can be said to act as emboli only when they circulate in clumps large enough to obstruct the capillaries. Protozoan parasites in the same way usually circulate through the capillaries, but certain worms, such as the Schistosomum, can behave as actual mechanical emboli, plugging and obstructing the vessels.

In the case of malignant tumors, the transportation of cells foreign to the blood is of particular importance, although these cells rarely act as gross emboli. It is perfectly clear, from a study of the gross anatomy of such invading tumors, that they frequently extend their growth through the wall of a vein and hang loosely in the blood-stream, so that fragments can be broken off and swept on by the stream. It is, however, by no means always possible to recognize the mode of entrance, and it seems likely that in many cases individual cells gain entrance into the thin-walled veins of the tumor itself, possibly as a result of mechanical trauma. Or in certain cases they may enter lymphatic channels and finally, by processes of growth and transportation, reach the venous circulation. The cultivation of these cells on the glass slide, however, has shown them to be endowed with a remarkable power of amœboid movement, so that Hanes and Lambert

have advanced the idea that the separate cells of the tumor may actively push their way through the endothelial lining of the vein and thus enter the venous blood-stream. The cells appear to be able to pass through such capillaries as those of the lung, and to set up their growth in more distant organs, where they find a suitable environment.

Results of Embolism.—The degree of anaemia produced by the occlusion of any artery will depend upon the relation of its branches to those of the surrounding arteries and to the other branches of its own trunk, because, just as in the case of the veins, such connections dilate to accommodate blood whenever it finds its way blocked through its ordinary channel. If these branches anastomose widely with the terminal twigs of the adjacent artery, a sufficient supply of blood may be maintained in its area of tissue. Indeed, this communication between the end-twigs of the arterial branches is so wide in some tissues, such as the muscles, skin, lungs, etc., that even a large artery can be closed off without causing a moment's delay or diminution in the supply of blood to the tissue. It can be seen, then, that the advent of an embolus in one of these arterial branches will cause no particular disturbance in such tissue as muscle or lung, or even in the stomach-wall.

This compensation for lost arterial supply can be seen most vividly if one injects a quantity of ultramarine blue in suspension into one of the gastric arteries. This fills the artery, with all its branches, with blue fluid, but the moment the stream of blue fluid is interrupted or its pressure lowered, the inflow of blood from the neighboring vessels replaces the blue material in that artery. In this case, however, the connections are between the larger branches and it is found that the minute twigs of the gastric artery thus injected remain permanently plugged with the blue granules and the tissue which they supply suffers.

In other places the communications are not nearly so free, so that if it becomes impossible for the blood to go through one branch, the connections with the adjacent branches may indeed be sufficient to keep the tissue living by furnishing blood to the terminal twigs, but they can do this only by actually increasing their own calibre; so that in such a case the anatomical development of a collateral circulation is much more plainly seen. Sometimes these connections are so minute as to be invisible under ordinary circumstances, but become quite conspicuous after they are dilated in this way.

Extraordinary examples of the development of such a collateral circulation are seen in connection with the larger arteries of the body. So when the aorta is tied, as in the experiments of Halsted and Porta, there appears after a time a whole brush of vessels which anastomose with branches below the point at which the ligature is applied and which reestablish the circulation. I have recently seen two cases in which there had occurred obstruction of the large abdominal arteries. In one instance it was the trunk of the celiac axis which had been gradually obstructed by an arteriosclerotic thickening of its wall, supplemented finally by the formation of a thrombus; and in the other it was the superior mesenteric artery which had been gradually but completely pressed together by the growth of a small aneurysm developed

from a point very near its orifice in the wall of the aorta. In neither of these cases was there the slightest disturbance in the appearance of the abdominal organs, for in both the pancreatico-duodenal artery had dilated and had assumed the burden of transmitting the whole supply of blood for those organs which would otherwise have been deprived of it—in one case in one direction and in the other case in the other. It

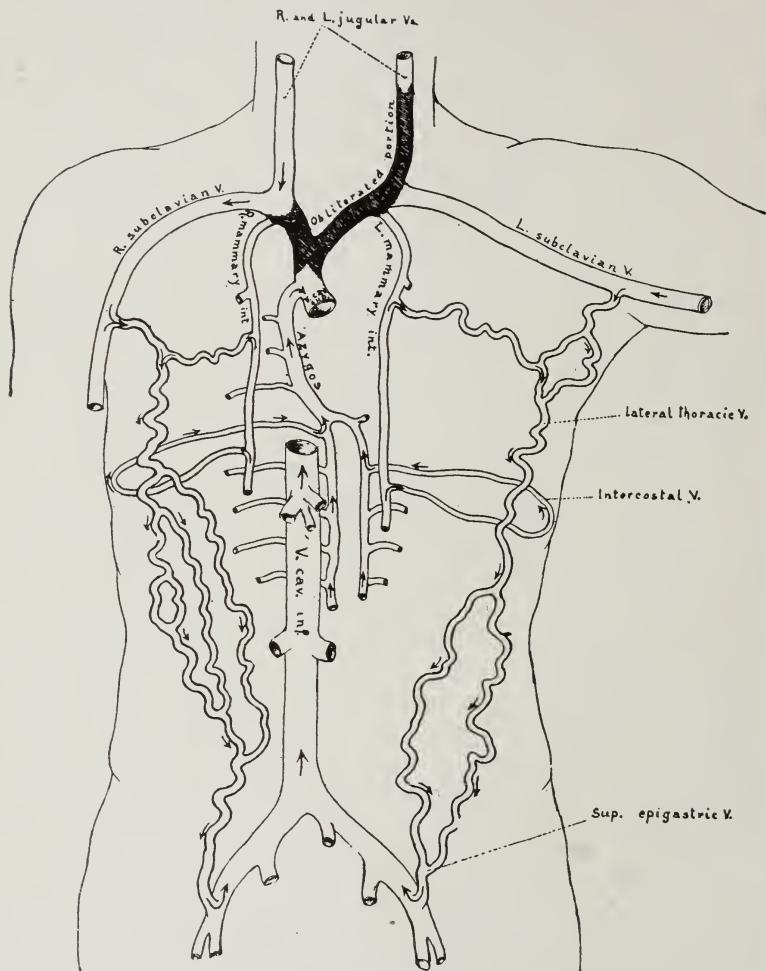
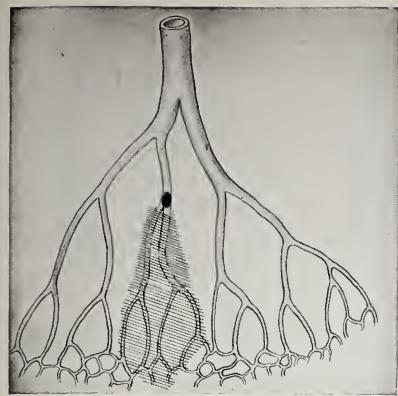


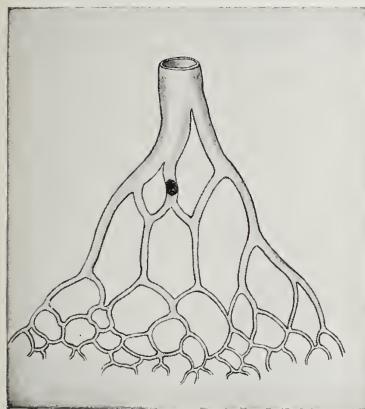
Fig. 9.—Collateral circulation after obstruction of vena cava superior (Osler).

is not merely in the case of the arteries that such a collateral circulation can be developed, for the same thing may be observed in the case of an obstruction of one of the great veins. In one case studied not long ago the superior vena cava had been completely occluded, and the venous circulation from the head took place through the enormously dilated veins of the abdomen* (Fig. 9).

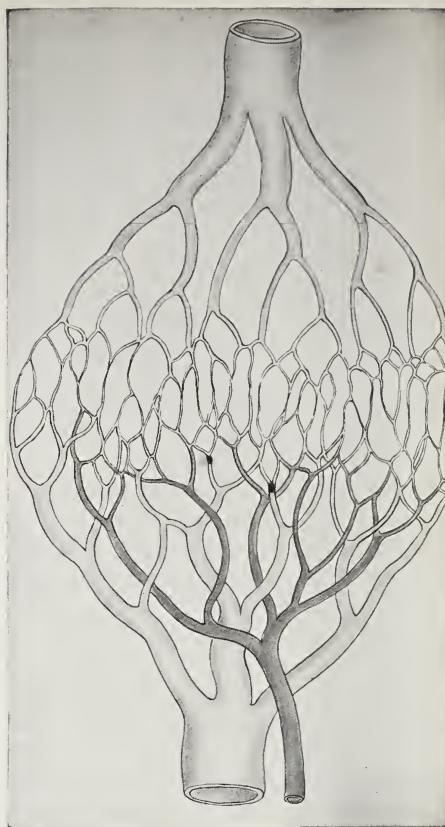
* Osler: Johns Hopkins Hospital Bulletin, July, 1903, xiv, 172.



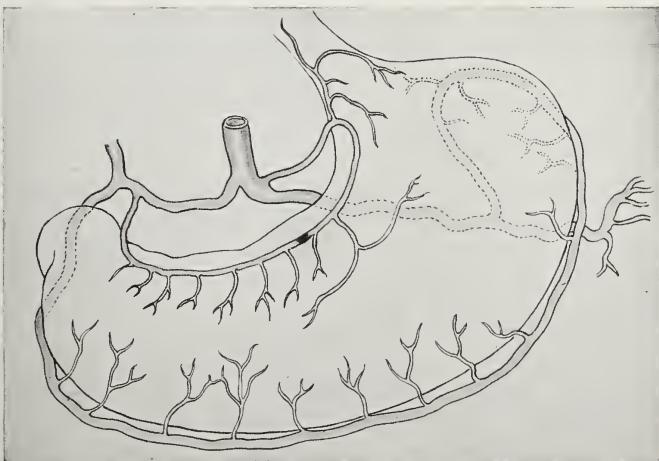
A



B



C



D

Fig. 10.—Diagram showing circulation after plugging of arteries: A, Terminal circulation; B, circulation with rich anastomoses; C, double blood-supply, as in the liver; D, circulation of the stomach with abundant large anastomoses.

In certain situations the tissues are entirely dependent upon receiving their supply of blood from a single artery. In these cases there is practically no chance for compensation through the pouring-in of blood from adjacent arteries, for there are no adequate anastomoses, and such arteries have been referred to by Cohnheim as "end arteries," and such a circulation as "terminal" circulation. The propulsion of an embolus into such an artery as this will inevitably cause complete anaemia of the portion of tissue which had hitherto been supplied by that artery (Fig. 10).

The effect of the diminution of the supply of blood to any part by way of the artery thus depends upon the degree to which the function of that artery can be replaced by the formation of channels connecting its region of distribution with other arterial supplies. The time which is occupied in this reestablishment of the blood-stream is of the greatest importance, for if the obstruction be gradually produced, it may reach a very advanced degree without there having appeared at any time an insufficiency in the blood-supply to the tissues; whereas if the cut-off be sudden, the tissue is likely to suffer.

Finally, there are some organs, such as the liver and lung, which enjoy a double circulation, both arterial and venous blood being poured into the tissues and escaping by way of a common efferent channel. In both these instances the flood of venous blood is far more profuse than the small stream of arterial blood, and doubtless contributes very largely to the nutrition of the tissues, although that is perhaps the main function of the arterial supply. In such cases the life of the tissue is somewhat more secure as far as its food-supply is concerned than in the case of those organs which are supplied solely from the artery; and, indeed, it is actually found that a very much more extensive disturbance is necessary to produce anatomical changes in these organs than in many others.

Quite aside from the patency of the arteries themselves or of the veins, a condition of local anaemia which is very effective in disturbing the nutrition of the tissues can be brought about by muscular contraction in those tissues which are largely made up of smooth muscle. Welch and Mall have pointed out that this violent spasmody contraction of the intestinal wall which arises from a sufficient interference with the entrance of the blood, results in the complete exclusion of the blood from that part of the intestine, and in that way takes a great part in the final destruction of the tissue. It is really this which renders the circulation of the mesentery and of the intestine, which is, from an anatomical point of view, so rich in anastomoses, comparable to a terminal circulation.

INFARCTION

The effect of local anaemia upon the tissue is found to vary with the degree of deprivation to which the tissue is subjected and with the nature of the tissue itself. As has already been indicated, the more complex the structure of the cell, and the more highly developed its specialization of function, the more delicate and susceptible to injury

it becomes. This is well seen in the case of the nerve-cell, whose function becomes impossible if its nutritive supply is withheld even for a few moments, and is irremediably destroyed in a very short time.

On the other hand, there is a long series of tissues with gradually decreasing susceptibility until we reach the least highly organized and consequently the most resistant among the connective-tissue structures which can withstand removal from any connection with the circulation for hours or even days, and still resume their functions as soon as they are placed in proper surroundings or grow again when transplanted into another animal of the same kind.

The injurious effects of anaemia become more severe the more complete it is and the longer it lasts, and they reach their climax in the death of the tissues. Slighter grades of anaemia may become evident in their effect only when great effort is demanded of the organ involved, as, for example, in the intermittent claudication spoken of above.

More complete anaemia, whether caused by the inability of the blood to reach the tissues or to give place to new blood, commonly causes the death of the affected part, and this is the all-important feature in the production of the so-called infarction. Other changes subsequent to this may alter very strikingly the appearance of the tissues, but they are of secondary importance. As in the clotting of blood and the formation of a thrombus, the death, or even the severe injury, of the cells is immediately followed by the setting free of some sort of ferment which causes the coagulation of the blood, and the intracellular as well as the intercellular fluids. The nuclei either fade or break up into small, deeply staining fragments, and in every other respect the cells lose the aspect which they possessed during life. They are dead cells entangled and held in a coagulum which involves the whole area of tissue, and the process is described by Weigert and called by Cohnheim "coagulative necrosis."

The area occupied by these changes is that to which the blood-supply becomes insufficient. It need not correspond exactly, therefore, with the distribution of the plugged artery, because there is almost always some compensation from the branches of adjacent arteries. Its form is generally stated to be pyramidal, but is not really so in most cases, although it may approach that traditional form. This is because the vessels in most organs really assume a rather fan-shaped arrangement, as is almost inevitable in any vessel which branches out regularly. Still in some, such as the kidney, there are blood-vessels which spring up almost at right angles from the main trunk, and which reach through the organ, so that we may readily find an infarct of a more or less cubical form in its cortex (Fig. 11). There is nothing typical about the form of the infarct in the intestine which merely occupies the whole wall of a certain length of the intestine. So, too, in the heart, the area of infarction is irregular in form. The pyramidal form is most nearly approached by the infarct of the lung, but even this is frequently quite irregular in its shape.

In all instances the infarcted area seems at first swollen and firm,

and projects above the surrounding surface of the tissue. This is true even in the brain in the beginning, although after a short time has elapsed the infarcts of the brain become soft and are commonly spoken of as areas of softening. Their resemblance to other infarcts in the early stages was pointed out by Marchand, who appreciated the fact that they too at the beginning present the appearance of a firm coagulum, although later the liquefaction of the myeline substance proves more than sufficient to overcome the firmness contributed by the fibrin and to make the whole area soft. The swelling and firmness of an infarct are due to the accumulation of a coagulum produced from the coagulable fluids which diffuse into the dead area from the surrounding tissue. In a short time the mass becomes dense and hard and may be appreciated immediately by the finger passed over the surface of the organ. There is no other disturbance in the architecture of the tissue at this stage, and the outlines of the cells may still be seen quite clearly.

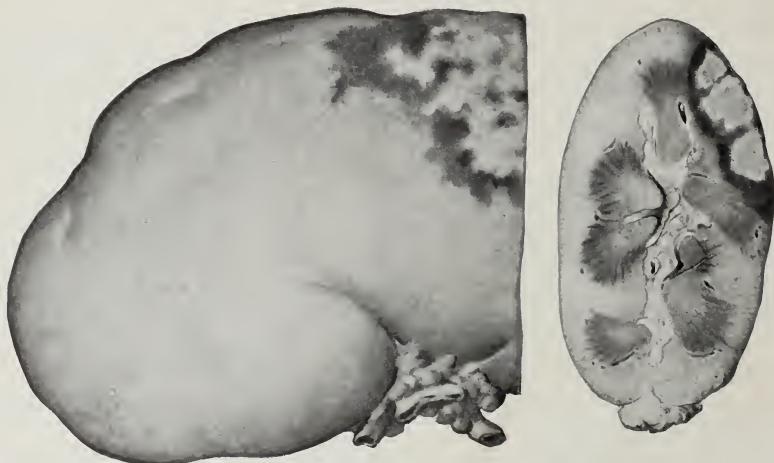


Fig. 11.—Anæmic infarction of kidney.

Even the outlines of the nuclei may still be seen, and as for the supporting structural framework, it is usually quite well preserved, at least in its outlines; but the whole area is dead and reminds one, on viewing it through the microscope, of the appearance of charcoal as contrasted with that of living wood, or of the streets of Pompeii as contrasted with those of a modern town.

The death with coagulation of the tissues converts them into a white or yellowish white, perfectly opaque, dull-looking mass so long as there is no infiltration or red corpuscles. We must recognize, however, two kinds of infarcts, in both of which the principles just described affect the result in an identical manner, but one is spoken of as a hemorrhagic infarct because, on account of the laxity of the tissue and the richness of the adjacent capillary circulation, red corpuscles ooze into the dead area. The other kind, which remains pale and opaque, is commonly spoken of as an anæmic infarct, although it is plain enough

that anæmia is the cause of the death of the tissue in both. The arrangement of the circulation and the density of the tissue seem to be the deciding factors as to whether an infarct shall remain anæmic looking and white, or, by being flooded with stagnating red corpuscles, assume a deep red color. So, in the kidney, we practically never observe a hæmorrhagic infarction, whereas in the lung and in the intestine the reverse is the case, and it is only with the greatest difficulty that we can produce experimentally an infarction which remains anæmic

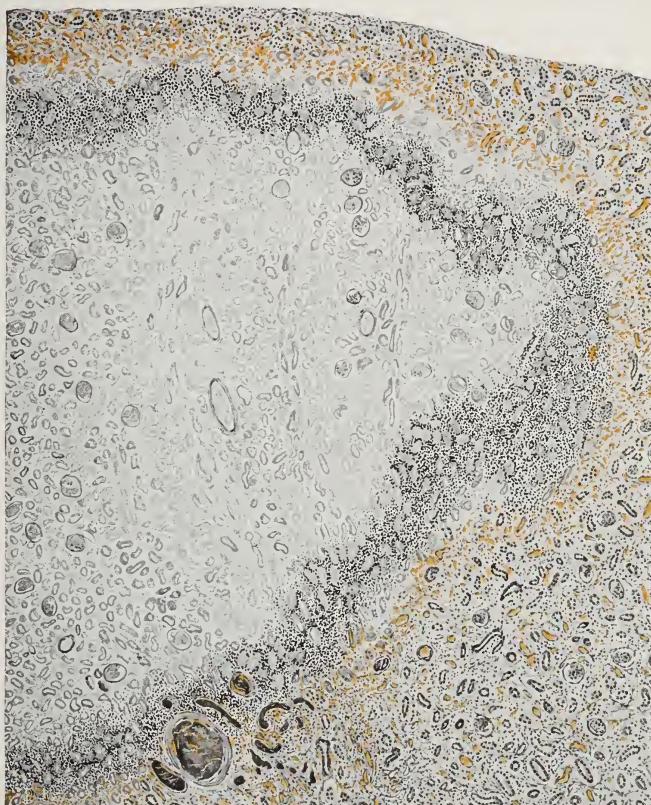


Fig. 12.—Margin of renal infarction showing necrosis of tissue with zones of hæmorrhage and leucocytic invasion.

looking. In other organs, such as the heart, the spleen, the liver, we may have sometimes anæmic, sometimes hæmorrhagic, types.

But it must be remembered that it is the failure of the current of blood that is fatal to the tissue, whether the block be in the artery or the vein. Indeed when the venous escape is obstructed the artery may force an excess of blood into the tissue. This, however, is useless because it merely stagnates and gives a hæmorrhagic character to the infarct, even in such organs as the kidney or liver. We have recently

seen instances of both when extensive thrombosis closed the renal or hepatic veins.

Kidney.—In the kidney, infarctions are likely to be quite small. They seem to arise as the result of the entrance of the embolus into one of the arcuate arteries, or even into one of the branches, passing thence into the cortex. One can nearly always find this plug on careful search and observe that the propagated thrombus extends both ways from it. The infarcts commonly occupy especially the cortex, but they may sometimes extend down into the pyramid of the kidney. One occasionally sees a ramifying, anastomosing area of infarction which occupies a great portion of the kidney, and such, indeed, was the result in a peculiar instance observed recently. In this case a stab wound had passed through a branch of the renal artery which happened to begin its branching outside of the kidney, and a haemorrhage occurred, which continued slowly for two or three days, being restrained apparently in part by the surrounding tissue. At the end of that time the kidney was removed at operation, together with the mass of blood



Fig. 13.—Infarction of spleen.

which had been extravasated. It was found that there was an extensive infarction occupying a portion of the kidney which should have been supplied by the injured artery. This was an instance of local anaemia, but not caused by the presence of a plug in the vessel.

On inspection of such a kidney containing infarcts it is possible to determine readily enough the position of the infarct even through the capsule, for the opaque yellow color shines through, but this opacity does not quite reach the surface, being covered by a layer of living and very hyperaemic kidney tissue, which receives its blood-supply from the capillaries which extend to it from the capsule. On incision one finds the infarct surrounded by at least two distinct zones, which differ in color from the opaque yellowish-white central portion. These zones are first a translucent gray line of varying thickness, and then an irregular band of deep red which borders the infarct and marks it out from the surrounding normal tissue. The gray zone is found, on careful examination, to be produced by an accumulation of the white cells of the blood which have wandered in there and have become more

or less broken up. The zone of haemorrhage is partly within the necrotic area and partly in the living area, and although it may, like the accumulation of leucocytes, be explained in part as due to the inflammatory reaction about the dead tissue, it seems probable that the anaemic changes in the endothelium of the capillaries play a part too in allowing the escape of red cells (Fig. 12).

Spleen.—Almost the same descriptions might be applied to the anaemic infarctions in the spleen, except that they are usually much larger and more irregular in form (Fig. 13). They, however, differ from the infarctions in the kidney inasmuch as there is no capsular circulation, which is necessary to keep alive any superficial layer of



Fig. 14.—Infarct of wall of the left ventricle from occlusion of right coronary artery. There is also some scarring and thrombus formation in the area of distribution of left coronary.

the spleen, so that the death of the tissue extends quite out to the peritoneal surface. There the dead tissue exerts the same influence upon the peritoneal fluid as it does upon the passing lymph, and there is deposited over the surface of an infarct in the spleen a layer of fibrin which roughens the surface. Sometimes one can make the diagnosis of the existence of an infarct of the spleen from pain which comes from the rubbing of this roughened surface against that of the adjacent peritoneum when a deep breath is taken.

Heart.—Exactly the same thing is true of infarcts of the lung, and even those of the heart wall; but in the kidney there is no opportunity for such an occurrence. The infarcts of the heart are particularly in-

teresting because of their great importance with regard to the function of the heart. The coronary arteries present some anastomoses one with the other, but, as has been pointed out recently by Spalteholz, these are insufficient to supply the really enormously active circulation which is necessary for such an organ as the heart. So, therefore, the arteriosclerotic narrowing of the coronaries often leaves traces of malnutrition of the tissues even when there is no actual infarct formed; but when to this there is added a thrombus formation, or when a vegetation from the valve sweeps into the mouth of the coronary artery, as has sometimes happened, the nutrition of the heart muscle is intolerably limited and the muscle dies. In one such instance recently observed there had been an aortic endocarditis with vegetations, and a plug, like a cork, still projected from the mouth of the left coronary artery. Part of the septum between the ventricles, together with the anterior portion of the walls of the right and left ventricles, formed a necrotic mass. The heart had become abnormally slowed from involvement of the auriculoventricular bundle, but still continued to beat until a sudden effort caused the rupture of the wall of the left ventricle with a fatal haemorrhage.

Other instances, however, have not so immediately led to death, but rather to recovery, with replacement of the dead tissue by scar. In that case a patch in the heart wall may be markedly thinned and comes to be composed of a fibrous tissue which has by no means the power of resistance or the strength of the muscular wall, and one frequently sees such an area bulged out into a sac which in time may rupture. Such an event is, however, by no means always the outcome of an infarction, but may depend on the gradual loss of the muscle substance from a partial anaemia.

It is important to note that obstruction of the left coronary artery in its descending branch produces changes such as have been described in the more anterior part of the interventricular septum, especially toward the apex of the heart, and these may extend into the right ventricle so that a thrombus formed there may set free an embolic mass which can plug a branch of the pulmonary artery. On the other hand, obstruction of the right coronary artery produces scarring and thinning of the more posterior part of the interventricular septum so that when the heart is viewed as it is ordinarily opened, there is seen a sudden hollowing out of the septum from the mid-line backward behind the papillary muscle of the mitral valve. All of this is the natural result of the distribution of these vessels, and modifications, of course, occur when the obstruction affects only smaller branches of the coronary arteries (see Figs. 14, 239, 240).*

Liver.—In the liver infarcts are very rare because of the extremely abundant blood-supply from two sources. It is stated that complete closure of the main trunk of the hepatic artery will produce complete necrosis of the liver, whereas closure of any of its branches has no special result. Obstruction to the main portal vein is said to diminish the production of bile, as has been shown recently by Voegtlind and

* MacCallum and Taylor: Bull. Johns Hopkins Hosp., 1931, xlix, 356.

Bernheim, but it does not interfere with the nutrition of the tissue. This is especially well seen in the numerous instances in which experimentally the whole of the blood of the portal vein has been diverted into the inferior vena cava by the so-called Eck's fistula. In that case undoubtedly the whole of the tissue of the liver must be supplied by the hepatic artery, but the animals live, and after a time show no very obvious change in the tissue of the liver, although it is stated that sometimes the liver decreases in bulk. Obstruction of the whole portal vein is not very uncommon, arising from the thrombosis of the branches from some point of infection or injury in the alimentary tract, and extending into the main trunk; or as the result of compression from without by gall-stones or tumor masses in the vicinity or in connection with cirrhosis of the liver. Closure of branches of the portal vein may be followed by the formation of haemorrhagic infarctions when there is some disturbance or enfeeblement of the general circulation, so that the hepatic artery does not succeed in making up the nutrition which is lost by the shutting off of the portal.

Lung.—In the lung also there is a double vascular supply, the whole current of venous blood rushing through the pulmonary arteries, while the bronchial arteries bring arterial blood to the tissue and anastomose with the pulmonary capillaries, thus returning their blood by the pulmonary veins. It appears from the work of Schlaepfer that when the pulmonary artery is ligated the bronchial arterial stream is sufficient to keep the tissue alive, although it contracts and becomes scarred. The pulmonary arteries anastomose with extraordinary freedom in the lung, probably largely by means of the extremely wide capillaries. On this account it proves to be almost impossible to produce an infarction in the lung of a healthy animal by throwing emboli into the pulmonary stream, because the nutrition of the obstructed area is immediately assumed by adjacent branches. Virchow did succeed in producing such infarctions, and this was the basis of his great work on embolism. Apparently he succeeded because the emboli which he used carried bacteria, and he caused, in that way, a far more extensive injury to the lung tissue than could be produced by sterile plugs. But, in general, infarcts appear in the lung only when the outflow of blood is also impeded (chronic passive congestion).

The mechanism of infarct formation in the lung is somewhat different from that elsewhere in the body for two main reasons. Like the liver, the lung has a double afferent blood-supply. Unlike the other organs the lungs must allow the passage of all the blood, with no chance of collateral circulation, and obstruction to the venous outflow such as is produced by mitral stenosis raises the arterial and venous tension so that there is no great difference between them, and at the same time lowers the output of the left ventricle and the pressure in the bronchial arteries. So that there is not much to choose between the anastomotic branches of the pulmonary artery and the bronchial artery in driving blood into an area to which the pulmonary artery has been obstructed, because the escape of this blood into the veins is rendered too difficult by the high pressure there.

The maintenance of enough motion in this blood to keep the tissue alive becomes too difficult and the tissue dies. Still the almost stagnant blood in those vessels remains at a high pressure level and through the dying walls of capillaries and alveoli blood oozes out and clots, and in the end that within the included vessels also clots.

Whether the lung tissue, long subjected to such chronic passive congestion with stretching of its vessels and partial stagnation, is more sensitive to the great reduction in the current than the normal lung would be, seems unimportant. In a normal lung obstruction of a



Fig. 15.—Hæmorrhagic infarction in lung. The obstructing embolus is seen in branches of the pulmonary artery.

branch of the pulmonary artery is followed by a sufficient collateral circulation running rapidly because the venous pressure is not heightened, and no infarct occurs. But in chronic, passive congestion affecting the lungs, however produced, when emboli are dislodged from some point on the venous side of the circulation and thrown into the branches of the pulmonary artery, there arise hæmorrhagic infarctions (Fig. 15). Sometimes one can recognize by symptoms the beginnings of such infarcts from the sudden pain and the spitting-up of blood, and possibly even from the change in the percussion note, which becomes

dull over the region of the infarct. When the lung is inspected, it is found possible to recognize these infarcts at once because they are solid, hard masses, often present in numbers and extending to the surface of the lung. The pleura over them is roughened by a layer of fibrin which destroys its gloss, and causes the pain of which we have spoken by scratching against the opposite pleural surface in respiratory movement. The infarcts vary greatly in size, from a diameter of about 1 cm. to such a size as to occupy almost the whole of the lobe. They have a tendency to a somewhat triangular or pyramidal form, but their margins are usually round, and they bulge out on the surface of the lung. They are very dark red—almost black—in color, and on cutting through them this is found to be true also of their interior portion. They are dry and sometimes of a remarkable hardness.

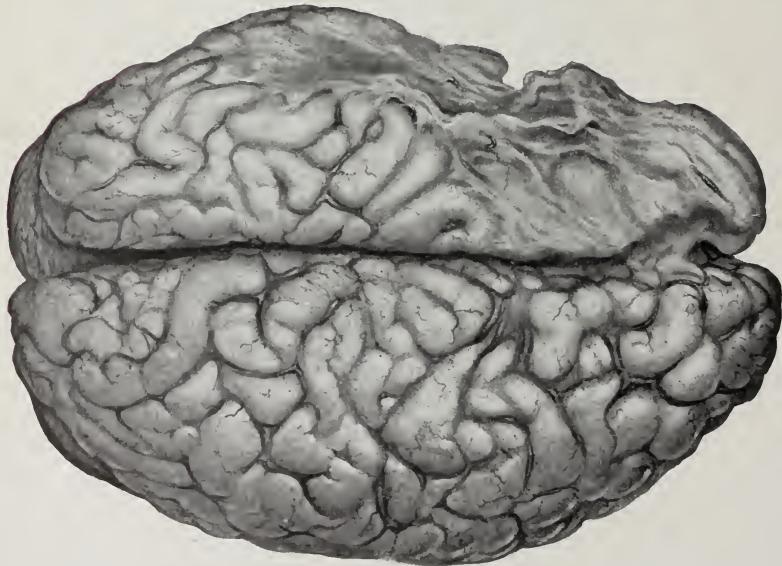
It is nearly always quite easy to see the embolus which has caused their formation lying in the pulmonary artery which forms the apex of the triangle. Usually such a plug is prolonged both ways by the clot which is formed about it, but sometimes this may not have happened, and cases are even recorded in which the embolus lay at a point somewhat separated from the actual region of infarction by an empty stretch of vessel. This is important because there has been so much dispute as to whether these infarctions were really caused by emboli or whether the clot in the vessel was the result of the infarction. It seems perfectly clear, however, that the weight of evidence is entirely in favor of the embolic origin of the infarcts. Von Recklinghausen lays a great deal of stress upon the formation of hyaline thrombi in the smaller branches of the pulmonary artery, but these, it seems to me, might be secondary. There is often a question as to whether we are dealing with a real infarction or with a mere haemorrhage into the lung substance. Such haemorrhages occur frequently from all kinds of causes, but they are never really comparable in appearance to infarctions—first of all, because they are almost never hard and dry, but rather soft and loose, and usually very irregular in outline, occupying any part of the lung without regard to any special arrangement and without necessarily approaching the surface of the lung. From such haemorrhages absorption of the blood takes place with extreme rapidity, and this may possibly account for their remaining so soft. On the other hand, it is quite difficult to understand why the haemorrhagic infarction should be so extremely hard unless it be that the coagulation of the red corpuscles is also brought about in the general coagulation of the necrotic lung tissue. Close examination of the area involved in the infarction shows that it is overfilled in every part with blood. Not only are alveoli themselves full of red corpuscles in even greater concentration than in the circulating blood, but these corpuscles are found also in the substance of the tissue.

The epithelial cells which line the alveoli disappear rather rapidly, but the framework of the lung is very resistant, and it may not appear to have been injured very markedly by the local anaemia. There are those who speak of resolution of infarctions of the lung, stating that there is no real necrosis, but that later the contents of the alveoli may

be absorbed as in a simple haemorrhage, and the lung resume its function. This, however, seems very doubtful, and one may feel sure that when the effect of the anæmia is such as has been described, much more complicated changes than a mere resolution or restoration to normal



a



b

Fig. 16.—Extensive old infarction of brain.

will take place. The difficulty in deciding this consists chiefly in the fact that when haemorrhagic infarctions are formed in the lungs the person is so ill as to die before any great length of time has been allowed for alterations to take place in the infarctions, and so it is that we commonly see at autopsy fresh haemorrhagic infarctions and

only rarely find areas of infarction which have lasted for a long time. When we do there is no evidence of resolution, but rather of a great shrinkage of the tissue, a loss of the red color, a deep yellow pigmentation from the débris of the red corpuscle, and the formation of dense, hard scar tissue in the place once occupied by the infarct. In this respect the haemorrhagic infarctions of the lung are quite similar to the anaemic and other infarctions in the spleen and in the kidney. Even in the fresh infarctions of the lung one finds always a good deal of the yellow pigment which comes from the disintegration of red corpuscles. This is not part of the fresh process, but rather a result of the long-continued stagnation of blood in the capillaries of the lung, which is the essential feature of a chronic passive congestion, and which, as we have said, constitutes the requisite basis for the formation of an infarct there.

Brain.—Infarcts occur quite commonly in the brain as the result of sudden or gradual occlusion of an arterial branch after it has left the meningeal part of its course and entered the brain substance where they become terminal vessels. Extensive infarctions of a haemorrhagic character also follow the thrombosis of the venous sinuses of the dura, perhaps especially that of the longitudinal sinus into which so many of the veins of the meninges empty.

The occlusion of an artery may be the effect of metabolism when a portion of a thrombus or a vegetation from the valves of the left side of the heart is carried there. But it may also result from the pressure of a tumor or aneurysm. Still, the most common cause seems to be the arteriosclerotic thickening of the vessel wall which gradually reduces the lumen to a very small calibre, after which the obstruction may be completed by a thrombus. Small infarcts produced in this way are often found in numbers at autopsy in the brain of a person who may have shown no symptom of their presence.

The opportunity to observe a perfectly fresh infarct in the brain is very rare. They are said to be firm and to project above the surface, but they very quickly soften into a semifluid mass because the greater part of the brain is composed of lipoid substances (myelin) which become converted into a more fluid form in the process of necrosis of the tissue. Phagocytic cells wander into such an area and load themselves with fat globules which they carry away. Eventually there is left a space traversed by a network of glia fibres, about which the surrounding tissues are stained with a yellow pigment. Such areas appear sunken below the surface of the brain and are deep yellow (*plaques jaunes*). But there is generally, just under the meninges, a thin film of grey matter which is kept alive by its contact with the meningeal blood-stream.

Of course, the size and especially the position of the infarct become all-important in determining its effect. In the brain where every part has its highly specialized function which cannot be assumed by the rest of the tissue, it should be possible to recognize the position of an infarct by the functional disturbance it produces. But this is difficult because of the complex interrelation of motor mechanisms, control of muscle

tonus, sensory and association tracts. When the infarct is very small and situated in a region not directly concerned with these recognizable functions, there may be a transient lapse of consciousness or no symptoms at all. When it is larger, the patient becomes unconscious and there is general flaccid paralysis as in an apoplectic stroke, because the pressure within the rigid cranium is increased almost as it is with the apoplectic haemorrhage; the blood-pressure is high and respiration disturbed. From this there gradually emerges in many cases a localized paralysis which may or may not be spastic. Speech and other func-



Fig. 17.—Margin of fresher infarct of brain showing fat-laden phagocytes. Several of these are shown enlarged below.

tions may be deranged. If as sometimes happens, this paralysis proves transient, it would seem that it may be caused by a lesion not involving the motor tract directly but in its neighborhood, thus causing temporary pressure upon it. Naturally, if the destruction is extensive, as in Fig. 18, interrupting the motor fibres in the internal capsule, a complete and permanent hemiplegia will result. This will be discussed later in dealing with cerebral haemorrhage which tears through the tissues with quite similar effects.

The infarctions from venous thrombosis have been seen in infants in whom the very accessible longitudinal sinus has been used for intra-

venous medication. The resulting thrombus causes such extensive destruction of the cerebral substance that death is prompt.

Intestine.—The infarctions of the intestine are usually haemorrhagic. They are perhaps most commonly produced, as in strangulated hernias, where the blood-supply is impeded by the crowding into the aperture, of the mesentery as well as the intestine itself. Other instances are seen in the so-called volvulus, in which a loop of intestine with long loose mesentery becomes twisted completely round on itself so that the blood-vessels in the mesentery are closed. Almost the same effect can be produced by bands of fibrous tissue such as arise in the form of adhesions between various abdominal organs and can be pulled tight over the vessels running to some portion of the intestine. The other type of artificial obstruction is, as in the infarctions just described, produced



Fig. 18.—Area of encephalomalacia interrupting internal capsule.

by an embolus or thrombus. As has been pointed out, the intestines are peculiarly susceptible to withdrawal of their blood-supply because they add to the anaemia by their violent contractions. The intestinal wall at first becomes absolutely pale with this contraction, but later on, with the death and relaxation of the tissue, it swells enormously and is infiltrated with blood. The swelling is particularly intense in the submucosa, which may attain the thickness of a centimetre, and the blood oozes through the mucosa into the lumen of the intestine and is passed in great quantities, giving the diagnostic sign of intestinal infarction.

The surgeon sometimes meets with this condition of swelling and haemorrhage before the complete death of the cells has occurred, and occasionally he may replace the enlarged loop from the hernial sac or liberate it from its constriction and see restoration to normal condition

follow his operation. It is a matter for his judgment, however, to determine whether the injury has passed the point at which this is still possible. Welch and Mall, in their experiments, have found that there is relatively little compensation for the cutting-off of the arterial supply through the mesenteric arteries, so that if even such a short length of intestine as 5 cm. be separated from its blood-vessels, it will undergo necrosis because the supply from the adjacent portion is insufficient.

One of the commonest causes of infarctions is the so-called *intussusception*, which occurs most commonly in children (Fig. 19). It may apparently be spontaneous, and, indeed, it seems to be produced by irregular peristalsis in the intestine, so that one portion not answering to the peristaltic wave is dragged by it into the next portion, to which the wave has actually leaped.* At any rate, such intussusceptions are found very commonly in the intestine of infants, where they have been produced postmortem, by the peristaltic action of the partially qui-



Fig. 19.—Intussusception in a child's intestine showing infarction of the inclosed portion. The mesentery is seen constricted in the neck of the receiving portion.

escent intestine. The portion which is telescoped into a receiving part below draws with it, of course, its mesenteric blood-supply. If the intestine be pulled out again at this moment, no harm is done; but if it remains thus imprisoned for any considerable time, there arises a moderate interference with the outflow of the venous blood from the enfolded part, which soon makes it swell to such an extent as to cause a very much more intense interference with the blood-supply. This circle of events continues to intensify itself, so that very soon the intestine acts as a constricting band to prevent the inflow or outflow of blood, and brings about the hæmorrhagic infarction of the interior portion.

* Albrecht v. Haller in his Pathological Observations, London, 1756, says, "I have learned how to produce an introsusception in frogs at pleasure. In these animals if you touch any part of the intestine with anything corrosive, it is immediately constricted, and soon after the part next adjoining to it gradually ascends and folds itself over the other so as in a manner to sheath it."

The question as to whether an infarct shall become haemorrhagic or not seems to depend upon a variety of things. Experimental studies have been made with regard to the infarction in the intestine, particularly by Welch and Mall, by Niederstein and Marek. The results of these experiments may be summed up in the following conclusions:

If a branch of the mesenteric artery or the mesenteric vein alone be obstructed, a haemorrhagic infarction results. If, however, the arterial channels leading to any portion of the intestine be absolutely blocked by plugging or tying every possible anastomosis, an anaemic infarction appears, even though the veins be left widely open. It is evident, therefore, that the haemorrhagic infiltration of the tissue which forms the peculiar feature of haemorrhagic infarction does not come, as Cohnheim thought, from regurgitation of the blood from the veins, but is the result of the oozing of blood through the walls of the enlarged capillaries and from the adjacent arterioles. Welch and Mall thought that the haemorrhagic character of the infarct in the intestine was largely due to the loss of pulsation in the diminished stream of blood that might still reach the tissue.

Infected Emboli.—Secondary changes are produced in infarctions by the invasion of bacteria. Thus an embolus may carry with it a quantity of bacteria when it originates from an already infected source, and is spoken of then as a septic embolus. It gives rise at first to the ordinary mechanical effects of plugging the blood-stream, but later there become evident the effects of the poisons produced by the bacteria, and the infarcted area becomes the seat of an intense acute inflammatory process, with all the softening and disintegration which follow upon the development of liquefying ferments both from the bacteria and from the leucocytes, which hurry to the spot as a part of the inflammatory reaction. The infarct may actually assume the appearance of an abscess, and it is sometimes difficult to say whether it started as an infarct or not. In most cases, though one sees distinctly the form and general character of the infarct, he finds that its central part is softened down into a grayish pulp while the periphery still retains something of its firmness. This softening is quite different from that which we have mentioned in the case of the infarcts of the brain, and probably seldom ends in healing and scar formation.

Healing.—Healing of the uninfected infarcts is by no means uncommon in such organs as the spleen and kidney, and it has been described already in the heart and brain. It consists in the replacement of the dead tissue by a scar tissue which constantly tends to contract so that finally, in either the spleen or in the kidney, one finds, as a sign of where the infarct was, a sunken, hard, scar-like area, usually rather opaque and colored yellow here and there from the remains of pigment derived from the dead cells. In such a scar there may remain some traces of the most resistant of the structures previously occupying that place, such as obliterated glomeruli in the kidney; but usually these are scarcely recognizable, although, on account of the contraction of the scar, they may be concentrated together in considerable numbers.

GANGRENE

All of these instances of anæmic necrosis which we have described under the name of infarcts have been in tissues somewhere in the interior of the body, completely surrounded by other tissues from which there could be derived by infiltration the ever-increasing supply of fluid which might undergo coagulation. This it was which formed the basis of the so-called coagulative necrosis. If, however, the anæmia



Fig. 20.—Gangrene of foot. Case of diabetes with arteriosclerosis.

affects an extremity or any such tissue as is not thus accessible to the adjacent coagulable fluids, a different appearance results. The necrosis of the tissue is effected in just the same way, but there is no opportunity for it to assume the character of a coagulative necrosis. At least the amount of fluid which undergoes coagulation is relatively small, and the extremity does not become rigid and hard as the result

of this process. Such death of an extremity is called gangrene, and it is commonly brought about in the same way as is the death of the tissue in infarctions, that is, by any one of the various processes which lead to diminution in the blood supply of the part, often aided by more general disturbances of circulation or by decreased vitality of the tissues from other causes, as, for example, in the case of diabetes, where gangrene of the feet is so common. It may assume one of two forms—the so-called "moist" gangrene or "dry" gangrene. In the former case the tissues remain moist, infiltrated with blood. They become opaque, dull looking, and livid in color. But the color does not remain as it is in the beginning, but rapidly changes through a series of shades to deep purple or greenish black (Fig. 20). The epidermis becomes loosened when rubbed, often leaving a raw, damp surface, which may readily become infected and undergo putrefaction. Such death of the tissues usually occupies a portion of the extremity which is sharply demarcated from the remainder by a line which separates the dead from the living tissue; but commonly this line moves upward with the advance of the necrosis until it reaches the point at which the blood-supply becomes sufficient to maintain constantly the life of the part above. Unless the leg be amputated at some point conveniently above this line, there may be a good deal of absorption of the poisonous products of putrefaction, and the tissue itself may fall away so as to expose the bone.

The other kind, the dry gangrene, occurs when all possible advent of fluid is shut off from the living tissue and mummification or gradual drying up of the extremity takes place. The writer studied one instance in an old man in whom some infection of the axillary glands had led to their scarring and calcification in such a way as to constrict the axillary artery and adjacent nerves. The pain from this constriction was such that an operation was performed in which the artery was ligated and removed with the constricting mass. Almost immediately there began the evidence of death of the fingers and of the hand and wrist, which assumed the dry form, and resulted in a few days in almost complete desiccation, so that his hand came to look like horn or some such transparent material, covering the bones.

Gangrene of the extremities is generally the result of disease of the arteries which narrows their lumen and leads to final occlusion by a thrombus. In the case of arteriosclerosis which is so frequently associated with diabetes, the thickening and rigidity of the walls of the main arteries is shared to some extent by the branches so that the establishment of an effective collateral circulation is difficult. The so-called thrombo-angiitis obliterans which will be described later, is another common cause of gangrene. Perhaps most striking is that type which has been observed in epidemic form as a result of ergot poisoning. It was known in the middle ages as St. Anthony's fire, and relief was sought for it in a pilgrimage to Paris, which at least acted as a preventive. The truth of the matter was, although it was by no means recognized, that the peasants of France ate bread which was contaminated with the ergot smut, and consequently suffered from that

peculiar poisoning which brings about an intense constriction of the arterioles. Death of the extremities was not infrequent, and in those pre-surgical days, from the ninth to the fourteenth century, it was no uncommon thing to have part of a hand or a foot torn off, after such necrosis, with a glove or boot. At the church in Paris the pilgrims were fed with bread from the monks' kitchen and most of them recovered.

There is one other important instance of the production of gangrene through anemia, which is extremely common and which occurs in those persons whose general powers of resistance have been lowered and who have been constrained to lie in one position in bed for a long time. This is the so-called bed-sore or decubitus ulcer, to which we have referred before. The term gangrene is used most loosely in referring to the death of tissues produced by bacteria or by other means when associated with putrefaction. Thus we shall meet with gangrene of the lungs, which is by no means necessarily caused by mechanically produced anaemia, but is dependent upon the destruction of the pulmonary tissue by various forms of bacteria associated later with the ordinary bacteria of putrefaction. Another instance is seen in the so-called noma, or cancrum oris, and in the hospital gangrene, which used to cause such mortality in the wards of the larger hospitals. In all these cases it appears, from recent studies, that a combination of fusiform bacilli and spirilla plays an important part.

LITERATURE

- Hanser: Lubarsch and Ostertag *Ergebnisse*, 1921, xix, 2, 147.
Welch: Allbutt's *System of Medicine*, 1899, vi, 228. (*Literature.*) *Trans. Assoc. Amer. Phys.*, 1887, ii, 211.
Welch: *Collected Papers*, 1920.

Welch's review of thrombosis and embolism should be read by every student.

CHAPTER III

DISTURBANCES OF INTERCELLULAR FLUIDS AND LYMPH

Their movement, character, and excessive accumulation. œdema, ascites, etc.

ŒDEMA, ASCITES, ETC.

It is apparent from what has been said that the well-being of the tissues is dependent upon the continuous and unobstructed circulation of the blood through them from the arteries and the veins; but the conditions are even more complicated, for there is a constant circulation of fluids with dissolved materials from the blood, from the arterioles and capillaries, out into the crevices of the tissue and into a position where they can come into immediate contact with the cells. In this process almost all the cells are left behind, but a certain number of them undoubtedly take part in this wandering-out from the blood-vessels. This type of circulation is complicated by the reentrance of the transuded fluid into the veins or into the lymphatic channels, and in every case the fluid must pass again a complete, continuous, and semipermeable membrane composed of endothelial cells.

The idea formerly held that these tissue spaces are in open communication with the lumen of the lymphatics must be abandoned in the light of recent anatomical work (MacCallum, Sabin), and it becomes necessary to regard the tissue fluid as having its own peculiar characteristics. It is with the tissue fluid that the cells have immediate relations, and this circulation must be quite active. Up to the present no method has been found by which this particular fluid can be drained away and studied, so that the statements are, to a certain extent, based on hypothesis.

The distribution of the fluids of the blood into the tissues, and the drainage of these tissues, proceed in such a way that no matter how rapid the circulation may be, there is at no time an excessive quantity of fluid among the cells. There are conditions, though, in which a disproportion in the rate of inflow and outflow occurs, and there arises an accumulation in the crevices of the tissue (*œdema*) or in the body cavities which are in a sense analogous to the tissue spaces. When this concerns the peritoneal cavity, we speak of it as *ascites*; collections of fluid in the pleural cavity constitute *hydrothorax*; in the pericardial cavity, *hydropericardium*. This may be the result of a general disturbance of the circulation, but it is misleading to speak of it without further qualification, as related to such a mechanical derangement of the blood flow, for even when general it is very commonly due to chemical changes in the tissues or in the blood itself. Accumulations of fluid may also be local, as in one pleural cavity or in the tunica vaginalis testis (hydrocele, Fig. 21), or in a joint, but then although it may seem

that the liquid is as clear and unassociated with infections as in the most innocent ascites, one can find evidences of an old inflammation which is evidently responsible.

Edematous tissues are swollen, ooze fluid on incision, and are inelastic on account of the spreading apart of the cells so that they retain the impress of one's fingers on pressure. Any organ may become so, but the most striking examples are seen in the subcutaneous tissues, especially in the extremities, and in such places as the external genitalia or in the soft parts below the eyes, where the tissues are loose. When the water-logged condition of the subcutaneous tissue is very general, it is spoken of as *anasarca*.

In those cases which generally result from diseases of the heart or kidneys the accumulation of fluid is often such that the skin becomes



Fig. 21.—Hydrocele. While the fluid was clear, one may readily see signs of old inflammation.

tense and shiny, and may even crack and allow the escape of some of the fluid. The tissues lose much of their opacity, and become almost agate-like in appearance, because the opaque cells are widely separated by the clear yellowish fluid. This is especially true of the lungs, and of such fibrous and muscular tissues as make up the wall of the intestine and gall-bladder.

Causes.—There are many things which seem capable of causing such damming-up in tissues, and, indeed, in spite of long study and experimentation we are not yet precisely informed as to the part played by each. Pathologists have proposed a great many widely different theories to explain this occurrence, and probably all of them contain

some part of the truth. Ludwig's school contented itself chiefly with the mechanical increase in filtration pressure which seemed to them sufficient explanation, although it is obvious that there are many instances of edema which can by no means be explained in this way. For that reason Heidenhain, Hamburger, and others introduced the conception of the vital secretory activities of the endothelial cells which were thought to pour the fluid from the vessels into the tissues. This idea involves a mystery which may, of course, be unavoidable, but which does not seem to help us further toward a satisfactory understanding of the condition. This is true, in fact, of all the theories which attempt to bridge over the difficult places by resorting to such vague terms as "vital activity," which, while they may express a present conception of the process, shed no new light upon it. In general, stress is laid upon the mechanical obstruction to the outflow of fluids, malnutrition, and poisoning of the tissues and endothelial cells which increase their permeability, disturbances of trophic, vasomotor and motor nerves, and more recently, alterations in the metabolism and in the state of nutrition of the tissues themselves, which may change their power of activity attracting and retaining water within themselves.

The first of these four general factors, the obstruction to the outflow of fluids, concerns both lymphatic and venous outflow, which are apparently in a sense compensatory to each other, for it has been observed that if the veins of an extremity are tied, the flow of lymph from the lymphatic trunk becomes greatly increased. No such observations appear to have been made upon the venous outflow when the lymphatics are obstructed. Mechanical obstruction of the flow in both veins and lymphatics arises when the heart fails in its duty of propelling the blood, and it becomes difficult for more blood to enter it. But such venous stagnation is felt by all the tissues, not only through the obstruction to the escape of fluids, but through the consequent obstruction to the entrance of new nutritive arterial blood. Thus there arise at once several factors which might favor edema. Filtration pressure, increased permeability of the endothelium from malnutrition, and, for the same reason, heightened osmotic pressure on the part of the tissues occur, and it is difficult to determine which of these is the most important. All are removed if the heart is supported to increased activity, when with the improved circulation, the edema disappears.

Local venous obstruction may bring about the same chain of events as in the so-called milk-leg, which is an edema produced by the obstruction of the femoral vein by a clot. This kind of local edema seems to be based on precisely the same principles as exist in the case of the general disablement of the circulation. It depends, to a certain extent, upon the suddenness with which the obstruction has been produced, and in any case disappears later if there be established a collateral circulation which allows the proper drainage.

Those types of edema which are ascribed to alterations in nervous activity rest on a very vague and indefinite foundation, and even such so-called angioneurotic edemas as have been long known and quite helplessly ascribed to nervous interferences are gradually revealing

themselves as effects of chemical disturbances of a complicated character. Naturally, those diseases of the nervous system which are followed by prolonged inactivity of the limbs result in cedema of these immovable extremities in just the same way as ankylosis of the joint or contractures of the tendons might produce it. In all such cases the circulation is impaired, the kneading action of the muscles which ordinarily propels the fluids in the limb is lost, and the tissues are badly nourished.

It is only because the fluid which exudes in the course of an inflammation differs quite markedly in its chemical composition from that

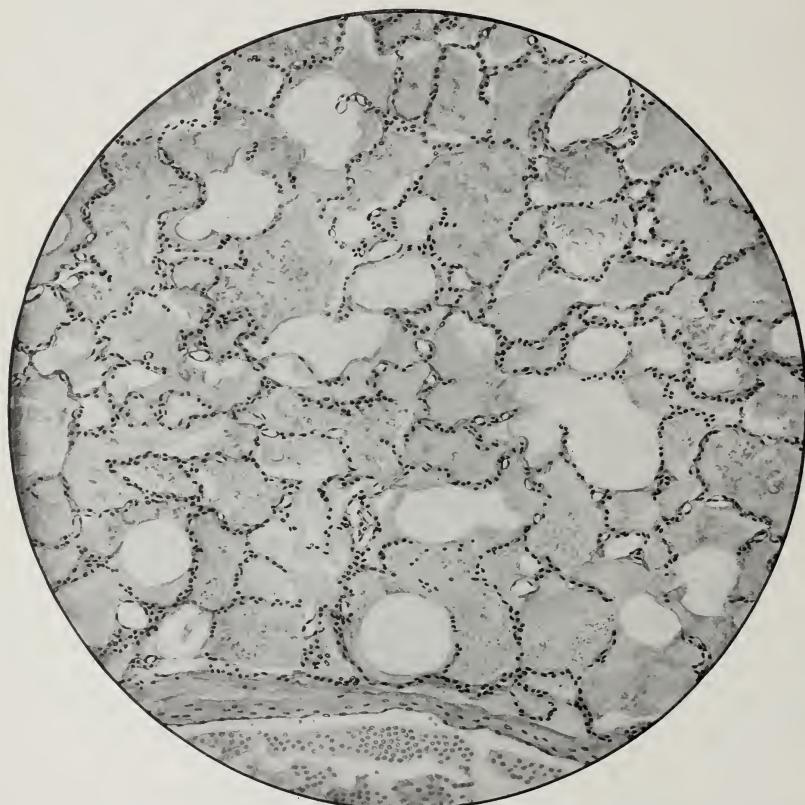


Fig. 22.—*Œdema of the lung. Alveoli filled with fluid coagulated by fixing agent.*

which we find in other instances of œdema that we seem to have especially good proof of the existence of an injury to the endothelial walls which makes them more permeable for the albuminous material of the blood.

In spite of much study the mechanism of œdema of the lungs is not yet clear. Welch, who produced it experimentally by compressing the left ventricle and thus producing an enormous disproportion in the work of the two sides of the heart, thought that it might result from such a

lung edema

disproportion arising spontaneously. It can be produced by adrenalin injections, and some have thought it of toxic origin. The fluid of the blood exudes into the alveolar walls, and especially into the alveoli, so that the air is expelled by the coagulable liquid. In the extreme examples of this agonized condition frothy fluid may run away from the nostrils and the patient dies practically drowned (Fig. 22).

Recent work on the mechanism of œdema has largely reversed the ideas current a few years ago. Emphasis is laid upon the osmotic pressure of the proteins of the blood within the capillaries, the importance of which was first shown by Starling. While the capillary endothelium is quite passive and allows the ready passage in either direction of water and electrolytes or salts, it is relatively impermeable for proteins. Of course, it is obvious that an endothelial lining cannot be quite impermeable for proteins since the tissues must obtain their albuminous material from the blood and later give off similar material which passes into the lymphatics through another endothelial layer. Still, the passage seems slow as compared with that of the electrolytes and water. Therefore, there should arise an equilibrium between salts within and without the capillaries except for the fact that the presence of the proteins disturbs this equality in distribution to some extent. This represents a small part of the osmotic power of the protein (Donnan equilibrium). Altogether, then, the presence of the protein within the capillary acts through its osmotic attraction in opposition to the hydrostatic pressure which would tend to drive the water out of the capillary into the tissue spaces. Albumens have a far higher osmotic power than globulins or fibrinogen because of the smaller size of their molecules. If the hydrostatic pressure is greatly increased, as in cardiac failure, or obstruction of the venous return, it overpowers the osmotic action of the protein, and œdema results.

If the kidney is diseased in such a way as to allow the escape of albumen into the urine, the blood becomes impoverished in albumen, the relatively inactive globulin remaining in disproportionate amount so that the relation between the hydrostatic pressure and the osmotic attraction of the protein which act in opposition, is altered and fluid passes out into the tissue spaces. Such is the œdema of nephrosis in which there is a great loss of albumen in the urine. It is not so simple in acute nephritis where an inflammatory process complicates the situation, nor even in chronic nephritis. The retention of salt which was formerly thought to be a prime factor in the production of œdema through the coincident retention of water in the tissues to maintain isotonicity is still thought to intensify œdema produced by protein loss but not in such an independent way to initiate it. It is the sodium ion rather than the chlorine which is of importance. But still there remains much that is obscure in the whole problem of œdema.

LITERATURE

- Cohnheim and Lichtheim: Virchow's Arch., 1876, lxix, 106.
Fishberg, A. M.: Hypertension and Nephritis, 1931.
Leiter: Medicine, 1931, x, 135.

- Loeb, Leo: Edema, Medicine, 1923, ii, 171.
- Meltzer: "Edema," American Medicine, 1904, viii, 19, 59, 151, 191.
- Müller, F.: Verh. Dtsch. Path. Gesellsch., 1905, ix, 64.
- Starling, E. H.: Lancet, 1896, i, 1331.
- Weech: Bull. New York Academy of Medicine, 1934, x, 269.
- Welch: Virchow's Arch., 1878, lxii, 375.
- Many papers by Van Slyke, Peters and coworkers. Literature in the paper of Peters, Medicine, 1932, xi, 435.

CHAPTER IV

THE STRUCTURE AND METABOLISM OF CELLS

Cellular doctrine; ultimate unit of life. Nucleus and cytoplasm. Mitochondria, plasmosomes, paraplastic substances, intercellular substances. Tissues and motile cells. Variations in the appearance of cell. Necrosis, coagulation, and autolysis. Death.

WITH the establishment of the cellular nature of the tissues, and Virchow's epochal revelation that disease may be referred to alterations in the cell, it may well have seemed that the ultimate unit of life had been reached and that no minuter element need be considered. Indeed, our doctrine of pathology is essentially a cellular one, although we realize that the cell is in all cases a vastly complicated structure, within which there are elaborate mechanisms, developed in almost infinite variety, and within which, too, we can discern evidence of the accomplishment of chemical processes which, in complexity and ingenuity of combination, surpass anything which can be carried out in the best chemical laboratories. Within one cell there may occur at once and side by side synthetic processes and decompositions which, in the laboratory, would require, if they were possible at all, the most elaborate apparatus and the most extravagant expenditure of energy. Therefore it is not surprising that many have sought for a still simpler unit of living matter.

But even though we can recognize minuter organ-like structures within the cells, we realize that they are merely coördinate parts in building up the cell, which is the ultimate mechanism which seems complete enough to live independently. The smaller parts may be specialized instruments for some particular function, but they cannot exist or carry on this work apart from the cell. Indeed, it seems that it is upon the nice adjustment and coördination of all the parts of the mechanism in the cell that life depends; when food and temperature conditions are favorable, the precisely adjusted mechanism begins to move as though by spontaneous combustion under the boiler of an engine all prepared.

While the modern studies of immunity seem to ascribe wonderful properties to the fluids of the body, and changes almost intelligent in their purposefulness in these fluids in response to noxious substances, all the chemical characters are controlled by the cells and there is little prospect of a return to the humoral theories of long ago.

It would serve no good purpose here to enter into the details of the various conflicting theories as to the nature of the substances which make up the body of the cell and its nucleus—all this may be read in the work of M. Heidenhain, the recent review of Benda and Ernst, and in other places. So little is firmly established that it will suffice here to mention those points which we seem to know most surely.

THE STRUCTURE OF CELLS

In spite of the great variety in form and size, and in special modifications of the cell-body for different functions, we may recognize the following parts:

- (1) The nucleus.
- (2) The centrioles or centrosomes.
- (3) Golgi's reticular apparatus.
- (4) The cytoplasm, in which are found—
- (5) The mitochondria.
- (6) The plasmosomes.
- (7) Various paraplastic substances.

(1) The nucleus differs from the general protoplasm in its density, its chemical nature, and its inner structure.

How it is separated from the rest of the cell is a matter still disputed, but it is clear that an active interchange of materials goes on between the nucleus and the protoplasm, and that the nucleus presides over the activities of the cell, especially over its reproduction by division, in which it is itself so intimately concerned. In the absence of a nucleus the protoplasm can remain alive a short time and carry on sluggish assimilation, but it soon dies. The minute structure of the nucleus is as much disputed as that of the cytoplasm. In most cases there is a homogeneous nucleolus, and in our fixed preparations there are various condensations of deeply staining chromatin material. Kite states that, from dissection of the living nucleus, he can show that the chromatin is not in definite masses in the resting cell, and that only the nucleolus is recognizable as a colloid material of different density from the rest. In the process of mitosis, however, the clumping of the chromatin into tangible masses, the chromosomes, is familiar to every one. Their longitudinal division into equal parts, and the separation of these parts by the action of the fibrils of the achromatic spindle into the so-called daughter stars, which later form two separate nuclei, is abundantly described in all books on histology.

(2) The centrioles or centrosomes are minute bodies, occurring in pairs outside the nucleus, and surrounded by modified protoplasm. They occupy varying positions in the resting cell, being often at the roots of the cilia in ciliated epithelium, in other cells often embedded in a dell in the nucleus. In mitosis they become active, separating to opposite poles of the cell and surrounding themselves with radiating, contractile fibrillæ (achromatic spindle), which exercise a mechanical influence upon the chromosomes.

(3) Golgi's reticular apparatus appears to be a network or basket-like arrangement of canaliculi filled with a peculiar lipoid material which is invisible by ordinary methods of observation, and only brought to view by impregnation with silver or by the blackening effect of osmic acid. The network is usually close to the centrioles, although it sometimes surrounds the nucleus. It varies greatly in the details of its form and arrangement in the cells of different tissues. During mitosis it disintegrates and the fragments separate to the two halves of the cell, arranging themselves roughly in relation to the radiations of the achro-

matic substance. It is present in what appears to be the usual form in tumor cells and becomes multiple in relation to the numerous centrioles in multinucleated giant cells. In recent years through the work of Nassonov and of Bowen, it has been found that the Golgi apparatus is intimately related with the process of secretion in gland cells. They describe the appearance of minute granules or globules of the secretion in the immediate neighborhood of the network gradually coalescing to form more obvious large globules in some cases, and leaving upon their discharge the Golgi apparatus to preside over the formation of more secretion. So, too, such vital dyes as trypan blue, when taken into the cell, occupy a place immediately in contact with the Golgi network. Whether this applies to other materials taken into the cell is left undecided. Whether the granules characteristic of highly active cells such as those of the hypophysis are to be regarded as secretion in themselves, or as capable of producing a diffusible secretion, also remains to be learned. But it is clear from such fragmentary information that the matter demands much further study.

(4) The Cytoplasm.—The divergent theories as to the nature of the protoplasm may be read elsewhere. It seems that the more recent study of the granular structures which are embedded in it has removed much of the support for the earlier theories, and the outcome seems to be that the cytoplasm is essentially colloid in its composition, obeying the physical laws which govern colloids in their various phases. Possibly a mixture of colloids of various densities, it has varying powers of water absorption and swelling. The admixture of fat-like substances alters its physical character somewhat. With regard to the surface of the cell, it has been suggested that some such condensation through the aid of cholesterol or lecithin admixture may exist. Overton's theory that there is an actual thin lipoid membrane which acts as a semipermeable sheath to each cell is well known, and has served in the explanation of the action of anaesthetics, but it still admits of criticism, as pointed out by Bayliss (Principles of General Physiology, 1918, page 138).

(5) The Mitochondria.—Altmann, in 1894, devised staining methods which made visible certain granules in the cell protoplasm which he regarded as elementary organisms, or the only living constituents of the cytoplasm. While this view cannot be maintained, there is much that is exact in his observations. Benda recognized by other stains granules, rods, and threads in the protoplasm which he called mitochondria, and which have been shown by many workers (Meves, Duesberg, and others) to be a very constant constituent of the cell-body.

Many names have been proposed indicating differences in form, such as *chondriocont* for the longer filamentous forms, *chondriomita* for those resembling a string of beads, etc., but the original term, *Mitochondria*, may well be used in a collective sense. The greatest variety of functions has been ascribed to them by different writers. Meves claims that they furnish the connective-tissue fibrillæ, that they transmit the hereditary characters of the cell-body, etc.

It is clear that we must as yet be careful in interpreting their func-

tion, and while it seems probable that they play some important rôle, it is possible that already too many different duties have been assigned to them. The literature has recently been reviewed by Cowdry.

(6) The Plasmosomes.—Benda distinguishes sharply from the mitochondria these granules, which he speaks of as concerned with the house-keeping of the cell, with the assimilation of nutritive materials, with the formation of secretory products as the result of their specific metabolism, and with the excretion of waste.

They are not to be recognized in themselves by any of the staining methods which we know now, but are readily enough made visible by

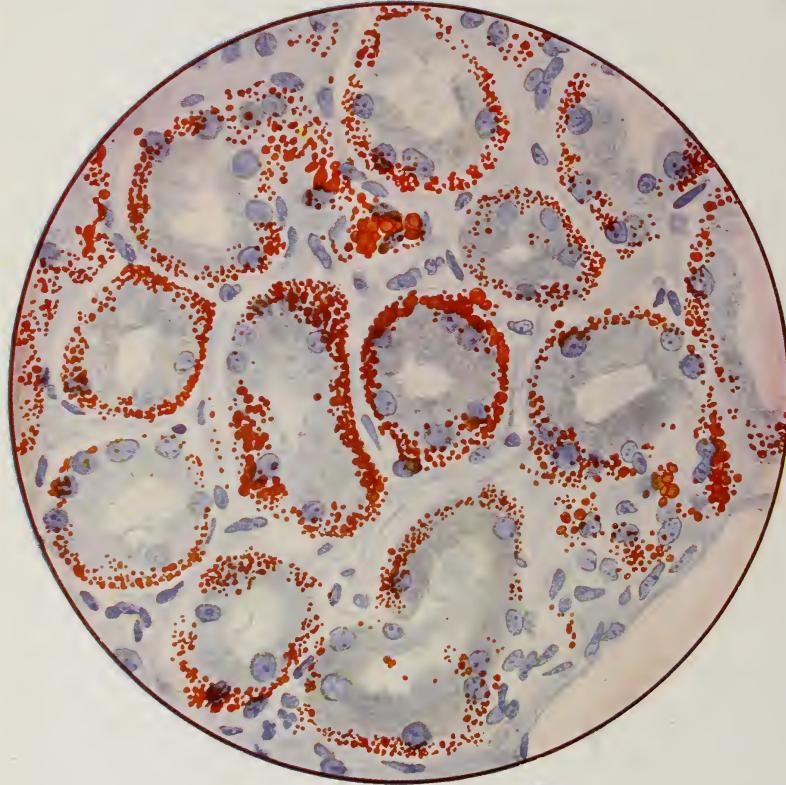


Fig. 23.—Fat-globules in the epithelium of the renal tubules. Sudan stain.

the substances which they store or secrete or by their power to store vital stains. That they are really distinct from the mitochondria is shown by their different position in the cell, by the fact that the mitochondria are recognizable as thin filaments in a cell in which, side by side with them, the plasmosomes are swollen with some absorbed material, or with a stainable secretion, and by the fact that in mitosis, mitochondria, and plasmosomes separately divide and continue their existence in the daughter-cells.

It is in connection with these that fats and carbohydrates are stored

in the cell. It is probably they that swell and become conspicuous in "cloudy swelling" or "parenchymatous degeneration." They in their varieties constitute the specific granulations of the leucocytes and other cells. To this class too belong, no doubt, the zymogen granules in many glands, even though in such a gland as the pancreas we can distinguish so easily the coarse, deeply staining zymogen granules in the acinar cells from the very minute granules of two types in the cells of the islands of Langerhans.

It is clear that the construction of the cell is highly specialized in most cases for the function which it is to carry out, and that it is

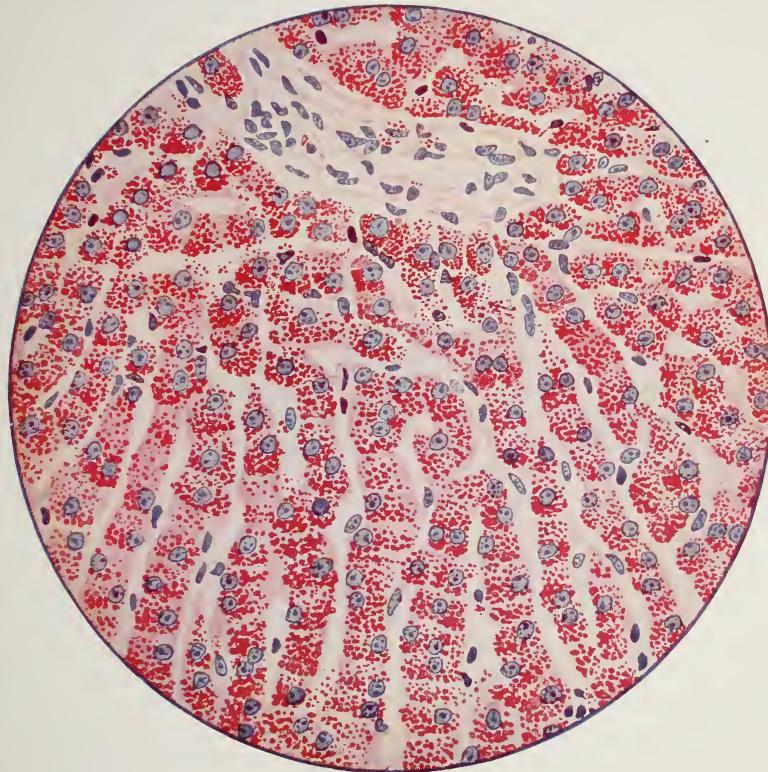


Fig. 24.—Liver of a normal well-fed dog showing glycogen in cells. Best's carmine stain.

supplied with the most perfect mechanisms for these purposes. Some of these are evident in the form of contractile bands in the protoplasm, or in long nerve processes like electric wires carefully insulated by sheaths of fatty material, or in mobile cilia which mechanically perform duties in the transportation of foreign particles. In others the tools of their trade are recognizable in the form of the granules which seem to prepare ferments by which the chemical processes which the cells effect are carried out. While these are visible in many cases, there are others in which, even when we know that the most multifarious chemical

reactions are being carried on, nothing of the mechanism is recognizable to our eyes.

(7) Paraplasmic Substances.—While the actual instruments of metabolism are thus often invisible, the materials which are being worked up by the cells, and more especially those which the cell is unable to dispose of, often remain conspicuous in the cell-body. Such "paraplasmic" particles, which may consist of fat-globules (Fig. 23), glycogen granules (Fig. 24), vacuoles filled with fluid, granules of pigment or calcium, often form an index of the activity of the metabolism of the cell, and are useful in determining its condition, although it must be remembered that there are doubtless many other substances equally burdensome to the cell, and accumulated in its protoplasm, because its metabolism is so sluggish as to make it unable to dispose of them, and these, because of their solubility or because they are inaccessible to our stains, are invisible. Certainly these substances are not to be thought of as alive, at any rate until they become, through assimilation, integral constituents of the chemical structure of the protoplasm.

TISSUES AND MOTILE CELLS.

It is, of course, clear in connection with this that the higher animals, at least, exist as communities of cells in which each district is made up of individuals which have specialized in some form of activity which is contributed to the good of the whole, and that in such a community there are many things in common, such as the blood-supply, the gaseous interchange, and the removal of waste. Just as in a town the water-supply, the air, and the sewage are of common interest, so we have seen that in the body whole districts may suffer from the failure of one of these common necessities.

Communities of this character, inasmuch as they hold together in a coherent grouping, we easily recognize as "tissues." It is not so easy to think of a constantly moving and changing group of cells like the blood as a tissue, although in every respect it deserves the same dignity as the community of liver-cells or kidney-cells. And so it is with those free lances, the wandering phagocytic cells, which straggle about in the tissues everywhere, but are ready on call to assemble at a point where they are needed. Intimately related to the mobile cells of the blood, they have the same claim to the honors of a community, although it must be remembered that they differ from the "fixed tissue" elements in refusing to hold together into a solid structure or to adopt any particular place as a permanent site.

The whole body is not composed of cells. Were the cells all removed, there would still remain a framework so complete that although we might see through it as through a basket, the whole form of the body in all its parts would be represented and much of its solidity would remain. This is the intercellular substance, which varies greatly in character in different places, being almost the whole of the skeleton and the bulkier part of all the connective tissues which permeate all tissues and organs. Whether this material is alive has been long discussed. Cer-

tainly the fibres of connective tissue, the matrix of cartilage, and the calcified substance of bone could not remain alive alone; but in the body all these things undergo constant change, being broken down and reconstructed, and there seems no doubt that they carry on a sluggish interchange of chemical materials—a slow metabolism.

VARIATIONS IN APPEARANCE OF CELLS

Alterations in the appearance of the cell arise constantly from variations in its activity, and one must be familiar with such physiological transformation in order to interpret correctly what might otherwise be looked upon as the effects of pathological processes. This presupposes that we are able to view the cells as they are in the height of their activity, but in truth this is seldom the case, since most studies of human tissue are made after the individual has been dead for some time, or after the tissue has been removed from the body at operation. Naturally, changes must be expected to occur in this interval, and it is easily realized that the more quickly the cells can be studied after their removal from the living body, the more nearly they will approach to their living condition. Naturally, too, there are great advantages to be gained by studying such cells at once without the application of any chemical reagent, a method once universal, but now far too little used. But it is realized that while much may be learned in this way, such tissues change rapidly, and we, therefore, preserve them by suddenly stopping all ferment action and coagulating the protein substances by the application of some fluid, such as alcohol or formalin. Advantage is taken of the fact that nuclei, protoplasm, etc., react differently to various stains, and in the end our microscopical preparations show us the cells sharply brought into relief by being coagulated, and by having each of its elements differently colored. We are accustomed to the appearance in the stained preparations of what was a normal cell and interpret diseased conditions of the cell by its divergence from this standard, but at the same time we know that the cell is really greatly changed from its appearance while alive. It resembles the living cell about as a boiled egg resembles a fresh laid one. In an autopsy upon a man who had swallowed a large amount of pure carbolic acid, which is an excellent "fixing fluid," the gastric mucosa was obviously dead and coagulated into a white layer long before the man died, but although it looked so abnormal, the microscopical section showed the most perfectly preserved normal gastric mucosa.

If, then, these are all dead cells which constitute our standard of the appearance of live cells, how shall we recognize injured or dead cells among living ones? It is very easy, because what we recognize is not the death of the cell, but the changes to which it is exposed, after death, *while still surrounded by living tissues and their fluids*, and which result partly from the action of ferment and partly from the formation of a clot in the substance of the dead cell and the coagulable fluids which may permeate it.

If only a portion of the gastric mucosa had been killed, so that the

man remained alive for a time, it would soon have been liquefied by the gastric juice. Exactly so a dead cell in the substance of the liver becomes the seat of clotting, and then is liquefied by the ferment of the passing fluids and mobile cells, and it is in some stage of this process that we recognize the necrotic cell. A cell which had just died would look quite like its living neighbor.

NECROSIS AND NECROBIOTIC CHANGES

It is important, then to consider briefly these evidences of the effects of necrobiotic changes, a matter which is simplified since they are the same throughout, whether the injury be caused by a poison, by starvation, or in any other way, unless, of course, the poison or mechanical

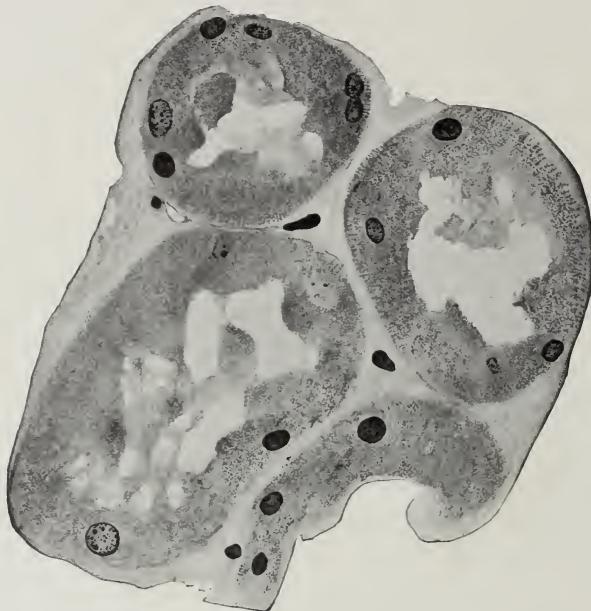


Fig. 25.—Renal epithelium showing pyknosis in several nuclei, with disappearance of others.

injury should in itself produce some peculiar change in the cell. With the cessation of life in the cell there is a short pause, during which the dead cell has every appearance of being alive, and then its protoplasm sets in a clot. The thromboplastic substance, or thrombokinase, which the dead cell radiates causes the coagulation of the fibrinogen in the passing blood plasma which perhaps filters into it, and in the end the body of the dead cell becomes a swollen mass, much denser and heavier than the body of the original live cell. All this is not done without changes in the appearance of the cell—changes which probably begin before the actual death and continue after clotting has occurred. The most conspicuous are alterations in the nucleus which may cause it to shrink and stain more deeply (pyknosis) (Fig. 25). Portions of its substance

may be extruded beyond its original outline in bizarre forms, or it may break up into several irregular, solid-looking, and deeply stained fragments, or even into a fine dust of black grains (*karyorrhexis*) (Fig. 26). On the other hand, it sometimes retains its form for a long time, but gradually fades until only the faintest rim takes the stain and in turn finally disappears (*karyolysis*) (Figs. 27 and 28). At the same time the structural details of the cytoplasm are lost, and merge into a dense, granular or vitreous mass, which assumes a deep pink stain with eosin. Later changes caused by proteolytic ferment lead to the erosion, disintegration, and final liquefaction and disappearance of the whole cell



Fig. 26.—Karyorrhexis. Edge of infarct of kidney.

remnant. Frequently the boundaries of many adjacent necrotic cells are lost before liquefaction occurs, and a granular mass remains in which nuclear fragments or the fine dust of them is scattered, but even then it is often possible to make out the positions of the original cells because the more resistant connective-tissue framework of the tissue persists.

Much of the disintegration and removal of the débris of such dead cells is effected mechanically by phagocytic cells, usually of the mononuclear type, which engulf particles in their protoplasm in addition to their activity in furnishing the proteolytic ferment. They in the end wander away with these partly digested fragments, the liquefied material is absorbed, and the area of cell death collapses or is partly filled by



Fig. 27.—Karyolysis in renal epithelium.



Fig. 28.—Death of renal epithelium with fading nuclei.

a growth of scar tissue. Sometimes, as in large infarctions or in tuberculous foci, the dead material may remain undissolved for a long time, and is walled off by a capsule of fibrous tissue.

Autolysis.—This liquefaction by means of a proteolytic ferment is exactly the process known as autolysis, except that it is recognized in that process that all tissues can liberate in varying degrees of intensity the proteolytic ferment necessary to dissolve their own cell-bodies. Even a piece of lung or liver kept sterile in a warm place will soften and finally liquefy, while tissues, such as spleen, which contain large numbers of specialized phagocytic cells which are particularly active in producing such ferments will dissolve into a turbid fluid rich in amino-acids far more quickly. Bradley and Morse emphasize the importance of a slightly acid reaction in accelerating this process. Dernby shows that in all tissues studied there are both pepsin-like and trypsin-like enzymes, so that autolysis would proceed most rapidly if the reaction were first slightly acid and then alkaline. Undoubtedly this mechanism is well adapted to rid the body of useless dead and crippled cell material, and it will be seen that it plays a great part in the restoration, to an untrammeled working condition, of all injured organs, and throughout life is the constantly active method of housecleaning which keeps the machinery in order.

Death.—Death of cells is thus a relatively complicated matter, but the whole body is a community of tissues which is not entirely disabled, even by the loss of many cells. As in the cell where the controlling nucleus is destroyed the protoplasm also dies, so in the body life is the expression of the working of a delicate machine which works because it is marvelously attuned to the environment. Because it has elaborate regulators, controllers, and safety-valves, it can compensate for many injuries, but when the limit of the influence of these is passed, the machine stops. Therefore there are many ways in which the balance can be made impossible at one point or another—points important enough to involve finally the all-important circulation and respiration. When they cease, all the tissues soon die, although for some time after the main machine has stopped working the various accessory machines are still in good working order, and need only the current of clean blood through their vessels to make them begin once more to work. Of course, the central nervous system is the great regulator, and one might say the master engineer, but life can go on without it if only some one will assume its rôle and arrange that the circulation should continue properly. So, though it is so familiar, it is difficult to define precisely what a person's death means or to say at just what moment the most important part of death occurred.

LITERATURE

- Benda: *Ergebn. d. Anat. u. Entwickl.*, 1903, xii, 743. *Verh. Dtsch. Path. Gesell.*, 1914, xvii, 5.
Bowen, R. H.: *Quarterly Review of Biology*, 1929, iv, 299, 484.
Cowdry: *Archives of Pathology*, 1926, i, 237. *General Cytology*, Univ. of Chicago Press, 1924, 311.

- Duesberg: Biological Bulletin, 1919, xxxvi, 71. Ergebni. d. Anat. u. Entwicklungs-
gesch., 1912, xx, 567.
- Ernst: Verh. Dtsch. Path. Gesell., 1914, xvii, 43.
- Guyer and Claus: Anat. Record, 1934, lxi, 57.
- Heidenhain, M.: Plasma u. Zelle, 1907, i.
- Maximow and Bloom: Histology, W. B. Saunders Co.
- Meves: Arch. f. mikr. Anat., lxxi, lxxii, lxxv, lxxvi, etc. Anat. Anzeiger, xxxi,
xxxiv.
- Morgan, T. H.: Heredity and Sex, Columbia University Press, 1913.
- Pappenheimer: Anat. Record. 1916, xi, 107.

CHAPTER V

DISTURBANCES IN THE NUTRITION AND METABOLISM OF CELLS

Course of metabolism: Disturbances resulting in accumulation of various substances. Degenerations. Atrophy: its causes. Hypertrophy and hyperplasia.

ORDINARILY the normal and abnormal metabolism of animals is studied by chemical investigation of the materials taken into the body in comparison with those excreted, taking into account the energy liberated in the form of heat, and the changes in the weight of the body. This gives a fairly accurate idea of the whole material interchange in the body, and when the normal balance is much disturbed, it is usually easy to recognize the effects anatomically.

It is known to every one that in early life the anabolic, or building-up, process should be in excess of the katabolic, or destructive, processes, so that growth proceeds through the assimilation and permanent retention of much of the food materials in the form of body tissue. In mature life such an exquisite balance is maintained that little change in the body weight occurs, while in the declining years the organs waste and the body shrinks because the katabolic outstrip the anabolic processes.

Substances taken in as food may be used directly for the building up of tissue, whereupon they become a relatively stable part of the body structure, or they may be burnt to produce energy, or stored for future burning. Such stores are essentially labile constituents of the body, ready at any time to be moved about or to undergo rapid chemical change. They thus constitute the ready fuel, and it is only after they are exhausted that the actual cell substance is consumed. It is like Palissy's furnace, into which, when the supreme effort was being made and fuel was finally exhausted, he cast his furniture.

Naturally, if the activities of the cells are restricted, the fuel will tend to accumulate—even if the cell is slightly injured, so that it can no longer make use of all the materials brought to it, we may expect them to collect in its body.

Under these circumstances we can often see the accumulated materials, although we can detect no evidence of injury to the structure of the cell, and it must be a matter of long experience to ascertain how much real injury corresponds with the heaping-up of such materials.

This is the basis of the so-called "degenerations," of which so much has been written. When it was thought that the globules of fat in a cell were the direct product of the decomposition of its protoplasm, this naturally indicated a great injury, but now if we think the fat merely a part of that which is transported from place to place, finally side-tracked in these cells, we cannot be so readily convinced of the injury to the cell, especially since we know that the same appearances can

arise in perfectly normal persons. It is almost as though we were to attempt to tell the condition of a flour mill which we suspect of being out of order by estimating the amount of wheat in its hopper at any given moment. It might be better to estimate the flour it has ground or to look for broken wheels in its machinery.

The situation is difficult for the following reasons: Of all the substances which enter into the material interchange of the cells, we can see only a few, such as fat. As shown by chemical studies, great disturbances of metabolic activity may occur without our being able to see the substances concerned, and, on the other hand, great variations in the quantity of the visible materials in the cell need not indicate an injury to the cell. Functional disability of the cell may exist without any obvious anatomical alteration, and yet cause this stagnation of food materials, while perfectly obvious anatomical demolition of the cell machinery may occur in such a way that no heap of fuel material collects to indicate the change. So we must interpret what we find with extreme care.

It is the aim of this chapter to discuss the anatomical changes in the tissues produced by injuries, which are accompanied by disturbances of metabolism. These changes may be so slight as to be invisible, and indicated only by the accumulation of materials which should have been used up, or they may be so intense as to have destroyed the structure of the cell.

The term *degeneration* is usually employed to indicate the effect of an injury sufficient not to cause the death of the cell, but to disturb its metabolism to such a degree that the raw materials or the products of its activities accumulate in it. It is loosely used in other senses, as in the case of hyaline degeneration, in which the cells die and are merged into a homogeneous mass, or amyloid degeneration, in which an abnormal substance is deposited in the crevices of the tissue.

It would seem desirable, if possible, to abandon the term degeneration entirely and to use others which refer more accurately to the disturbances of metabolism or to the actual injury of the cell. But even if we attempted this, it would probably be unsuccessful, for the words are so deeply rooted and express so concisely a complex and obscure idea.

It must be observed that a rather limited number of raw materials are normally concerned in the chemical processes of the body, although they are presented in an almost infinite number of combinations, and pass through many further changes in the cells, but the body can deal with other things which are not good food or drink or air to breathe, in ways which are sometimes surprising and always more or less definitely adapted to its protection.

Normally we take in water, air, protein, carbohydrates, and fats, together with smaller but continuous supplies of the salts of sodium, potassium, magnesium, and calcium, combinations of iron, phosphorus, sulphur, iodine, chlorine, and minimal amounts of various other substances. The lack of any one of these will be severely felt, and may produce an astounding upset of the whole machinery of the body.

At other times, when the facilities for dealing with one or other of these substances are disarranged, it may become necessary to eliminate them from the food if life is to be prolonged—carbohydrates are withheld from the diabetic and salt from the waterlogged sufferer from Bright's disease.

ATROPHY

In order that growth should occur, or even that the tissue should maintain its status, the machinery of the cell must be in working order. We may imagine that, by reason of age, this machinery might deteriorate or that in other ways it might be incapacitated.

Evidently when this deterioration appears, the oxidizing or katabolic processes go on, although the more difficult building up proceeds but haltingly until the cell is hopelessly in arrears and wastes away.

The cell laboratory does not start up into activity merely because food is presented—rather it is controlled in its synthetic and analytic processes by influences from without—from the nervous system, perhaps indirectly through the organs of internal secretion. They set the pace and determine the rate of work. Without them tissue-cells will grow a little in such a culture as has lately become possible, but this growth is so meagre that their importance has become more than ever clear. When the cell does nothing, we might perhaps, at first thought, expect it to remain unchanged, and so it would if we assured its complete inactivity by putting it in formalin, but the inactivity of a cell is more like a household in which the bread-winner stops work.

Of course, grosser influences may have the same effect—hunger may deprive the tissues of nutrition, pressure may so constrict the cell that nourishment is impeded, or poisons may wreck the machinery. The atrophy of tissues is, therefore, not a simple matter, and perhaps were the effects as different in appearance as the causes, we might have many words to describe it. And even though we may discover the primary reason for the great change, we cannot always be sure of the immediate cause because a vicious circle started each time, any part of which may be responsible for the end result. Can we be sure, when the muscles of a limb atrophy from disuse, whether the inactivity of the muscle-cell directly halts its metabolism, or whether the cell wastes because but little blood comes to it now, either because it fails to assist the circulation, or because the vasomotors adjust the supply to its needs as an inactive rather than an active cell?

Wasting of the tissue may be caused by starvation, by old age, by mental disease, by derangement of the internal secretions, by infections and intoxications, especially when associated with fever, by inactivity; especially when caused by paralysis, by mechanical pressure, and by various other causes.

Hunger.—According to the state of nourishment with which it starts, the animal body can survive the complete withdrawal of food for varying periods. If water is available, the length of time that elapses before serious symptoms or death results may be several weeks, especially in certain persons who have trained themselves to fast. It is even longer in dogs. Aside from the sensations of hunger (which soon decrease).

and weakness, there are usually no particular symptoms until rather late, when phenomena of intoxication with nervous symptoms arise on account of the irregular decomposition of fats into β -oxybutyric acid and acetone, with related substances. This acid intoxication, which may bring on coma, is not, as a rule, seen in fasting dogs.

In a starving person the absorption of oxygen and exhalation of carbon dioxide continue, the excretion of urine goes on, although the faeces disappear. Wasting occurs first in the stored substances, such as fat, glycogen, etc., then in the tissues themselves, beginning with those which are least called into use. Of the muscles, the active ones retain their bulk longer than the idle ones. The liver shrinks, and the parts which retain their full size for a long time are the central nervous system, the heart, and the bones, although the last probably become rarefied.

While complete deprivation in this way brings about the rapid wasting of the body, there are many mechanical and other conditions which lead to the same result more slowly. Any obstruction to the passage of food through the mouth and oesophagus to the stomach may gradually starve the sufferer, and so may an obstruction at the pylorus, since nourishment is not sufficiently absorbed from the stomach and is usually vomited after a long stay there. Besides this, there are various nervous disturbances, which result in inability to take food (anorexia nervosa) or to retain and digest it, and lead to extreme emaciation.

Senility.—With the advance of age, wasting becomes evident in many organs, if not in all, although the inconstancy with which it appears leads one to wonder whether other factors do not also play a part. The skin becomes thin and satiny, and the disappearance of fat and muscle tissue beneath it throws it into wrinkles. The hair, after becoming white, falls out, the teeth loosen and decay and fall out. The muscles waste away and grow weak, and the ligaments which bind together the bones stretch and weaken. Deprived of its strong muscular and ligamentous support, the back bends forward. The bones become rarefied, so that they break more easily and heal with greater difficulty than in a young person.

The internal organs decrease in size and turn brown, and every cell, through its shrinkage and the accumulation of pigment, can be recognized as that of a senile organ. The liver becomes a flabby, shrunken organ, of a dark-brown color, made up of lobules far smaller than the normal; often whole layers of liver tissue disappear, so that on the surface of the organ blood-vessels, bile-ducts, and the fibrous skeleton of the liver lie exposed (Fig. 29). The heart becomes small and brown, with tortuous coronary arteries showing through the watery, brownish fat. The fat of the epicardium has disappeared, and its cells are separated by fluid which gives the gelatinous appearance to the tissue. The heart decreasing in size is too small for the coronary vessels, which must take a tortuous course. The valves often become ballooned out and the chordæ tendineæ stretched until they are much too long. Each heart muscle cell greatly reduced in thickness shows at the poles of its nucleus great quantities of a yellowish-brown, granular pigment which

stains a little with Sudan III (brown atrophy) (Fig. 30). This is one of the little known group of lipochrome pigments which seem to arise everywhere with the wasting of the cell-body. The formation of a pigmented ring about the margin of the cornea (arcus senilis) is another analogous process—there, too, the pigment is probably of the group of lipochromes. The brain withstands this shrinkage for a long time—at



Fig. 29.—Superficial atrophy in a senile liver, exposing the vessels and the framework of the organ.



Fig. 30.—Brown atrophy of the heart. Pigment-granules at the poles of the nuclei of the wasted fibres.

least so far as its external appearance goes, though in the end the convolutions become narrower and separated by wide sulci in which fluid collects. Long before this the mental deterioration may have given an index of the disappearance of association-tracts and the disabling of the cells.

In the skeleton, aside from the general rarefaction of bony tissue

(Fig. 31), conspicuous deformities may occur, such as the gradual erosion or hollowing away of the outer table of the skull over the parietal regions until deep grooves are formed over these regions—sometimes so deep as to penetrate the inner table and leave the brain covered only by a soft tissue.

Mental Disease.—We know very little about the control of metabolism from the central nervous system, but every one is familiar enough with the lean and hungry looks of the fanatic and the sleek plumpness of such as are content and sleep "o' nights." Possibly it is the constant



Fig. 31.—Senile osteoporosis. Section of rib showing great thinning of the cortex and atrophy of the lamellæ. With the disappearance of calcium, the lattice figures become evident in the Haversian systems.

activity of the one and the folding of the hands of the other that cause these differences, but mere muscular activity seems not quite sufficient to account for it all.

In some mental diseases the influence of excitation or apathy is very striking—in the manic depressive insanity, or *folie circulaire*, the patients pass through periods of the wildest maniacal excitement, which alternate with others of apathy and depression. In the maniacal periods they become emaciated in the extreme, only to grow fat when they pass into the state of depression.

Deranged Internal Secretions.—These are intimately related with the mental condition, and it is possible that it is in some way through them that the mental disturbance acts to affect metabolism. Psychic disturbances change the secretion of the adrenal (Cannon), and possibly they do the same thing with the thyroid in such a disease as exophthalmic goitre. Wasting characterizes that disease, while in the absence of the thyroid, in deficiency of the hypophysis or of the ovary or testis, fat accumulates. Evidently these organs have the most intimate relations with the general metabolism, and are in most direct control of it, for their integrity affects not only the disposition that is made of the labile substances, but also the growth of the tissues.

Febrile Disease and Tumors.—In infections and intoxications accompanied by fever the whole metabolism is so adjusted that the katabolic

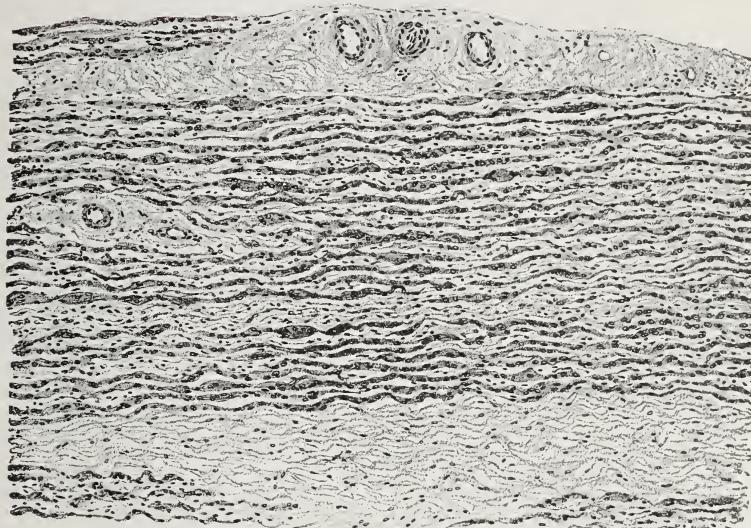


Fig. 32.—Atrophy of muscle with pigmentation and concentration of sarcolemma nuclei.

processes are in excess, and it is thought that in time the tissues themselves are attacked and oxidized. It is, therefore, not surprising that extreme degrees of emaciation are found in cases of protracted infections with fever—the long-standing cases of pulmonary and bone tuberculosis or typhoid fever are examples.

But the same appearances sometimes accompany the ravages of certain tumors, even when there is no bacterial infection, no ulceration, and no fever. Not all tumors can do it, nor are the emaciation and evidence of poisoning dependent altogether upon the size of the new-growth—instead, such symptoms as weakness, pallor, loss of weight, lowered resistance to infection, and all the other signs of what has long been called "*cachexia*," may be the first indication of the existence of any tumor. For this reason, although one might imagine that much food and body substance would be used up or diverted to the formation

of a large new-growth, it is necessary to believe, when the tumor is very small, that it disturbs metabolism through some poison which it distils or whose formation it favors.

In such emaciated people the fat from the wasted subcutaneous tissue seems to be lodged in the liver and other internal organs whose cells are unable to dispose of it.

Inactivity.—More local in its effects, and scarcely capable of causing anything resembling the general emaciation which is seen under the foregoing conditions, inactivity may stop the growth of the tissues of the young and lead to the wasting of those of adults. In such organs as



Fig. 33.—Atrophy of muscle-fibres. Juvenile muscular dystrophy.

muscles the forced repose which follows the rigid splinting of an extremity or the unbending fixation of a joint is quickly followed by a decrease in the size of the muscle which can be seen to be the effect of wasting of the separate fibres until, with the loss of fibril after fibril, they are reduced to remnants of thread-like thinness or disappear entirely (Fig. 32). Generally, the sarcolemma nuclei remain and collect together until they form long headed rows in the collapsed sheath. But they disappear also in time, and their place is taken by a little fat or by fibrous tissue which contracts so as to pull the joint into a fixed position.

When the inaction follows the cutting of the nerves or destruction

of the motor nerve-cell in the anterior horn of the spinal cord (as in infantile paralysis), the wasting is even more rapid and complete. It seems that even when the normal muscle is perfectly quiescent there are impulses reaching it constantly through the nerve which maintain its tension or tone. A kind of tremulous, tuned-up state is kept up which prevents its complete inertness, and this involves a certain metabolic activity.

When the nerve is cut, all these impulses cease and the muscle sags down quite flaccid—compared with the oxygen and carbon dioxide exchange of the intact resting muscle the metabolism of this paralyzed muscle is almost nothing, and hence, no doubt, its rapid wasting. Doubtless, as was suggested before, the decreased blood supply to a paralyzed limb adds to the tendency to waste, although it cannot be regarded as the most important factor.

Other things than muscle waste in these same circumstances—the bone, the ligaments, even the skin, become atrophic in a paralyzed extremity.

We have little experience with changes that might occur in internal organs deprived of their nerve-supply, but they are rendered inactive in other ways, and chiefly, perhaps, by the occlusion of their ducts or by compression. Examples of the former are discussed elsewhere (hydro-nephrosis, pancreatic duct occlusion etc.).

The secretion accumulates and distends the duct, finally compressing the gland tissue so that the nutrition of the cells is interfered with. The whole gland may be converted into a thin-walled sac containing the secretion under high tension. The other factors which play a part in completing the destruction of the tissue are no doubt the compression of the blood-vessels, which now run in the tense wall of the sac, and the stoppage of the function of the secreting cells.

We know little about the actual mechanism of secretion, but it seems probable that if the concentration of any element of the secretion in the sac becomes very high, it will be impossible for the cell to continue to pour more of that substance into the solution. That part of the cell's metabolism will come to a standstill, although it is shown that if the sac be emptied, secretion will begin again at once. It is possibly somewhat as though two salts were in solution. If from these a new salt can be formed which alone of the four possible combinations is capable of escaping by osmosis from the solution, that salt will be formed and escape until all its constituents are gone. Not so if it cannot be removed—it will be formed until a balance is reached and then all interaction will cease.

This is different from the cessation of metabolism which follows section of the nerve, but it is equally capable of exposing the cell to continued, if gradual, breaking-down processes.

Pressure.—Continuous pressure, if applied to sensitive tissues firmly enough, may cut off the entrance of blood completely so that the tissue dies. This is the fate of the skin and underlying tissues in the formation of bedsores or "decubitus ulcers" in bedridden and emaciated persons whose tissues are already poorly nourished. Where their prominent bones touch the bed, the skin is kept pressed bloodless and quickly dies. But if the pressure is less violent, the cells of the tissue dwindle away slowly. This is once more a question of inadequate nourishment,

for not only are the blood-vessels partly closed, but the cells themselves are compressed, so that absorption of nutriment and the carrying on of their functions sink to a low ebb.

This is seen particularly well about a tumor-nodule growing in such an organ as the liver—all the surrounding cells and capillaries are flattened and gradually disappear.

One might expect the accumulated food-stuffs, such as fat-globules, to disappear first, and after that the cell-body itself, but it appears that if the cell is caught with

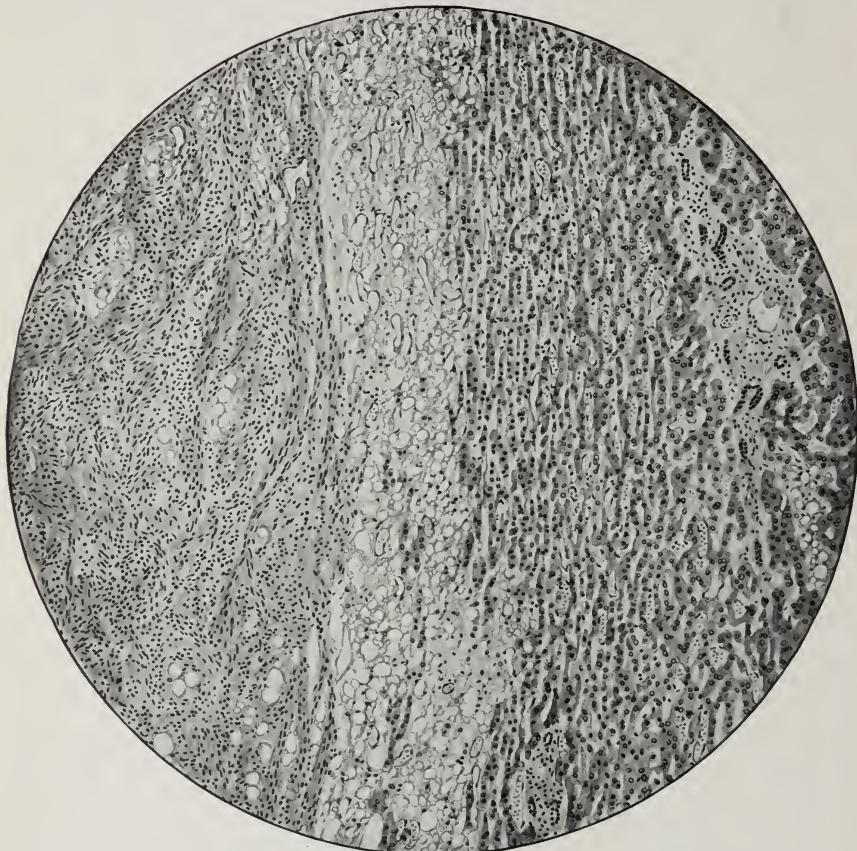


Fig. 34.—Compression of liver-cells about a metastatic tumor-nodule.

fat-globules in it, it may be unable to use them up before it itself is quite disabled, perhaps by lack of oxygen. Therefore the liver-cells immediately next to the advancing tumor-nodule may be loaded with fat, though most exposed to pressure (Fig. 34).

The effect of pressure in distorting and perverting the growth of tissue is seen in the misshapen heads of some French peasants and certain Indians, in the crippled feet of the Chinese women, and the constricted livers of the fashionable white women of past generations.

Another example commonly adduced is the effect of aneurysms upon the tissues upon which they impinge. Soft tissues yield in front of them—hard tissues, like bone, are hollowed out before them. But I cannot believe that this is merely a pressure atrophy, for one finds the bone actually comminuted, as though with a hammer, and the fragments bathed in blood and attacked by great phagocytic giant-cells (osteoclasts). In the vertebral column the centra of the vertebrae are thus excavated, while the invertebral discs project unchanged (Fig. 35).

Decreased blood-supply is commonly held to be a prominent cause of atrophy without questioning more closely the nature of the examples that are always presented. Decreased blood-supply does occur in re-

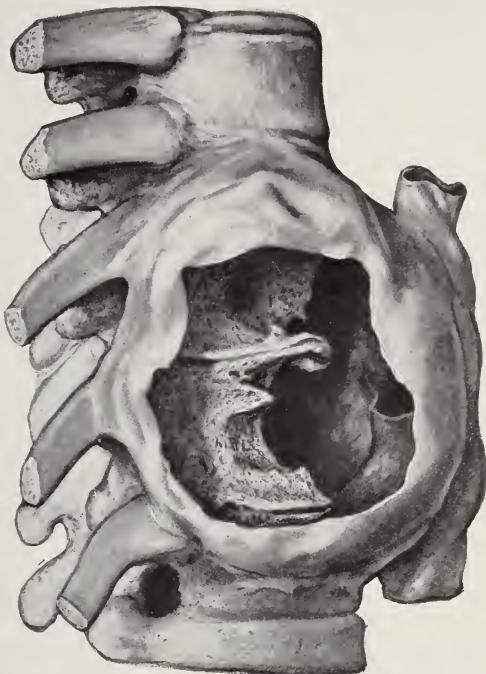


Fig. 35.—Destruction of vertebrae by aneurysm. Dried specimen with aneurysmal sac *in situ*.

gions or organs which we find in a state of atrophy, but it must be asked whether it is cause or effect. The blood-supply may be decreased by pressure on the supplying artery, or by contraction of the vessel or the narrowing of its lumen by abnormal thickening of its wall.

If effective occlusion of the vessels occurs rapidly, the tissue dies—if gradually, a collateral or roundabout circulation is developed and no effect is produced.

Probably such a situation as is found in the kidney in which arteriosclerotic narrowing of the blood-vessels limits the blood-supply without recourse, could be most satisfactorily given as an example of atrophy of the tissue from this cause, although, as in the senile ovary

or uterus, in which the arteries become gradually obliterated, the wasting of the kidney might be explained otherwise.

In a kidney recently observed there were two supplying arteries, one of which had long been occluded by a thrombus. That half of the kidney was shrunken, in sharp contrast with the other half.

Hypertrophy and Hyperplasia.—Both terms imply an increase in the bulk of a tissue, but hypertrophy is used to indicate an enlargement and strengthening of an organ brought about by increase in the size of its elements. Hyperplasia, on the contrary, is the result of an increase in the number of these elements or cells. Nevertheless it is sometimes difficult to determine except by exact enumeration of the cells, as in the case of hypertrophy of the heart wall, whether the increase in the bulk does not represent both processes.

Hypertrophy has often the character of physiological growth in response to the free functioning of an organ and its consequently improved metabolism. One might look in this way upon the muscles of the practised athlete. In a different sense there is hypertrophy in the uterine wall in the course of pregnancy.

But from the point of view of the pathologist, hypertrophy is usually the response to some abnormal strain, as in the case of the great thickening of the heart wall when its function is made difficult by obstruction or by whatever causes heightening of the blood-pressure. In all these cases it seems to be a work hypertrophy. No sharp distinction should be drawn between hypertrophy and hyperplasia, because the same causes, usually the demand for extra work, give rise to the enlargement of organs through the increase in the number of their constituent cells. The distinction is a futile one at any rate, since, as a rule, both are involved. A compensatory enlargement of the kidney when the other is destroyed is due to an enlargement of the tubules and glomeruli, but that is only possible through an increase in the number of lining cells.

Numerous instances will be given later in which the destruction or disabling of portions of the tissue of organs is followed by a new formation of equivalent tissue somewhere else in the organ. This is compensatory hyperplasia; it is also regeneration. The organ in a broad sense undergoes, as far as its units go, a compensatory hypertrophy, and becomes once more able to perform its full function. It is seen from this that the terms must continue to be used rather loosely, and it must be realized that in attempting to understand the processes themselves we are brought face to face with the problems of the causation of tissue growth in general.

Whether other impulses than the demand for functional activity can initiate growth is still unknown. The long-standing dispute between the followers of Weigert, who declared that the new formation of tissue might occur only when injury or the production of some defect had disturbed the normal equilibrium, and those who maintained that external stimuli of the most various sorts could occasion new growth of tissue, still persists. In practically every case arguments can be brought to prove one side or the other, and, indeed, it seems that it is chiefly

owing to our lack of precision in defining the nature of the stimuli that we find difficulty in arriving at a conclusion. To say that disturbance of equilibrium is a cause of new growth is to employ a vague expression which may indicate a condition many steps removed from that which is actually at work. So, too, the analysis of the action of chemical or physical stimuli is generally incomplete and stops far short of the point at which they actually influence the cell. When, for example, we say that an extensive haemorrhage stirs the bone-marrow cells of reproduction of red corpuscles, it is easy to say that equilibrium between the blood and blood-forming tissue is disturbed, but it is quite as possible that chemical substances formed somewhere because of inadequate transportation of oxygen or disturbances in the relation of acids and bases from incomplete removal of carbon dioxide directly affect the bone-marrow and stimulate it to new formation of cells.

CHAPTER VI

DISTURBANCES OF FAT METABOLISM

Neutral fats and lipoids. Their source, absorption, distribution, and functions.
Pathological disturbances.

If we attempt to discuss the disturbances of metabolism in their relation to pathology, we must remember that the methods of pathological anatomy which show alterations in the tissues consisting of destructive changes of the cell structure, on the one hand, and accumulation of the materials concerned in metabolism, on the other, must give us only the most incomplete and even misleading idea of what is taking place. Many of the protein or albuminous materials are in solution and invisible, and even when we make them visible by coagulation, it is impossible to recognize them definitely. The same thing is true of the carbohydrates, since glycogen is the only form that we can demonstrate histologically. Sometimes we can see fats and lipoid substances, but rarely when they are in the form in which they take part in the actual function of the cell—rather it is when they are stored and inactive, or when they are thrown out of the current of the life of the cell as stagnant material, that they can be seen. Indeed, we are doubtless wrong even in trying to consider proteins, fats, and carbohydrates separately, for in their relation to the processes of life they seem to combine into the really important substances with which we are only indirectly acquainted. Fat we know as it appears in adipose tissue or in globules in other cells, but fat in what may be a lipoid proteid combination as it exists invisible in the cell and recoverable from it only after the cell is reduced to débris by digestion, we scarcely know, although it is probably in that form that it is most important.

It seems that in these combinations, varied as they are, we may find the agents of many of the extraordinarily efficient chemical processes that go on in the body. This should be the ground for discussion in pathology. It should form one of the principal chapters, if we only knew enough to bring it into the field; on the other hand, it seems hardly worth while to describe in detail the various places where abnormal accumulations of some of the inert separated constituents of these specialized expert bodies are laid up so that we can see them.

If we could do more than guess at the nature of most of the disturbances that wreck the machinery and heap up the raw material or the slag, it would be something, but even that is commonly obscure. Nevertheless, we must tell what we can with our surmises about the true inwardness of the actions which have left these traces.

Of all these substances, as long as we have been in the habit of separating them into three great classes it has been the custom to regard the proteins as the most important, the real basis of life, the sub-

stance of protoplasm, while the fats and lipoids or fat-like materials were looked upon as fuel and as useful in other vaguely understood ways, possibly as insulating materials in the nervous system or even as padding underneath the skin to keep the body warm. Carbohydrates seemed essentially fuel for rapid burning; now, however, in Ivar Bang's phrase, the lipoids are beginning to be recognized as actors of extreme importance, with rôles of unsuspected delicacy and complexity. Even yet the carbohydrates have not met with what may be a deserved recognition, but it is becoming clearer that it is the ensemble action, and not the part played by the isolated fragments, which we salt out or extract with ether, that brings about the wonders of life.

FATS AND LIPOID SUBSTANCES

The fat-like bodies soluble in organic solvents, such as ether, alcohol, chloroform, or benzol, are defined by Bang as lipoids. It is perhaps common, however, to speak of the neutral fats as fats, and of the rest as lipoids, since that must have been the origin of the word.

Of this great group there are almost innumerable examples, and the series may perhaps be extended to forms as yet unsuspected, but in human physiology and pathology comparatively few concern us.

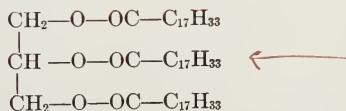
These are as follows, according to Bang:

1. Fats—lipoids of the aliphatic series containing only C, H, and O, without N or P.
2. Cholesterines—lipoids of the aromatic series containing only C, H, and O, without N or P.
3. Phosphatides—lipoids containing N and P in addition to C, H, and O.
4. Cerebrosides—lipoids containing N but not P, together with C, H, and O.
5. Other important but little understood lipid substances, which include the lipochromes.

The details of what is known chemically of these substances must be read in such works as those of Leathes, Bang, Jolles, and others, and only the barest outline can be given here.

Fats.—These, which form the great bulk of the subcutaneous and other depot fat, are esters of glycerin with fatty acids. For the most part those which occur in the animal body are triglycerides of stearic, palmitic, and oleic acids, but in certain secretions, as in milk, butyric, caproic, and other fatty acids occur.

A typical formula is as follows:



which is triolein.

The difference in their melting-points and other characters, and in the proportions in which they occur in the fat of different animals, are all well known, and one realizes that if sheep-fat is more solid at room temperature than human or dog fat, it is because it contains more tristearin and tripalmitin and less triolein.

Such fats may be saponified or broken up by the action of alkalies into glycerol and soaps, or combinations of the alkalies with the fatty acids. In another way they may be separated into their constituents, glycerol and fatty acid, by the action of a ferment (lipase), and this action is reversible.

The cholesterines occur in wide distribution throughout the body as constant constituents of the cells and body fluid, either free or in combination with fatty acids (cholesterine esters), often in solution, but sometimes, as in the adrenal cortex, in the form of globules. Crystals of free cholesterine are found under pathological conditions. The formula for the cholesterine found in the human body is given as $\text{C}_{27}\text{H}_{46}\text{O}$. It is a complex terpene, bearing no relation to fats, carbohydrates, or

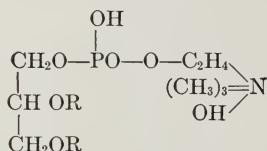
proteins, but consisting probably of a saturated cyclic system with the character of a secondary alcohol, since it can form ketones, and also with fatty acids, esters. It crystallizes in flat, rhombic plates which often show broken or reëntrant angles.

The phosphatides are of the very greatest biological importance, and enter extensively into the structure and function of many organs. They fall into the following groups (Bang, Thudichum, Aschoff):

1. Monoaminomonophosphatides (lecithines, cephaline) (glycerophosphoric acid esters of two fatty acids and choline).
2. Monoaminodiphosphatides (cuorine, etc.).
3. Triaminodiphosphatides (sahidine, etc.).
- All of these contain unsaturated acids. Of the phosphatides containing saturated fatty acids we have:
4. Diaminomonophosphatides (sphingomyeline, etc.).
5. Triaminomonophosphatides.

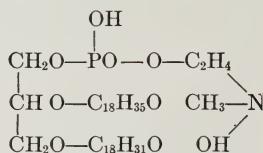
Of these substances, the knowledge is essentially vague, since practically none of them can be obtained in a pure state, partly on account of their labile character. The best known are probably the lecithines and cephalines, although they too are enveloped in a haze of uncertainty, and one cannot say whether these fragile substances which are strained out of the brain and other organs ever existed there in the form in which they come to light.

Lecithine, which forms sticky, waxy white or orange masses, is given the formula:



That is a glycerophosphoric acid ester of two fatty acid radicles (one of which is unsaturated) in combination with choline. It is soluble in alcohol and other lipid solvents except cold acetone; it units with acids and bases, with carbohydrates and with proteins (vitelline, lecithoalbumin).

Kephaline is a resin-like, crumbling, hygroscopic substance, soluble in ether, etc., but not in alcohol or acetone. It is the chief phosphatide of the brain, and is otherwise widely distributed. Bang gives the following probable constitution:



which is a glycerophosphoric ester of stearic and linoleic acids with a monomethyl-choline.

The Cerebrosides.—These are glucosides, and being disintegrated, yield a sugar, galactose, fatty acids, and a nitrogenous substance, but no phosphoric acid. They occur in the white substance of the brain, the blood, spermatozoa, etc. The most important are perhaps the phrenosin and kerasin of Thudichum.

The other little understood lipid substances, which include the pigmented fatty granules found in wasting cells (lipochromes), and probably various substances concerned in immunity, remain to be investigated.

It has been said that these substances are sometimes recognizable as such (neutral fats, cholesterol esters, etc.), but most of them are extracted from the organs by the aid of various solvents, and freed from impurities by different chemical manœuvres. It is, therefore, hard to feel sure that in the living organs they exist in the form in which

they are finally studied and not rather in some easily disturbed combination with proteins or other substances. Some of them are readily dissolved out of the cells, in which they can be seen as globules of pure fat; others appear to be loosely adherent or adsorbed in fine, invisible layers about other substances in the cells. They can be extracted too without great difficulty, although they cannot be seen with the microscope in the cell. Still others are so firmly held that they seem to be in chemical combination with the materials of the cell, and these, naturally invisible in the cell, can be extracted only after its tissue is digested or hydrolyzed so that its chemical compounds are disintegrated. That there is constant change in their relations is indicated by the way in which the simpler fats undergo lipolytic decomposition into glycerin and fatty acids, followed by the formation of soaps, their decomposition, and the reconstruction of fats.

As Aschoff says, the pathological anatomist is most interested in determining in what form these lipoid substances become morphologically visible, and by what means their specific composition can be recognized. The chemist, on the contrary, must be content with analyzing the lipoids which remain to him after his tortuous methods of extraction, separated thus by a gulf from their original relations, and perhaps even entirely changed in their characters. It is the biologist who must try to combine these two sets of information and attempt to learn the functional rôle which the lipoids play in the body.

The anatomist applies with success certain methods to the study of fats in the tissues. There are stains which color all lipoids, such as sudan, others which stain neutral fats red, phosphatides blue, such as Nile-blue sulphate; osmic acid is blackened by fats of unsaturated acids; cholesterine esters are doubly refractive. Phosphatides and soaps form bizarre myeline figures, and so on. Great ingenuity has been applied to the recognition and distinction of fatty bodies by these methods (which must be read in the works of Aschoff, Kawamura, Versé, and others), but they are still very imperfect and unreliable, except in the simplest situations.

It is pointed out by Kutschera-Aichbergen that the attempt to recognize different lipoids by their staining properties is open to gross error if these staining properties are established by staining pure substances (Kawamura). They stain quite differently, if at all, in the tissues. Acetone will remove neutral fats and cholesterine and the acetone soluble phosphatides. After that tissues which still contain lecithins, cerebrosides, etc., give no stain whatever to indicate the presence of these substances. It is evident that our ability to analyze the lipoids in tissues by staining methods has been greatly over-estimated, since the lipoids which are soluble in ether or alcohol but not in acetone cannot be stained at all.

SOURCE, ABSORPTION, TRANSFORMATION, AND DEPOSITION OF FATS

Since similar substances occur in the tissues of other animals, it is probable that a great source of the fats in the human body is to be found in animal food. Some are derived from vegetable foods, and

others are produced in the body from carbohydrates, and since carbohydrates can be formed from the decomposition products (amino-acids) of proteins, no doubt fats are thus indirectly derived from proteins.

Taken into the intestine, the absorption of fats occurs by the action of lipolytic ferment, which produce glycerin and soluble soaps, which are reconstituted into fats in the intestinal wall, or by direct passage of unchanged fats, perhaps with the aid of the bile. Whether in the reconstitution in the intestinal wall the foreign fats are remoulded into human fats is uncertain. Undoubtedly, some foreign fats go through unchanged to the tissues, but since the fats of animals are characteristic, the remoulding must take place somewhere, possibly in the course of numerous decompositions and reconstitutions which accompany the wanderings of fat in the body. It appears that the sterols characteristic of plants are not absorbed in the intestine, nor utilized even if injected intravenously. Cholesterol, on the other hand, is synthesized in the body of mice on bread or bread and fat diet in which the fat seems to have no effect. Thus, synthesis occurs only when there is need for cholesterol and there is constant breaking down and excretion of any excess in the tissues (Schoenheimer). The cholesterol introduced into the intestine is absorbed, appearing in the intestinal lymphatics as a mixture of cholesterol and cholesterol esters, so that there must be a fermentative action in the intestinal wall. It is stored in various tissues, adrenal cortex, liver, spleen. The student should read the excellent review of the complicated question of cholesterol metabolism by Gainsborough. The advent and transformation of phosphatides and cerebrosides are even more obscure.

LITERATURE

- Frohlicher u. Stüllmann: Biochem. Ztschr., 1934, cclxxiv, 21.
Gainsborough: Proc. Roy. Soc. Med., 1935, xxviii, 989.
Heinlein: Ztschr. f. d. ges. Exp. Med., 1933, xci, 638.
Lundgren: Science, 1935, lxxxii, 130.
Schoenheimer and Breusch: Jour. Biol. Chem., 1933, ciii, 439.

Distribution in the Body.—Neutral fats are, as every one knows, lodged, sometimes in enormous quantities, in what are roughly known as fat depots, among which the subcutaneous and intermuscular tissues, the bone-marrow, the mesentery, omentum, and retroperitoneal tissues, the epicardium, the tissue about the kidneys, and the tissues of the orbit furnish examples. In very obese persons the fat, after filling these places to their utmost, seems to overflow into the most unexpected localities—adipose tissue extends through the wall of the heart and appears under the endocardium; it pushes apart the lobules of the pancreas, and even spreads round to the free surface of the intestines. In every case the fat is inclosed in cells. In the infant one may readily observe that the adipose tissue falls into lobules which are easily separated. These are seen to be sharply outlined, gland-like structures, provided with an extremely rich capillary circulation, and composed of polygonal cells with very granular protoplasm which contains only the beginnings of the accumulation of oil-globules which will ultimately

distend them (Fig. 36). Such lobules are quite distinct from the surrounding loose connective tissue, which contains no fat, and are very conspicuous in any section which passes through adrenal or thyroid since a comparison with those glands is at once suggested. They have even been described by Pende as organs of internal secretion, and perhaps the specificity of the adipose tissue is almost sufficient to justify him in such an idea. In later life they disappear because so much fat gathers in their cells that the protoplasm becomes a mere film about

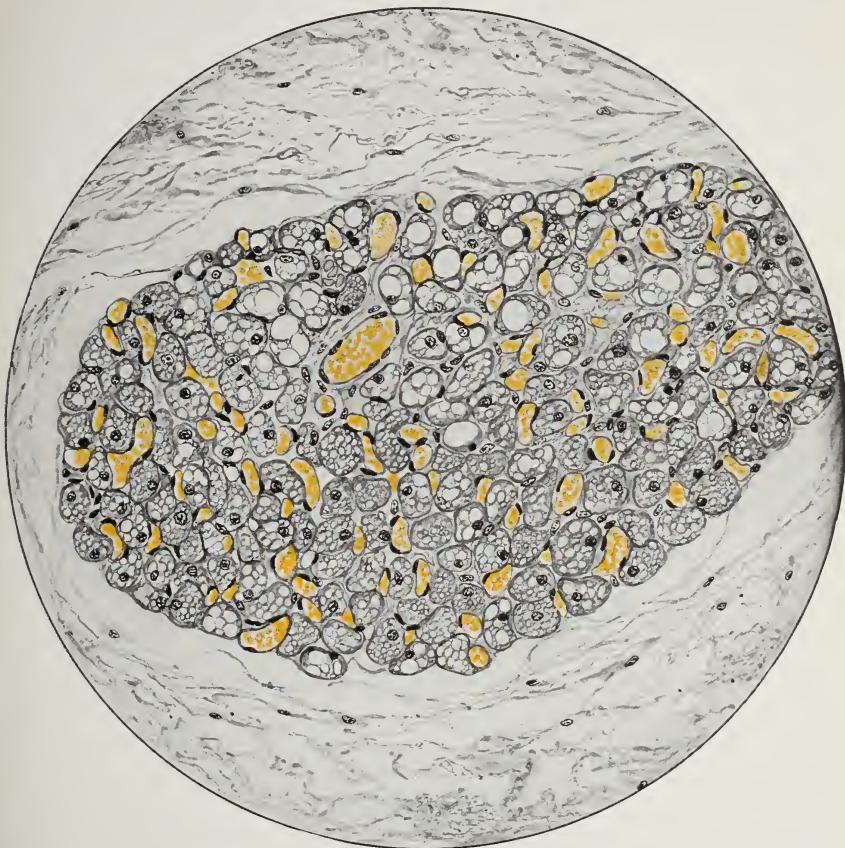


Fig. 36.—Adipose tissue of fetus. Lobule of specialized connective tissue in which fat accumulates.

the great oil-globule—the separate lobules of this tissue swell until they touch one another, the intervening fibrous tissue is lost to view, and we seem to have a homogeneous adipose tissue.

It would be interesting to be able to show that all adipose tissue is of this nature, but probably in obesity fat accumulates in other connective-tissue cells which have no specific relation to its metabolism.

Cramer recognizes as brown fat certain lobules of adipose tissue, especially readily seen in rodents, which contain a preponderant amount

of lipoid materials as contrasted with the ordinary neutral fats. These he thinks have a more specific importance than the general adipose tissue and retain their fat when in hunger the neutral fats waste.

Neutral fat occurs in the blood plasma and in the lymph and chyle, and thus indicates the mode of transport from one part of the body to another, and from the digestive tract to the tissues. It is found in the cells of many parenchymatous organs, such as the liver, adrenals, and others, where it may be merely stored, or where its presence may be explained in other ways which will be discussed later.

There seems to be little evidence to show that such neutral fats, aside from being foods and the source of energy, play any very complex part in the life of the cell. On the contrary, although we do not know exactly how they are distributed in the tissues, we cannot escape the impression that the phosphatides, the cholesterine compounds, and cerebrosides are absolutely essential elements in most of the important functions of the cells. Each new investigation reveals their silent and unsuspected participation in the most fundamental processes.

It is known that even when the microscope, aided by the most effective staining methods, reveals no trace of fat in the tissues, a large quantity can be extracted by chemical methods. A perfectly normal human kidney which shows no recognizable fat yields 10 to 20 per cent. of its weight upon digestion and extraction. This fat must have been in some extremely fine state of division, or else in chemical combination, such that it failed to give the usual staining reactions.

None of the hypotheses about this disposition of lipoids in the cell has up to now been satisfactorily proved, and they are the subject of much dispute. It is Overton's idea that each cell is bounded by a very thin lipoid membrane which controls the entrance and exit of the substances which reach the cell. According to this idea, drugs like narcotics, which are usually soluble in fats, gain easy access to the cell, although it does not appear quite easy to understand how these substances leave the lipoid membrane to enter the watery cell-body. On the other hand, the passage of salts in and out becomes difficult, and the theory is forced to resort to the vital activity of the cell to explain these things. Nevertheless, the idea of a lipoid enveloping membrane for cell and nucleus is very generally held.

Within the cell similar lipoid membranes are supposed to line vacuoles and perhaps to cover some of the specific granules—at any rate, there is much to show that the fine globules of fat which appear in the cell protoplasm do so in relation with mitochondria, or, as Benda claims, rather with the vegetative granules, the plasmosomes. These granules accumulating fat about them finally take on the form of globules. But even with these explanations it is evident that there must be much lipoid material in the cell in an invisible form.

FUNCTIONS OF FATS AND LIPOIDS

The most obvious and best known function of the fats lies in their acting as food-stuffs. In their oxidation to set free energy in the form of heat or work, they require more oxygen than do carbohydrates, so

that the respiratory quotient or ratio, $\frac{CO_2}{O}$, is about .795. They form, of course, since they can be conveniently stored, the ideal material for the accumulation of a source of energy. Nevertheless, we must suppose that they also take part in aiding the growth of the tissues through furnishing material for their constructive processes.

If it be true that they form lipoid membranes about each cell, each nucleus, and each vacuole, it must be agreed that they are primarily instrumental in regulating the assimilation of the cell and in permitting it to control in a way the substances which present themselves for absorption.

The part played by lipoid substances, especially the phosphatides and cerebrosides, in the construction of the nervous system, must be of prime importance, although we approach its contemplation so awkwardly by extracting them from the ground-up brain. From their arrangement in the myeline sheaths of the nerve-fibres, it would appear that they may act as insulating substances which insure the passage of the nervous impulse to the correct end-organ; in other words, that they serve a purpose analogous to that of the rubber and shellac in a complex electric cable, or even in the brain, to that of the more elaborate insulation in the interior of the dynamo.

In their relation to enzyme action the neutral fats are played upon by lipases which occur everywhere in the organs and fluids of the body, as well as in the digestive juices. Anti-lipases which inhibit this reversible action exist also. The lipases which must exist to control the decomposition of cholesterine esters and of the phosphatides (lecithinase, cholesterase, etc.) are not yet even certainly demonstrated. Bang objects that experiments carried out to show that such lipoid substances may influence the action of other ferments are inconclusive, but Jobling has shown that the decomposition products of some fats—unsaturated fatty acids and their soaps—have the most decisive inhibiting action upon proteolytic ferments, their power being in a sense proportional to the degree of unsaturation of the fatty acid. So universally is it true that such unsaturated fatty acids can impede the action of proteolytic ferments that many pathological conditions (such as the persistence of caseous tuberculous material in its solid form) can be shown to be due to their presence. If they are rendered impotent by saturation of their unsaturated group with iodine, the proteolysis goes on rapidly and the caseous tubercle or gumma rapidly softens.

In the complex process which occurs in the clotting of blood Howell has shown that the thromboplastic substance derived from the tissue is a lipoid, kephaline. It has been shown that certain lipoid substances, especially cholesterine, can act as inhibiting or neutralizing agents toward such haemolytic poisons as saponin, cobra poison, etc., through forming with them an innocuous compound. Hanes showed that the relative immunity of puppies from chloroform poisoning is due to the large amount of cholesterin esters in their tissues. When artificially introduced into the tissues of adult animals a similar protection is

conferred. In the so-called Wassermann reaction lipoid substances, essentially aminomonophosphatides (lecithin, etc.), soluble in alcohol and extracted from heart muscle, are used with the syphilitic serum to combine with the complement and thus withdraw it from the completion of the haemolysis of sensitized corpuscles, as would occur if the serum were not from a syphilitic. Cholesterol intensifies this action of lecithin.

Our knowledge in this direction is very slight; nevertheless it is enough to suggest the possibility that lipoid substances may sometimes accumulate in an organ for the protection of the cells of that organ from toxic injury. On the other hand, lipoids may act as toxic substances or as activators of toxins. Of these, the toxic ones are foreign lipoids, such as may be extracted from bacteria. The fats from the tubercle bacillus may produce lesions somewhat resembling those caused by the organisms themselves. It is in connection with haemolytic poisons, such as cobra venom, that lipoids (lecithin) are found to behave as activators. Regarded at first as representing the complement according to Ehrlich's theory (Kyes), it now seems more probable that the lipoids may aid in transferring the poison to the cell, since the "lecithid" is apparently only a solution of the venom in lecithin (Bang). The direct production of immunity against lipoid substances used as antigens has given some vague results, but the matter still remains to be investigated.

Undoubtedly the lipoids fill an important position in many ways, in relation to the processes of immunity, but for the further discussion of the matter reference must be made to works upon that subject (Jobling).

Cholesterine compounds are known to exist in the circulating blood and in the adrenal cortex, as well as in other tissues. What must be a significant index of their importance is found in the course of pregnancy, when there comes a gradual but great increase in the quantity found in the blood, a great storing in the corpora lutea, and, with the end of pregnancy and beginning of lactation, an outpouring of cholesterine esters with the first milk. After that the proportion decreases in the milk, and in the blood sinks back to normal. Why this should be is not known, but the flooding with cholesterine esters seems to have a protective influence of some kind, since under those circumstances animals will survive the loss of the adrenal gland far longer than non-pregnant controls, and, indeed, the injection of cholesterine esters seems to have the same influence (H. A. Stewart).

LITERATURE

Browning and others: Jour. Path. and Bact., 1910, xiv, 484.

Kolmer and Richter: Amer. Jour. Clin. Path., 1934, iv, 235.

Stewart, H. A.: 17th Internat. Cong. of Med., London, 1913, iii, 173.

PATHOLOGICAL DISTURBANCES OF FAT

So far we have attempted to review the normal relations of the lipoid substances in the body, and finding our knowledge so woefully incomplete there, we turn not very hopefully to their study under pathological conditions.

Obesity.—From what was said of the normal use of fats as food we may judge that a certain balance is maintained in the storehouse of the body. Nevertheless, the consumption of a great excess, especially an excess of fats and oils and of carbohydrates, tends, in persons who lead an inactive, sedentary life, to cause the accumulation of excessive fat in all possible depots in the body. Even the secreting cells of parenchymatous organs, such as the liver, become somewhat richer in fat than normal, although it is by no means in obese people that one finds the great collection of fat in the liver-cells. The storing-up of fat can be prevented and the fat made to disappear by active exercise, massage, etc., or even by hot baths, which seems to hasten its consumption. But every one has noticed that the obesity which comes from mere sedentary habits and overeating is in most persons a mild kind of disability; other people, even with the greatest abuse of these things, remain quite thin, while there are certain unfortunates who, in spite of efforts to limit their diet strictly and to take abundant exercise, grow enormously fat. It seems possible that in these cases there may exist some defect in such organs of internal secretion as the thyroid or the hypophysis, whose secretion appears to enhance the activity of metabolism in general. In known cases of hypophysis defect in young persons great obesity arises with retardation of sexual development, and in cases in which the thyroid has been destroyed a similar, if less extreme, obesity may arise.

Diabetes.—In pancreatic diabetes another disturbance of internal secretion in which the consumption of carbohydrates is made difficult, an abnormally violent attack is made upon the fats, which are turned into the blood-stream for transportation in such a way as to give the serum a milky appearance (diabetic lipæmia). The irregular consumption of these fats leads to the production of the poisonous acetone bodies. (See Diabetes.)

Degeneration of Nerves.—It has been pointed out that lipoid bodies form the coatings of nerve-fibres, as though to insulate the axis-cylinders within these myeline sheaths. When the nerve dies through being cut through or from the destruction of its cell-body, the lipoids of the myeline sheath about the dead axis-cylinder disintegrate, leaving globules of the decomposition products which now blacken with osmic acid in a way foreign to the myeline itself (Figs. 37 and 38). Saponine attacks and combines with the lipoid sheath of the nerve and causes paralysis. Many other substances, most of which have certain affinities for lipoid materials, cause injuries to the nerves, followed by inflammation or by paralysis. Lead palsy, arsenical and alcoholic neuritis, the neuritis occurring in the intoxication associated with pregnancy and in diabetes, are examples of this vague connection. Beriberi, a form of multiple neuritis, is supposed to result from the lack of a lipoid constituent belonging to the covering of the rice grain, since it occurs in persons fed on polished rice. This is not yet satisfactorily proven, but all these things point to the possibility of a common character in the affection of nerves due to disturbances in their medullary sheaths.

Anæmias.—The same vagueness and uncertainty prevail with regard to the part played by the lipoids in the production of some forms of anaemia. Faust and Tallquist thought that the pernicious type of

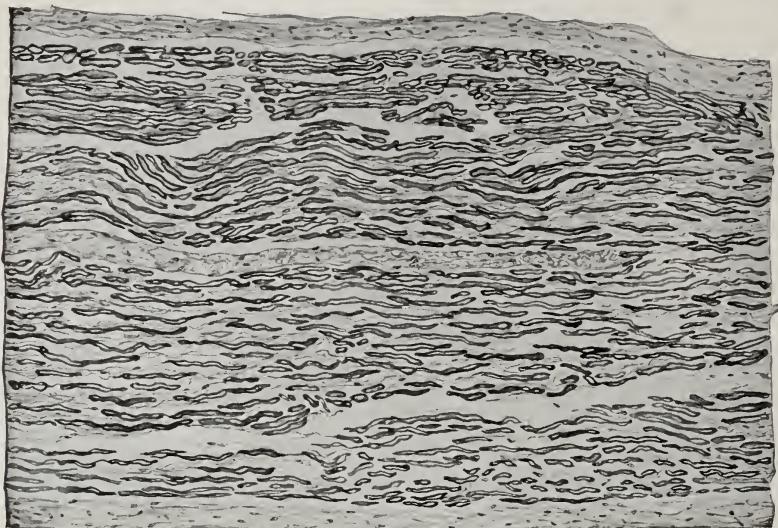


Fig. 37.—Normal nerve. Osmic acid (Marchi) tinges the myeline sheaths gray.

anaemia caused by the bothriocephalus was due to a lipoid which they later stated to be oleic acid, but this is scarcely probable. On the other hand, many of the toxic materials which produce anæmia, such as ben-

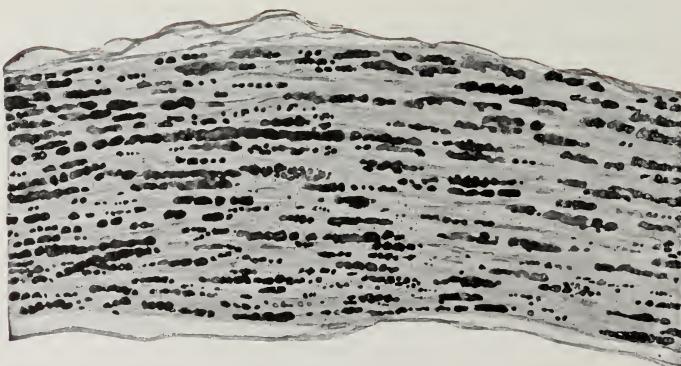


Fig. 38.—Degenerated nerve (Marchi). Lipoid medullary sheath reduced to fat-like globules which stain black with osmic acid.

zole, are solvents of lipoids or soluble in them, and it may be through this relation that the lipoid constituents of the red cells are attacked. The whole question of haemolysis has intimate dependence upon the lipoid content of the cells.

Abnormal Accumulations of Fats and Lipoids in Organ Cells.—One type of evidence as to the rôle of the lipoids in pathological conditions which has scarcely been touched upon is found in the anatomical recognition of abnormal accumulations of these bodies in the cells of the organs. This, which has always formed the chief interest of pathological anatomists, is, after all, at most only an indication of the disability or injury of those cells, and has relatively little bearing upon those functions of the lipoids which are beginning to show themselves as of fundamental importance.

Both neutral fats and globules or granules of other lipoids, especially the cholesterine esters, and probably also the phosphatides, may appear

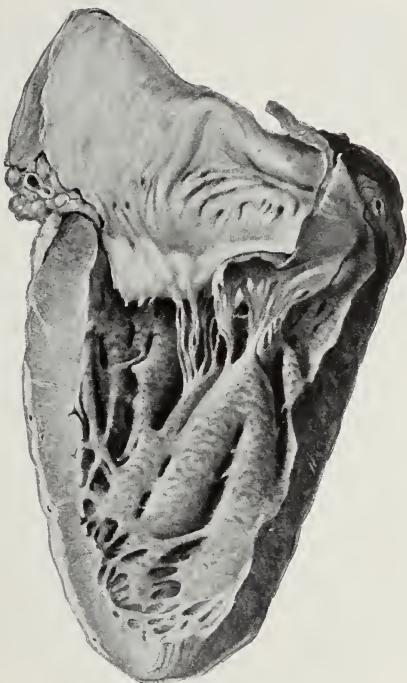


Fig. 39.—Fatty heart, showing motting of myocardium.

in abnormal situations. Since they are normally present in some organs, we recognize their abnormal character by their unwonted situation or sometimes by their quantity.

The source of these fats has long been the subject of dispute, the main question being whether they are derived from the substance of the cell in which they are found, or transported thither from some depot of fat or other source. This problem has lost much of its interest, since we have learned that much of the fat is transported, while some is made visible (fat phanerosis) by being liberated from its invisible combinations in the cell. The old question as to the production of the

fat-globules at the expense of the protoplasm of the cell is now hardly discussed in that form.

A few examples of such fat accumulation may be mentioned before considering further the nature of the process.

In the heart one may find, in cases of long-standing anaemia, or chronic infection, or intoxication, or in disturbances of the coronary circulation, especially in the inner layers of its muscle, a yellowish pallor which, on close inspection, is found to be due to innumerable minute streaks and patches of opaque yellow which shine through the endocardium and give the checkered appearance which has long been called



Fig. 40.—Fatty heart muscle. Fat-globules in fibres stained with osmic acid.

tigering or the faded-leaf appearance (Fig. 39). Ribbert thinks that the patches correspond with minute irregularities in the distribution of the capillary blood supply, and that local anaemia produces them. Microscopically it is found that the yellow patches show heart muscle-fibres in which myriads of minute globules, ranged in transverse and longitudinal rows, lie in the sarcoplasmic discs (Fig. 40).

In the liver, where there is normally some fat in the cells, various conditions can arise. The whole organ may be enormously enlarged, yellowish white, with swollen round edges, and on section greasy to the touch, rigid, and inelastic. In such a liver almost every cell is found

stretched with one or more globules of fat, so that the nucleus is flattened to one side and only a thin film of protoplasm remains. In others fat is found about the efferent vein, in the middle zone, or about the portal veins, but not with such sharp consistency that one can well associate these forms of distribution with different ætiological factors. Whenever there is a destructive lesion of the liver-cell, as in chronic passive congestion or focal necrosis involving part of each lobule, fat generally accumulates in the cells just adjacent to the injured cell, and therefore usually between them and the portal vein radicle. Sometimes the fat is in large droplets, sometimes in small ones or granule-like particles. Probably these arise differently, but they can surely not be made the basis for declaring, as Virchow did, that the first indicate a physiological infiltration, the second a "fatty degeneration," in which the fat is produced at the expense of the cell-body. Wolff shows that sudden hunger causes the appearance of fat in the cells and so, too, does feeding with an excess of fat. In both cases the cells may soon regulate themselves in spite of the fat brought to them and return to their normal appearance.

In the kidney, fat-globules collect in the epithelium of the tubules, most often in the convoluted portions and in the glomerular epithelium, but appearing also in the conducting tubules (*cf. Fig. 23*). They lie usually near the base of the epithelial cells at first, but later, when the quantity is greater, they may occupy most of the protoplasm. Such fat is sufficient to give a very opaque yellow color to the labyrinthine portions of the renal cortex, and in much scarred and distorted kidneys it is seen in patches where the tubular tissue is best preserved.

In the aorta and smaller arteries which are the seat of arteriosclerotic processes fats accumulate in the intimal thickenings and give them their opaque yellow color.

But it is impossible to refer to all the situations in which the cells may thus be the lodging-place of abnormal fats. Somewhat different in principle are those collections of fat which form in the living tissues around foci of necrosis in the brain, in which multitudes of phagocytic cells are found loaded with globules of fat derived from the disintegrating brain substance. These are analogous to the fat-laden zones of tissue about infarctions or abscesses or in the neighborhood of tuberculous lesions which have destroyed much tissue. The cells bordering upon a growing tumor are laden with fat, and so are those whose nutrition is affected in any other mechanical way by the cutting off of the blood supply. Even the malnutrition which comes in company with general anaemia, such as pernicious anaemia, brings with it extensive stagnation of fat in all the organs.

Not all this fat is alike chemically or physically. Nearly always there are globules of neutral fats, but in the kidney, in the sclerotic plaques of the aorta, in the desquamated epithelial cells of the alveoli adjoining tuberculous lesions in the lungs, in the phagocytic cells about infarcts of the brain, and in a thousand other places, many of the globules have a different nature. They shine dully; under the polarizing microscope they show a brilliant outline; on heating they disappear;

on cooling again they start back into view suddenly as brilliant, round, doubly refractive globules, showing a Maltese cross of light. These are chiefly cholesterine esters and have the characters of the *myeline bodies* described by Virchow (Adami). Cholesterine crystals are often associated with them, and probably various soaps, although these must be of a rather evanescent character. Whether combinations of phosphatides and cerebrosides occur in these places too, our present technical methods do not reveal clearly, but by methods of fractional extraction it has recently been shown that certain phosphatides (lecithins, etc.) do exist in considerable quantity in such places as the atherosclerotic plaque. For this reason it seems inaccurate to emphasize, as Aschoff and others have done, the occurrence of degenerative changes in cells accompanied by the lodgment of two distinct types of fatty substances, glycerine esters and cholesterine esters. Doubly refractive globules usually contain cholesterine esters but are not exclusively composed of them (Kutschera-Aichbergen).

What explanation can we offer for the accumulation of these fatty bodies in the cells? Briefly, the results of the long discussion are about as follows: Virchow's idea that the fat might reach the cell from elsewhere and appear there as an infiltration in the case of normal cells, or be produced at the expense of the protoplasm, when it was to be spoken of as a fatty degeneration, held sway for long years. These two types were distinguished by the large size of the globules of fat in the infiltration, their very small size in degeneration. But Rosenfeld showed, in a long series of investigations, that the cells of the liver received fat from distant depots when the animal was poisoned with phosphorus. He starved dogs and then fed them on mutton fat until it was stored in quantities in their subcutaneous tissues—phosphorus poisoning then loaded the liver with mutton fat. If the dog was so starved as to have no subcutaneous fat, none appeared in the liver after phosphorus. It seemed to Rosenfeld that all the fat came from outside. But an organ with abundant fat-globules in the cells need contain no more fat on chemical analysis than one which shows none microscopically—the production of a fatty degeneration need not increase the total quantity of fat in the organ. Beside the fats found, there are often cholesterine esters which are not to be obtained from the subcutaneous tissue, although they may well be transported from other sources, such as the adrenal, where they have been stored.

In view of these and other facts the following explanations of the appearance of fat in the tissue-cell seem possible:

1. An excess of fat may be brought to the normal cell.
2. A normal amount of fat may be brought to a cell which is injured, and therefore incapable of using up its fat with normal rapidity. Such injury may or may not be anatomically obvious. Impaired circulation, impaired oxygen supply from general anaemia, or toxic injury to the cell in the course of infection are among the causes which might give occasion for the condition. Fat would accumulate because it was not properly consumed.
3. Injury of many types might disintegrate the physical or chemical

combinations of lipoids which are known to exist in invisible form in the cells, and thus make the lipoids visible as such in the cell-body (fat phanerosis).

4. Tissues in the neighborhood of areas of cell destruction may absorb or engulf by phagocytic activity the fats set free from those disintegrating tissues, as in the case of an infarct of the grain or other organ.

That fats are redistributed in the body in cases of infection and intoxication is shown not only by the demonstration of the fats in transit in the blood, but by the enormous accumulation of fat in the liver in certain cases in which the rest of the body is greatly emaciated.

LITERATURE

- Anitschkow: Ziegler's Beiträge, 1913, lvi, 379; 1914, lvii, 201.
Aschoff: Ziegler's Beiträge, 1910, xlvii, 1.
Bang, Ivar: Ergebni. d. innere Med., 1909, iii, 447. Chemie u. Biochemie der Lipoide Wiesbaden, 1911. XVII. Internat. Cong. of Med., London, 1913, Sect. III, i, 151.
Chalatow: Die anisotrope Verfettung, Jena, 1922.
Dietrich and Kleeberg: Ergebni. d. allg. Path., 1924, xx, 2, 913.
Kraus, Ribbert, Albrecht, Rosenfeld: Verh. Dtsch. Path. Gesellsch., 1904, vi, 37-73.
Kutschera-Aichbergen: Virchow's Archiv, 1925, cclvi, 569.
Leathes and Raper: The Fats, Monographs on Biochemistry, 1925.
Levene, P. A.: Many Papers in Jour. Biol. Chemistry, 1913-
Lubarsch: Ergebni. d. allg. Path., 1897, iii, 631.
Thannhauser, Hueck, Verse: Verh. Dtsch. Path. Gesellsch., 1925, xx, 1.
Wolff, E. K.: Virchow's Archiv, 1924, cccli, 297.
Leathes and Bang review the whole chemistry and metabolism of fats. Kraus, Ribbert, and others review its pathological aspects, and the paper of Aschoff is especially useful. Anitschkow and his pupils are especially concerned with the part played by cholesterol in pathological conditions.

CHAPTER VII

DISTURBANCES OF PROTEIN AND CARBOHYDRATE METABOLISM

General character of protein metabolism. The purine bodies. Gout. Cloudy swelling. Hyaline metamorphosis. Amyloid infiltration. Carbohydrate metabolism. Glycogen.

Protein Metabolism.—It is somewhat surprising, in view of the great importance of protein materials in the constitution of the body and in the composition of our food, to find ourselves able to say so little with regard to the pathological anatomy of alterations of the metabolism of these substances.

Doubtless it is altogether the result of our inability to see or make recognizable the abnormalities that may arise. We cannot tell, as we can in the case of fats and carbohydrates, whether a tissue is loaded with an excess of protein material. Indeed, we know rather little about the relation of labile or food protein to tissue protein. But one may recognize the abnormal loss of protein in the urine in renal disease, the passage of albumoses into the urine in disease of the bones (myeloma, etc.), and the occurrence of various amino-acids there when the liver has been extensively destroyed (leucine and tyrosine in acute yellow atrophy of the liver). Under other circumstances there occur cystinuria and alkapttonuria, both resulting from disturbances of protein metabolism, and producing, in the one case, urinary concretions of yellow crystals, in the other, a pigmentation of the cartilage.

Disturbances in Purine Metabolism.—Variations occur also in the quantities of urea, uric acid, ammonia compounds, etc., in the urine, and these naturally have a direct relation to the protein metabolism. Nevertheless, it is rarely possible to gather any real clue as to the protein metabolism from their variations. The disproportion in this regard is seen especially well in the case of uric acid, a substance playing an important rôle in gout. From the variations in its reaction it would never be possible to diagnose gout, because even greater variations occur in a healthy person.

GOUT

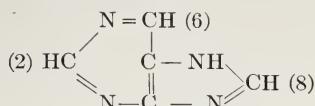
This is a disease the cause of which is unknown. It may even be said that the essential nature of the disease is quite unknown, since the disturbance of a part of the protein metabolism, which is accompanied by striking symptoms, is evidently only the effect of some underlying disarrangement of the machinery of intermediary metabolism, which is obscure.

Profound alterations arise in the metabolism of the purine substances, such that uric acid, the common end-product of fermentative decompositions and oxidations of these complex bodies, is retained in the tissues in the form of salts of soda and calcium, and lodges itself in cartilages and elsewhere, causing great pain to the sufferer.

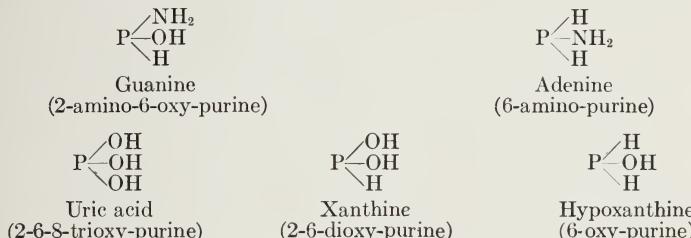
Chemistry of Purine Bodies.—The investigation of the chemical nature of the complex bodies which finally yield uric acid has been made by Kossel, Fischer,

Brugsch and Schittenhelm, Burian, Jones, Levene, and others, and may be read in Jones' monograph (*Nucleic Acids*).

It appears that compounds containing nitrogen and phosphorus, which have long been known as nucleins or nucleoproteins, can be extracted from the tissues, and in special abundance from those such as thymus, lymph-glands, or materials like pus or spermatozoa, in which cell nuclei form a large proportion of the mass. These names are being abandoned since it has been shown that they mean nothing definite, and that the characteristic constituent is a nucleic acid. It is from the nucleic acids that the peculiar and important alloxuric bodies are derived by the action of ferments. These, in so far as they interest us, are guanine, adenine, hypoxanthine, xanthine, and uric acid. All are chemical derivatives of purine.



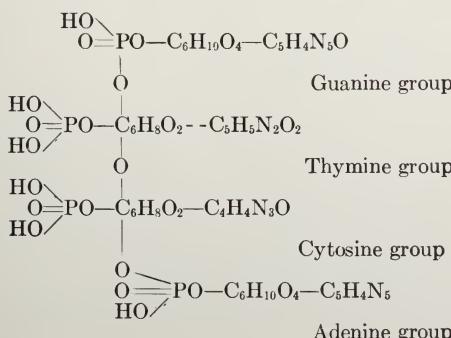
Representing the purine ring, with its three replaceable hydrogen atoms, by the abbreviated expression, $\text{P} \begin{array}{c} \diagup \text{H} \text{ (2)} \\ \diagdown \text{H} \text{ (6)} \\ \diagup \text{H} \text{ (8)} \end{array}$, the relation of the five purine compounds to one another is seen in the following diagram (Jones):



Uric acid can be formed from the amino-purine by deaminization and subsequent oxidation—from the oxypurines by oxidation. The deaminization is brought about by special ferments, guanase and adenase, which are distinct and vary greatly in their localization with animal species. The lack of guanase in the pig's tissue seems to be the explanation of the deposition of guanine which sometimes occurs there (guanine gout).

As a brief indication of what precedes this, the following may be quoted from Jones' monograph:

Thymus nucleic acid, according to Levene, is a combination of four mononucleotides, each of which is a nucleoside united with phosphoric acid. Hexose, joined to the nitrogenous ring compound or purine group, is a nucleoside. From this point of view the nucleic acid is a tetranucleoside, made up of four mononucleotides. Levene and Jacobs give the following formula for animal nucleic acid:



The disruption of this complex takes place by the action of two ferments, which first split the tetranucleotide into two dinucleotides, after which they in turn are split into mononucleotides. These ferments are phosphonuclease and purine nuclease. Levene and Medigreceanu find that nucleotidases split the nucleotides to nucleosides, which further separate into carbohydrate and purine base under the action of a nucleosidase.

The liberation of the guanine and adenine is well in the line of uric-acid formation; the fate of the pyrimidine groups, thymine and cytosine, is still uncertain. Dr. Levene tells me that he has been unable to find an enzyme which will decompose the nucleoside in which they occur, and that since they cannot form uric acid, they are possibly excreted as urea or in other forms. Only 50 per cent of the nucleic acid nitrogen can be counted on for the production of uric acid, namely, that in the guanine and adenine groups.

The tissues of the lower animals contain a ferment, uricase, which can decompose uric acid, but no such ferment exists in human tissues, and uric acid is excreted as such.

Uric acid is derived from the food or from the waste of the tissues. It occurs in the blood in small amounts, and is excreted in the urine in quantities up to one gram daily. The amount excreted is increased by the feeding of substances rich in nucleic acid. The solubilities of uric acid are interesting and important, since it has been stated by Gudzent that the monosodium urate exists in the blood in two forms —one, the easily soluble, unstable lactam form, the other the isomeric, stable, relatively insoluble lactim urate. The change from one of these forms to the other may, according to him, account for the precipitation of the urates in the tissues. More important seems the more recent work of Schade, who shows that uric acid or its salts may, through the influence of alkalies (hydrates), pass into a condition in which it is far more soluble than usual, and that, in reaching the crystalline form from this oversaturated solution, it passes through a colloid stage in which it is relatively stable. Materials which protect this colloid stage and antagonize precipitation occur, such as glycerin, urea, albumen of the serum, nucleic acids, etc. The application of this knowledge has not yet been made.

Gout is a hereditary affection most common in men, often transmitted by women who have themselves shown no symptoms. It is common in those who overeat, and yet it occurs as well in the poor. It is often associated with lead-poisoning, on which account a type "saturnine gout," has been spoken of. Renal disease is a frequent but not constant accompaniment or sequel, and some writers, thinking that the gout might depend on renal disease, have specified another form, "renal gout." But for these separate forms there is little good evidence.

There seems to be an underlying hereditary tendency to develop the actual disease in these persons, although much may be done to ward off its appearance by careful avoidance of foods rich in purine. Whether it can be prevented in this way remains uncertain. Alcohol has always been thought an important cause of gout, although its actual influence is not clearly defined.

Acute attacks are characteristic, with remissions in which the condition is fairly good. Chronic forms also occur in which acute attacks appear as exacerbations of the more continuous process. The acute attack begins with violent nocturnal pain in a joint, followed by fever and chills and evidences of inflammation in the joint.

Before the attack the excretion of uric acid in the urine is diminished; during the attack it is much increased. It is clear from this that there is no real inability on the part of the kidneys to excrete uric acid. Between attacks it is about normal, although it may be diminished

(Garrod). There is generally an increased amount of uric acid in the circulating blood, both in the intervals and during the attacks. The average amount in Pratt's cases was 3.7 mg. per 100 grams of blood contrasted with 1.7 mg. in the non-gouty cases studied by Adler and Ragle.

Gudzent points out the fact that the deposit of sodium urate in the tissues occurs without pain and without causing any inflammatory reaction, while in the acute attack of gout in which pain is unbearable and an intense inflammation arises, operative exploration of the affected joints has shown no deposit of urates. He comments on the wide divergence of opinion in different countries as to what in the diet is productive of attacks of gout, and concludes that it is some unsuspected constituent different perhaps in each case and peculiarly noxious to that individual. In other words, he suggests that the acute attack of gout is an allergic phenomenon brought on by taking into the body the par-

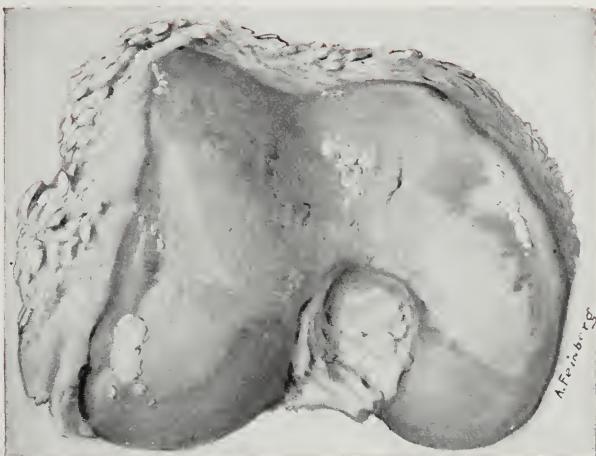


Fig. 41.—Knee-joint with white deposits of urates. Gout.

ticular substance to which the patient has become sensitized and by no means the excessive consumption of purine bodies or of alcohol. The peculiarities of the excretion of uric acid, before and after the attack, he thinks may be parallel but not more intimately associated with this allergic disturbance.

It is, of course, difficult to understand the sharp localization of an allergic reaction in one joint, but possibly there arises some predisposing factor there.

Anatomically, the most prominent feature of the disease is the extraordinary deposition of needle-shaped crystals of monosodium urate in the substance of the cartilages. Such opaque, white, chalky deposits are very conspicuous when an affected toe-joint or knee-joint is opened (Fig. 41); they lie a little beneath the free surface, and extend only about one-third of the way through the cartilage, rarely entering the bone. Microscopically in sections of the joint sheaves of these fine

crystals are found embedded in the matrix of the cartilage, often surrounded by an area of hyaline, pink-staining altered cartilage. Ebstein thinks that necrosis of the cartilage is the necessary forerunner of their deposit, but in this he is not supported by the other writers, who feel that the changes in the cartilage may be secondary to the crystalline deposit.

Besides the joint cartilages, the neighboring ligaments, tendons, and synovial membranes may occasionally be subjected to the precipitation. Olecranon, prepatellar, and other bursæ are especially likely to be affected. Other sites are the edges of the cartilages of the ear, the eyelids, the larynx, the kidneys, especially the pyramidal portion, where masses of crystals may form in or between the tubules, and many other



Fig. 42.—Gout. Uratic tophi about the finger-joints.

situations. But the cartilages of the joints, especially of the great toe, the fingers, and the knees, form the site of predilection. Such accumulations of crystals, when they become bulky, are called tophi, and in the course of chronic gout tophi of great size may form in and about the joints, causing their great deformity and disability (Fig. 42). They become encapsulated, cause a persistent mild inflammation, and may sometimes, through stretching the skin to atrophy, break through and appear as chalky concretions exposed to the air.

Digestive and nervous disturbances, arteriosclerosis with myocardial disease, and circulatory disabilities, chronic nephritis with scarring of the kidney are common accompaniments of the disease. The patients finally die from some intercurrent affection. Lucke suggests that when

gout is inherited, diabetes and obesity may accompany it. While allergic reactions play a rôle in some cases, the influence of the vegetative nervous system seems important and in analogy with diabetes insipidus, perhaps even the hypophysis. But none of this is very well established and it seems important to lay stress on the purine content of the diet, since, during the war, when that element was greatly restricted, gout became very rare.

LITERATURE

- Berglund, Pratt: Med. Clin. N. Amer., 1924-25, viii, 1635.
 Brogsitter: Histopathologie d. Gelenk-Gicht, Leipzig, 1926.
 Ebstein: Gicht. Wiesbaden, 1906, II. Aufl.
 Garrod: Nature and Treatment of Gout and Rheumatic Gout, London, 1859.
 Jones: Nucleic Acids, Longmans, Green & Co., 1914.
 Levene and Jacobs: Jour. Biol. Chem., 1912, xii, 411.
 Lucke, H.: Dtsch. Med. Woch., 1934, ix, 1783.
 Löffer: Schweiz Med. Woch., 1933, lxiii, 1188.
 Lockie and Hubbard: Jour. Amer. Med. Assoc., 1935, civ, 2072.
 Magnus Levy: Harvey lectures, 1909-10, 251.
 Minkowski: "Gicht," Nothnagel's Handb., vii, 2. Neue Dtsch. Klinik, 1929, iv, 183.
 The student will find the lecture of Magnus Levy particularly useful, but above all should read Gudzent, Klin. Woch., 1926, v, 1069. Dtsch. Med. Woch., 1935, lxi, 901.

CLOUDY SWELLING OR PARENCHYMATOUS DEGENERATION

When the liver and kidneys and some other organs are inspected in the body of a person who has died of typhoid fever, pneumonia, diphtheria, or any one of many other acute infections or intoxications, they are commonly found swollen, inelastic, or pasty, and on section very dull and opaque in appearance. It is often said that the liver looks as though it had been boiled. In frozen sections the epithelial cells are seen to be much enlarged and very granular. In the renal epithelium the free edge of the cell is ragged and irregular, projecting far out into the lining of the tubule—even far enough, sometimes, to meet the opposite cells and greatly narrow the cavity of the tubule (Fig. 43). The same appearance is found in the kidney if the work of both is suddenly put upon it by the removal of the other. This cloudy opacity of the cells with swelling has long been known, but even yet its nature is not clear. Virchow thought it the expression of a nutritive stimulus and increased absorption of food material. Cohnheim, on the contrary, thought it a kind of localized coagulation process. It is known that the altered appearance is not necessarily indicative of an irrevocable change in the cell, for after the acute infection is past, the cells recover this normal appearance. This was, therefore, regarded as one of the mildest forms of "degeneration" of the cell.

The protein nature of the abundant granules which crowd the body of the swollen cell has been generally accepted and proven by their solubility in alkalies and acetic acid, and by their positive xanthoprotein reaction, as well as by other tests, and the problem remains as to their origin and their relation to the essential structures of the cell.

The confused literature is reviewed by Ernst in his recent paper without arriving at any definite conclusion as to the nature of the

granules, although he raises the question as to their relation to the preexisting granules, and states that the weight of evidence is in favor of their being derived from the mitochondria and their variations.

In the renal epithelial cells there are found, especially in the more chronic forms of nephritis, but occasionally in the acuter form, globules of much larger size than any of the granules ordinarily seen, globules of a density and high refractive index to make them at once conspicuous objects (Fig. 45). These, it is true, vary greatly in size, and are thought by some writers (Pfister) to show gradual transitions into the ordinary

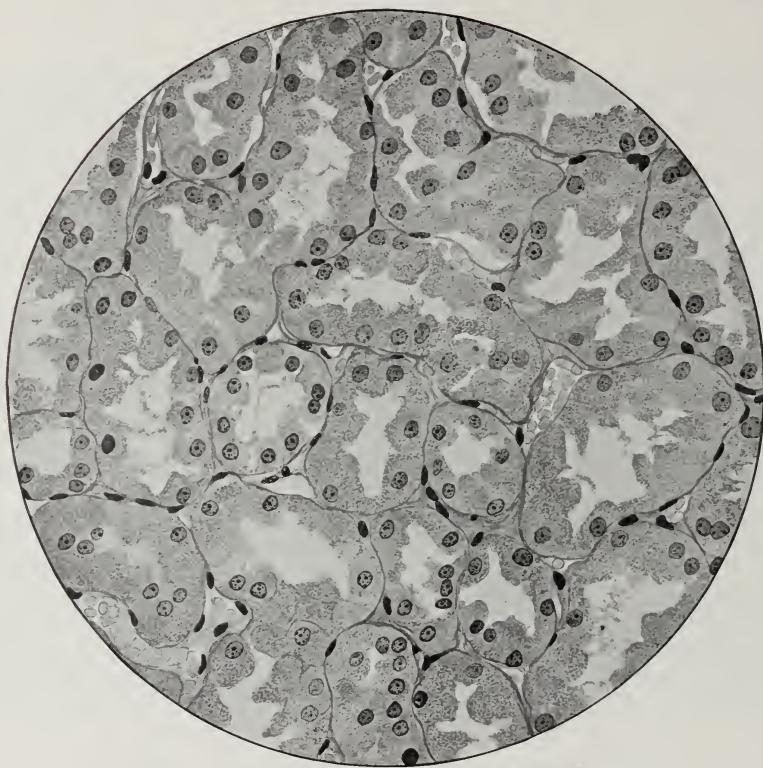


Fig. 43.—Cloudy swelling of epithelium of renal tubules.

granules. Fahr objects to this since, as is well known, the large droplets stain sharply with the Weigert fibrin stain. They probably play a prominent part in the formation of hyaline casts in the tubules. (See H. Jackson, Am. Jour. Pathol., 1927, iii, 285.)

Anitschkoff has tried to determine the relation of the granules in cloudy swelling to the mitochondria by experiment, and finds that, by the application of hypotonic solutions to the cells, the mitochondria swell up into droplets, which after a time, take the specific stain only at their margins. The production of cloudy swelling is, he thinks, a complex process, consisting of a series of changes in the mitochondria

which begins by their decomposition into smaller granules, which then swell into droplets sometimes large enough to touch one another and give the whole cell a web-like appearance. This is analogous to the swelling of colloid, which is intensified by acids, as shown by M. Fisher, and corresponds with the observation of Orgler upon the increase in the water contents of the altered tissues. Naturally, this process is reversible under experimental conditions, but it is not so easy to assume that this is true in the body, where the granules may burst, or, as in the kidney cells, be discharged into the tubule. Further, a distinction



Fig. 44.—Cloudy swelling of epithelium of liver.

must be maintained between the increase in the mitochondria in cells undergoing hypertrophy, and the swelling and disorganization of those structures in injured cells, where the change can be regarded as the effect of excessive function only in the beginning, if at all. Dibbelt, in studying the effect of diphtheria toxin in the kidney, finds in the same way that the first effect consists in a stimulation of the mitochondria to activity, followed by a molecular disintegration, with the liberation of lipid substances. Fahr, on the other hand, in discussing the hyaline droplets in the kidney cells, makes a sharp distinction between mitochondria and secretory granules. Normally, droplets dis-

tinguishable from the mitochondria by their staining reaction exist in the epithelium of parts of the tubule. Pathological droplets staining intensely by Weigert's fibrin stain occur, however, in different situations in the tubules, and are thought to be not merely evidences of the activity of secretory granules, but new formed globules, indicating the disintegration of the cell.

All this is very contradictory and confused, but at least one may see that it is scarcely believed any longer that the granular opacity of the organ cells in infections and intoxications is due to the accumulation of protein food materials, but that it is intimately related to changes in the specific granules of the cell. More study is necessary to make the matter quite clear.

LITERATURE

Anitschkoff, Dibbelt, Ernst, Fahr: Verh. Dtsch. Path. Gesellsch., 1914, xvii, 81, 103, 114, 119.

Landsteiner: Ziegler's Beiträge, 1903, xxxiii, 237.

HYALINE DEGENERATION

This expression is loosely employed to class together, in the present state of our ignorance, a great many unrelated substances, usually recognizable only with the microscope, which have in common, besides their protein nature, only their translucent clear or hyaline appearance and their tendency to stain brightly with such acid dyes as eosin.

Naturally, there can be nothing chemically specific about such a heterogeneous group, and it is easy to withdraw from it such a constant and sharply characterized substance as amyloid, which, although it is hyaline and stains with eosin, is easily recognized by special microchemical reaction as well as by its peculiar distribution.

Ernst has pointed out the possibility of dividing these substances into two groups, according to whether the hyaline material is derived from the metamorphosis of epithelial and other cells or from connective tissue. This rough subdivision, which is open to many criticisms, is based on the reaction to the van Gieson stain with which epithelial hyaline stains yellowish brown, while connective-tissue hyaline takes the red fuchsin stain.

Since we know so little of the chemical nature of the various substances, nothing remains but to describe their appearance. In all cases the death of the tissue precedes its conversion into a hyaline material, so that we are dealing with necrotic and usually coagulated cells which have undergone even further change in assuming the hyaline aspect.

Epithelial Hyaline.—In areas of necrosis in such organs as the liver or kidney or skeletal or cardiac muscle, the protoplasm of the dead cell coagulates, of course, with the aid of coagulable fluid, which filters in from adjacent capillaries and tissue spaces. But it does not at once become glossy or hyaline. Instead, it seems to require time and perhaps compression or the infiltration of more coagulable fluid before the details of the structure of the cells are quite lost and fused into a homogeneous, shining mass. A good example is found in the clumps of

hyaline material sometimes found shrunken in the interior of the sarclemma sheath of the fibres of the rectus abdominis muscles in typhoid fever and the pneumonias following measles and influenza (Fig. 46). Many other instances will be referred to in other places.

This, which involves the whole cell, must be very different from the process which gives origin to the globules or droplets of hyaline appearance so often seen in the renal epithelium (Fig. 45). Other hyaline droplets which seem to be formed in some analogous way are the so-called Russel's fuchsinophile bodies, which may be found in tumors or in old granulation tissue. Perhaps the "corpora amyacea" which occur

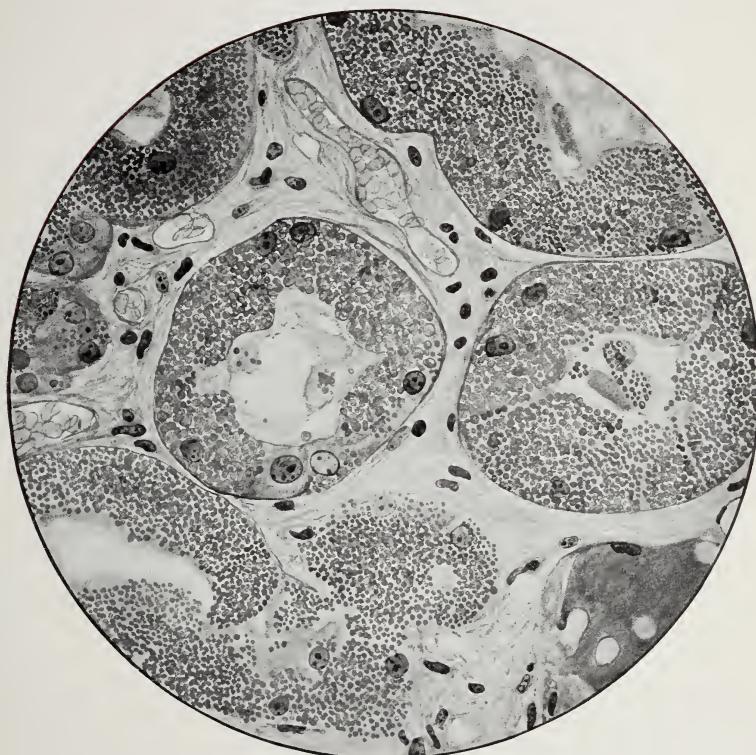


Fig. 45.—Colloid or hyaline droplets in the epithelium of renal tubules.

in the alveoli of the lung and in the prostate may be regarded as similarly formed by the stratified accretion of the hyaline débris of cells, or the secretion of epithelial cells around some nucleus which itself may be a dead cell.

The globules of hyaline material seen in diseased renal epithelium are sometimes spoken of as colloid droplets, and the condition is called colloid degeneration. This is confusing, and it is obviously wrong to speak of the accumulation of the colloid of the thyroid even when excessive, as a colloid degeneration, since it is only the normal secretion of the gland.

The hyaline casts found in the renal tubules which have in themselves the general character of hyaline material must be derived from disintegrated and amalgamated epithelial cells, together with their secretions, and they are found to stain in a corresponding way.

Connective-tissue Hyaline.—In the framework of lymph nodes draining malignant tumors, or tuberculous lesions, hyaline material was first described. But the same appearance is found in scar tissue and encapsulated necrotic tissue in various situations. It is characteristic, too, of the walls of arterioles in various organs, especially in the spleen.



Fig. 46.—Hyaline changes in muscle. Typhoid fever.

and kidneys, in that peculiar condition which we speak of as arteriolosclerosis. There the hyaline material which thickens the wall of the arteriole and narrows its lumen, generally contains fat and may be stained with Sudan. Its relation to high blood-pressure and to disease of the kidney remains a problem. In the walls of the vessels of the uterus or ovaries when they shrink in old age, one also sees the vitreous or hyaline change which narrows their lumen (Fig. 47). In the ovary every corpus luteum, when it loses its specific cells, is finally reduced to a cell-free, hyaline, shining mass, the corpus albicans or candidans.

We must, one supposes, regard such hyaline fibrous tissue as dead,

and frequently there are evidences of coagulative processes which have occurred all through it, after which it has become more compact and glistening. Often calcium is deposited in such dead tissue. But while it is hyaline, it takes, with greater or less brilliancy, the fuchsin red of van Gieson's stain, because its inherent chemical value is not quite lost by its becoming melted down into hyaline.

Thrombi, after long standing, fuse in the same way into a formless, homogeneous mass in which fibrin, platelets, nuclei of leukocytes, and red corpuscles lose their identity in the uniform hyaline mass. This is



Fig. 47.—Hyaline vessel-walls in a tumor of the uterus.

especially true in the lower strata of the thrombi that occupy old aneurysmal sacs, where one may no longer be able to distinguish the hyaline thrombus from the hyaline fibrous wall of the sac.

More rapidly produced are the hyaline thrombi which appear in the capillaries, especially in the renal glomeruli in some infectious diseases (diphtheria, hog cholera, plague). They fill the capillaries like a homogeneous injection mass, and can usually be stained by the Weigert fibrin stain, so that they veritably look like a colored injection. It was thought that they too were composed of fibrin, but Flexner has shown that they consist sometimes of agglutinated red blood-corpuscles.

Unsatisfactory as it is, this general conception of nondescript hyaline materials derived by necrobiotic processes from the cells and tissues is useful so long as we are quite unable to define their nature any more closely.

LITERATURE

Lubarsch: "Hyaline and Amyloid Degeneration," Ergebni. d. allg. Path., 1897, iv, 449.

AMYLOID INFILTRATION

There was observed long ago, by Rokitansky and the Viennese school, a curious material lodged in the substance of various organs, and this was later studied in greater detail by Virchow. This *amyloid* was so-called because of its resemblance in some of its chemical reactions to starch. It is a translucent, glistening substance, usually so firm and often so abundant as to enlarge and render rigid the organs in which it occurs.

It is in persons who have passed through a long wasting illness that it is found. In the organs of those who have died after suffering for



Fig. 48.—Amyloid infiltration. Sago spleen.

months or years from some exhausting suppurative process, such as an old osteomyelitis, some chronic destructive infection, such as tuberculosis or actinomycosis, or from such protracted intoxication as may accompany syphilis, chronic nephritis, or cancer, this substance is not uncommonly discovered at autopsy. With the improvement in surgical technique, which eliminates much of such chronic suppurative and tuberculous disease, it is less common than formerly, but it is still frequent enough in homes for the incurable and such places.

The spleen, liver, and kidneys are perhaps the commonest sites for its deposit, but it occurs in every other organ at times, not even excepting the brain.

In the spleen it appears in two forms, in one of which it is confined to the Malpighian bodies, and stands out as clear, rounded globules against the red background of the splenic pulp (Fig. 48). Virchow,

recalling a favorite red-wine soup with sago, named it very appropriately sago spleen. In the other form the amyloid is diffusely spread through the splenic pulp, and being everywhere mixed with the tissue, it is less translucent and glistening.

In the liver it may be very inconspicuous, but if abundant, the liver is greatly enlarged and firm, and on section the lobulation is rendered invisible by the diffuse infiltration of translucent amyloid. Minute streaks of yellowish, opaque liver tissue stretch through it, and there are usually patches of liver which are practically free from any admixture of it.

The kidneys are often pale, large, smooth, and firm, but on the other hand they may show any stage of the distortion which follows the extreme scarring of the organ and still be found to contain amyloid. This is lodged in the glomeruli and in the walls of the arterioles and straight conducting tubules, and occasionally one may discern it with the naked eye, although usually it is too finely divided for that.

The adrenals may contain much or little. In extreme cases the organ is greatly enlarged and composed almost entirely of translucent amyloid, almost like an enlarged mould of the normal structure. In the intestinal wall it is sometimes possible to recognize its presence by the pallor and rigidity of the mucous membrane, but this is rare.

In lymph-glands it is not commonly abundant, but in a recent case in which it was widely distributed the cervical lymph-glands were greatly enlarged and were found to be composed of almost solid masses of amyloid.

While the condition of the spleen, liver, and adrenals is easy to recognize, one might overlook its existence in the kidneys and in other organs. In its detection great help is afforded by the peculiar microchemical reactions which can be applied to the fresh organs. They are as follows:

1. A solution of iodine stains the tissues in general yellow, but makes the amyloid stand out sharply in deep brown. This is especially striking if the tissue is made acid in reaction with acetic acid. If strong sulphuric acid is used instead, the amyloid turns blue or black with iodine, and hence its supposed resemblance to cellulose.

2. Various aniline dyes, such as methyl-violet, methyl-green, thionin, etc., cause the amyloid to show a metachromatic stain; that is, it stains red while the tissue takes the obvious blue or green color of the dye.

These stains can be applied to frozen sections in which the amyloid also shows its acidophilic character, staining intensely pink with eosin, and brownish with van Gieson's stain.

When thus brought into distinct relief by specific stains, it becomes quite clear that the amyloid substance is merely poured into the crevices of the tissue, and not situated in any of the cells. It is a true infiltration, as though melted paraffin had been forced into the tissue-spaces and allowed to solidify. In the spleen it crowds the cells of the Malpighian body, between which it lies until most or all of them atrophy and disappear (Fig. 49). It may also appear in the substance of the walls of the smallest blood-vessels, sometimes between the muscle-cells

of the media, sometimes in the intima. The vessels of capillary calibre are most commonly chosen for such a coating of amyloid.

In the liver it is found in only one situation, and that is about the endothelium of the capillaries, and hence between those cells and the liver-cells. The amyloid becomes so bulky in that situation that it presses on the capillary and liver-cells, and causes the latter to melt away into thin threads of protoplasm and finally to disappear (Fig. 50).

The same crowding is apparent to an extreme degree in the adrenal, where the tissue is practically reduced to nothing in advanced cases.



Fig. 49.—Amyloid infiltration of Malpighian bodies of spleen.

In the intestinal mucosa amyloid accompanies the minute blood-vessels in the villi. Application of iodine makes each one brown separately, so that the mucosa assumes the appearance of brown velvet.

In the kidney it lodges in the glomerulus, between the endothelium of the capillaries and their epithelial covering, and consequently soon narrows the capillary to a very minute calibre or obliterates it. Elsewhere it is found as a mantle for the tiny arterioles and venules in the cortex and pyramids, and also for the conducting tubules. It is easy to understand that the application of iodine to the cut surface of such a

kidney would reveal the glomeruli as brilliant, chestnut-brown points in a tissue everywhere very finely streaked with brown (Fig. 51).

It is unnecessary to describe in detail the distribution in other organs, where it follows the same principle of infiltrating between capillary endothelium and the adjacent cells. Wherever it is present in abundance it causes atrophy of the pre-existing tissues. Its distribution is usually sufficient to distinguish it, even if specific stains cannot be applied, from other hyaline materials which stain with eosin but have not the peculiar chemical character of amyloid.

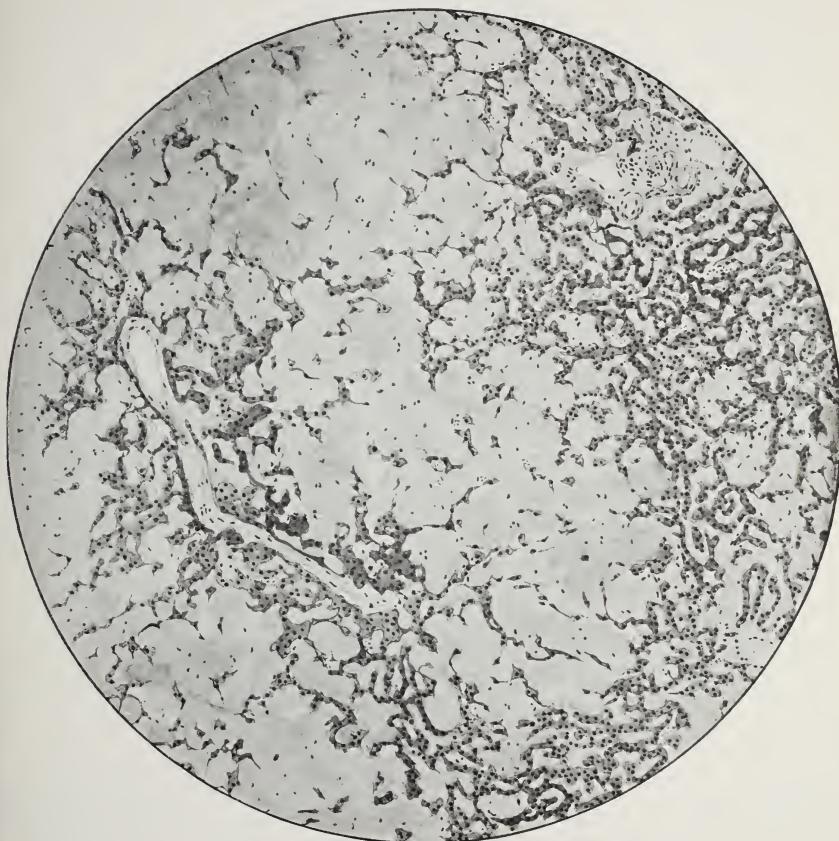


Fig. 50.—Amyloid infiltration of liver. Compression and atrophy of liver-cells.

Besides the general amyloid infiltration there occur localized amyloid deposits, sometimes in the form of tumor-like masses, usually in connection with cartilage-containing structures, such as the bronchi (Herxheimer, Schilder).

Chemical Nature.—Amyloid is a very resistant substance, which apparently persists, when once formed, although some experiments tend to show that when it is produced in animals it will disappear after a time if the animal is allowed to recover from the injections of bacteria or toxin

which are used to produce it. It was thought not to be attacked even by digestive ferments, but now it has been shown that it can be digested slowly by artificial gastric juice. In the attempt to determine its chemical nature it was first extracted in a fairly pure form by taking advantage of its solubility in baryta water. Oddi then discovered that while different specimens vary widely in composition, all sorts of amyloid contain chondroitin-sulphuric acid, a substance found normally in cartilage, but whose structure is still unknown. Krawkow thought amyloid



Fig. 51.—Amyloid in glomerulus. The amyloid lies between the endothelium and the capsular epithelium in each capillary.

to be a compound of chondroitin-sulphuric acid with a histone. Details of the rather fruitless attempts to determine its composition may be read in Neuberg's paper. The more recent studies of Haussen, Eppinger, and others make it seem doubtful that chondroitin-sulphuric acid is a constituent of amyloid.

Much has been said of its experimental production. Krawkow succeeded in this by repeated injections of bouillon cultures of *Staphylococcus aureus*, but others have found that turpentine or other pus-producing poisons or cultures of various other bacteria or their toxins

will also cause its appearance. The horses used for the manufacture of diphtheria antitoxin often show amyloid changes in their organs, and so do mice and rats inoculated with transplantable tumors.

A point of peculiar interest is that amyloid seems to go through several stages in its formation—at first it will not stain with iodine, although giving a metachromatic stain with methyl-violet. It is only in the latest stages that it will give the blue or black color with sulphuric acid and iodine. The early stage of non-stainable amyloid recognized by Davidsohn was called *achroöamyloid*. Quite recently we observed an instance in a young man with advanced pulmonary tuberculosis in whom a typical sago spleen, enormous, bacon-like liver, and advanced renal amyloid were found. Nevertheless, although the diagnosis was unmistakable to the naked eye, none of the amyloid would stain with iodine.

Kuczynski has found it possible to produce amyloid in mice by injecting casein or egg-albumen parenterally, that is, somewhere outside the intestinal tract, or by feeding very excessive amounts of these substances. He thinks it a decomposition product of protein which, becoming too concentrated in the blood, is deposited in the crevices of the tissue. By interrupting the administration of casein he shows that amyloid once formed may be reabsorbed by the action of ferments produced by plasma cells and other wandering cells and by the phagocytic activities of reticulo-endothelial cells. Smetana, by the use of Kuczynski's method of injecting nutrose in mice, has studied early stages in the formation of amyloid. Congo red is a specific stain for this substance and, if injected during life into the circulation, produces an accurate vital staining, marking out its earliest appearance. With such methods Smetana finds that amyloid is formed not especially as an infiltrating substance, but rather at the expense of the tissue and that the specific phagocytic cells (reticulo-endothelial cells) are actively concerned in its formation, but it seems possible that they may have acted merely as phagocytes. Letterer concludes that amyloid is dependent upon the interaction of an antigen produced by disintegration of the tissue of the body and a precipitating antibody.

LITERATURE

- Grayzel: Arch. Path., 1934, xvii, 50.
 Kuczynski: Klinische Wochenschrift, 1923, ii, 2193.
 Letterer: Virch. Arch., 1934, cccxi, 34.
 Leupold: Ziegler's Beiträge, 1918, lxiv, 347.
 Lubarsch: Verh. Dtsch. Path. Gesellsch., 1930, xxv, 155.
 Neuberg: Verh. Dtsch. Path. Gesellsch., 1904, vii, 19.
 Schmidt: *Ibid.*, 1904, vii, 2.
 Smetana: Bull. Johns Hopkins Hosp., 1925, xxxvii, 383. Jour. Exp. Med., 1927, xlvi, 619.

CARBOHYDRATE METABOLISM

Although the metabolism of carbohydrates plays a most important part in the material interchange in the body, none of the forms in which these substances exist can be made visible in the tissues except glycogen.

The whole history of the utilization of starches and sugars is so intimately bound up with the problems of diabetes mellitus that it may be most advantageously discussed in that connection. (See Chapter LIII.)

Here it will suffice to say that glycogen, the colloid polymerized form of sugar which is adapted to temporary storage in the tissues, is a substance evidently easily attacked by certain ferment, so that it quickly disappears after death from the tissues, easily soluble in water but insoluble in very strong alcohol or in boiling water. It stains brown with iodine and can be stained bright red with carmine by the method of Best, after fixation in absolute alcohol. In tissues thus treated one can demonstrate it in quantity in the cells of the liver of a well-nourished animal and less abundantly in the cells of other tissues, such as the voluntary and heart muscles, the cartilages, many epithelial cells and particularly in the tissues of embryos and in rapidly growing tumors. Some organs, such as the pancreas, ovaries, breasts, thyroid, etc., seem to contain but little. At times in inflamed tissues, and about areas of necrosis, it may accumulate in unusual quantity.

But starvation, violent muscular work and various poisons which cause muscular spasm, such as strychnine, tend to cause its disappearance. Phlorizin, probably by another mechanism, also does this. Diabetes, as we shall state in another place, is accompanied by great disturbance in the formation and distribution of glycogen. The amount stored in the liver is greatly decreased, but it persists in the heart muscle and appears in large globules in the epithelium of the kidney.

LITERATURE

- Armstrong, E. F.: Simple Carbohydrates and Glucosides; Monographs on Biochemistry, 1912.
Pryde: Recent advances in Biochemistry, 1926.

CHAPTER VIII

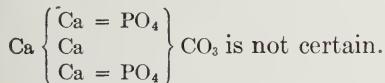
DISTURBANCES OF MINERAL AND PIGMENT METABOLISM

Calcium: its source, distribution, deposition in necrotic and other tissues. Its relation to various functions of the body. Iron: its distribution and functional importance. Disturbances in its quantitative relations. Chlorosis. Haemochromatosis. Pigment: function and distribution. Endogenous and exogenous pigmentation. Jaundice. Dust diseases.

CALCIUM METABOLISM

It is perhaps especially in the case of calcium that the investigations of the last ten years have shown how little we know of what is apparently an almost all-pervading rôle. It has turned out that calcium plays some part in so many unsuspected places that the tendency is perhaps rather to ascribe too much to it.

Bone Formation.—Of course the most conspicuous function of calcium is in furnishing the solid material of the bones. There it exists in the form of calcium phosphate and calcium carbonate in proportions which are known, and which are the same as those found in those deposits of calcium anywhere else in the body that so often occur under pathological conditions. But whether this is a mere mixture of phosphate and carbonate, or a more complex substance perhaps represented by the somewhat fanciful formula



The solid material is deposited in the remaining matrix of the cartilage, along the line of ossification in the growing bone under the influence of osteoblasts, and similarly on the surface of the bone lamellæ and beneath the periosteum, but no one knows yet the chemical conditions under which this occurs, and the various theories are unsatisfactory. Howland and his co-workers felt that precipitation would occur at the appropriate hydrogen ion concentration when calcium and phosphorus were present in adequate proportions, but would fail to occur if these proportions were not satisfied. Robison, with his co-workers, supplies the much needed local impulse by finding in the growing bones an enzyme which will hydrolyze a hexose monophosphoric ester. When applied to the soluble calcium hexose monophosphate this results in the formation of a precipitate of calcium phosphate. This phosphoresterase is also present in the intestinal mucosa, in the kidney and in the liver, but not in cartilages which do not ossify nor to any great extent in bones of old people which have completed their growth. There are in the blood two phosphoric esters, only one of which is attacked by the enzyme. This extremely interesting discovery is still being studied by Robison. It seems that it would fit very conveniently in

the most difficult place, that is, in explaining the local deposit of calcium rather than diffuse precipitation of calcium in all tissues.

A good deal has been written, especially by Gierke and his students, and disputed by many, about the presence of iron in growing bones; that question has not been completely settled. It seems that since a trace of iron facilitates the precipitation of calcium phosphate in vitro, it would be very helpful if it could be shown that iron really is deposited along the line of ossification prior to ossification, but the matter requires much further study. The fact that bone is constantly being eroded away



Fig. 52.—Process of calcification in normal line of ossification in fetal bone. Blood-vessels with osteoblasts depositing bone on remaining matrix.

and rebuilt throughout life, would make necessary some continuous agency rather than merely a ferment present during the actual growth of the young bone.

Calcium circulates in the blood and other body fluids in combinations which are not clearly known. It is thought to be held in supersaturation (Holt and others) and to be partly in ionic form, partly in diffusible but not ionic condition, partly in protein combination. The total calcium amounts to about 10 mg. per 100 c.c. of blood. Calcium is taken in with various foods and excreted chiefly by way of the mucosa of the colon, although some is excreted in the urine. But the proportion

of calcium in the blood is jealously maintained and made up by solution from the tissues, perhaps especially the bones, if in any way there is a tendency to deplete it. That there are conditions which can lower its level in the blood is now well known and will be discussed later (Tetany, etc.), and it appears that its constancy is maintained by the secretion of the parathyroid which at need draws calcium from the tissues. If parathyroid extract in excess be injected, too much calcium is poured into the blood which becomes thick and dark and circulates.

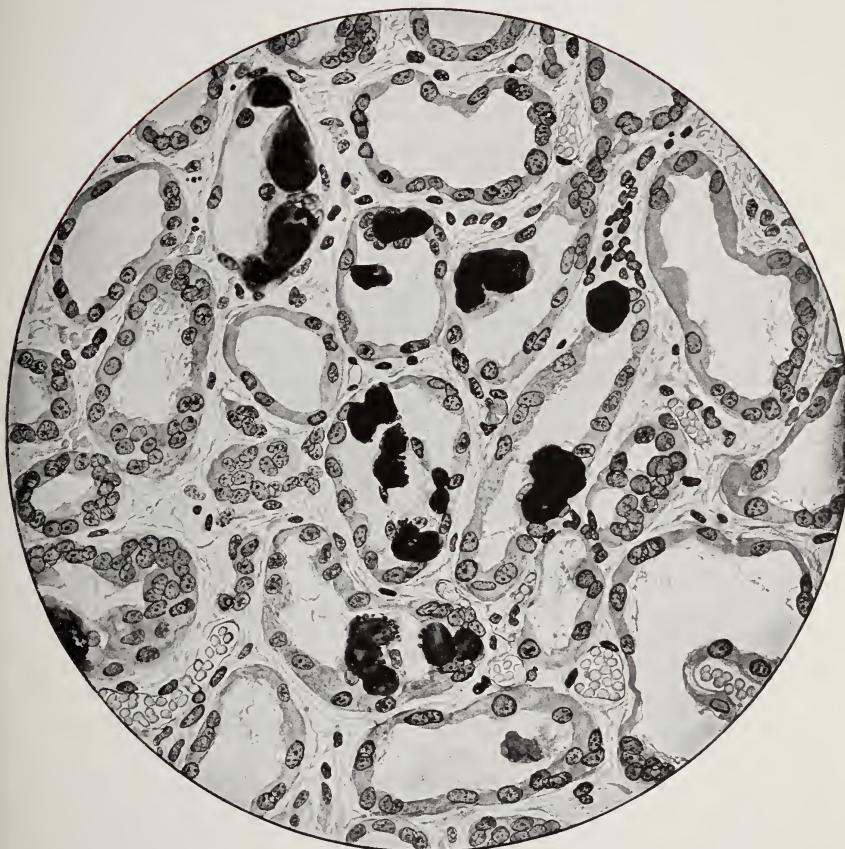


Fig. 53.—Calcification of necrotic renal epithelium. Sublimate poisoning.

with difficulty—sometimes so as to cause the death of the animal. Sometimes, too, a hyperactivity of the parathyroids, which may be greatly enlarged, is thought to be the cause of softening of the bones (osteomalacia) by withdrawing too much calcium into the blood.

In this connection the maintenance of the exact normal level of the blood-calcium is important because it has a controlling influence upon the excitability of the motor nerves and their neuro-muscular junction. When calcium is insufficient, the excitability increases until twitching

and convulsions occur, but these can be stopped at once by an intra-venous injection of a calcium salt.

So, too, as Loeb has shown, the relative proportion of calcium and potassium is important in the maintenance of the heart beat.

We have already mentioned the essential part played by calcium in the coagulation of blood and the later stages of thrombus formation.

Calcium is intimately associated with the processes of menstruation, pregnancy and lactation, but beyond the possible draining of this element from the tissues for the supply to the fetus and for the furnishing of the great amount contained in the milk, we are not informed as to its rôle. The normal functions of calcium in the body are doubtless by no means completely enumerated in this brief list and we shall return to them in connection with rickets, tetany, various abnormal conditions of the skeleton, etc.

At this point, though, we may consider the deposition of calcium in solid form in abnormal positions in the body. It is a phenomenon perfectly familiar to all who perform autopsies, and not only in the case of old people, because some cases of the most extensive calcification have been observed in children.

The conversion of tuberculous caseous lymph-nodes into masses of stone-like hardness, or mortar-like grittiness, is very familiar, and quite as familiar are the formation of irregular, jagged plates, like scales of oyster-shell, in the wall of the atheromatous aorta, and the conversion of a myoma of the uterus into a ball of stone-like hardness. Less conspicuous, but identical in character and chemical composition, are the small deposits of lime, sometimes only in microscopic granules, in cells and tissues wherever the normal metabolism has been abolished and the tissue or cell reduced to a dead, clotted or hyaline mass. Whether calcium is ever deposited in the bodies of live active cells is questionable. One gains the impression that it is always in hyaline, inert, interstitial substance, or in dead cells, although it sometimes suggests itself that the deposits of lime mechanically pushes aside and injures the neighboring cells.

The problem of the mechanism of this deposit is the same as in the growing bone. A very great deal of thought has been expended upon it without reaching any satisfactory explanation. Wells leans to the idea that it is a purely physical phenomenon through which certain substances absorb to themselves calcium salts in quantity, while others do not. He points out the great difference in this respect between pieces of epiphyseal or other ossifying cartilage and pieces of tracheal cartilage, or of other non-ossifying tissue when embedded in the animal body or immersed in appropriate calcium solutions. Klotz had the idea that in some way fats, through their decomposition into fatty acids and the formation with these of insoluble calcium soaps which later give rise to calcium carbonate and phosphate, constitute the basis of calcification. Howland and his associates measured the concentration of calcium and phosphates in the serum, and held that the supersaturation of calcium in this colloid-containing fluid is largely maintained by the high carbonic acid tension. When the carbon dioxide tension becomes low be-

cause the tissue is inactive or dead, conditions are favorable for precipitation.

None of this is very satisfactory, nor is the idea of Rabl, partly explained away by Dreyfuss, that disturbances of acid-base equilibrium caused by the acid or alkaline character of the food are responsible for calcification. There are regulating mechanisms which correct such general disturbances.

It is only possible to speculate here upon this problem. It seems that some local chemical process must be responsible for the precipitation of calcium in the dead materials exposed to the circulating fluids, as well as in the bone. Whether this is the effect of a ferment, such as Robison has found, is not yet decided. Iron is practically always demonstrable in areas of calcification and its rôle is yet to be determined; possibly it is merely absorbed by the calcium salt, or precipitated by phosphoric acid liberated in that position. The parathyroid secretion seems to withdraw into solution the calcium already deposited in bones so that it appears in excess, possibly in ionic form, in the blood. Tumors of the parathyroid are often accompanied by extensive calcification of arterial walls, and long administration of an excess of parathyroid extract not only softens the bones but produces deposits of calcium in soft tissues. Here some other local process must be at work to precipitate from the excess in the blood the granular calcium in these areas of the tissues. At any rate, the common feature is found in the necrosis and hyaline metamorphosis of the tissue which becomes the seat of calcium deposit, and it may be supposed that this sets free locally chemical substances or ferments which determine the precipitation of the lime. Although this does not apply to growing bone it seems probable that a similar local process is provided there. No doubt the reaction of the tissue is important—indeed, it is generally stated that abnormal calcification takes place in such situations, as the mucosa of the stomach, the lungs and the tubules of the kidney where, on account of the ready loss of acid, the tissues might be supposed to be left in a relatively alkaline state, but it is difficult to apply this argument to the lymph nodes, the walls of arteries, and especially to the bones.

In the course of ordinary anatomical investigation we may expect to find calcification in a number of places. When the kidneys have been injured by corrosive sublimate poisoning, the dead epithelial cells, which are dislodged into the tubules, become masses of calcium. Infarcts in the kidney rarely do so unless they have existed for a very long time. In rabbits, however, even a brief obstruction of the renal artery, enough to injure profoundly the epithelial cells, is followed by extensive calcification throughout the whole kidney. Exudates such as are found in an old empyema or purulent pleurisy often become the seat of massive deposits of lime-salts when they have been encapsulated for a long time, and similarly, old fibrinopurulent exudates in the pericardium, after a sort of healing and encapsulation, become so loaded with lime that the heart is enclosed in a rigid sheath. The peculiar hyaline plaques which are so commonly found in the capsule of the spleen or liver, frequently become converted into plates of hard lime, or at times

are even replaced by bone. So, too, encapsulated parasites such as trichinæ, or old echinococcus cysts, become calcified. All sorts of tumors, especially when they grow slowly and have finally a defective circulation in their internal parts, undergo the same change. It is quite interesting that such tumors as spring from bone seem to carry with them in many cases, though not in all, the peculiar power of forming bone in living tissue far away from the bone proper. A baby born abnormally from an extra-uterine pregnancy, into the body cavity instead of into the outer world, becomes converted into a calcified mass (lithopædion) if it remains there long enough. And so on, any dying tissue embedded in the living tissue and accessible to the circulating fluids will gradually tend to become calcified and doubtless the principles concerned are the same, although acting more slowly, as those at work in those juvenile cases in which extensive calcification of tissues throughout the body occurs.

As to the part played by the so-called vitamines and by light in the metabolism of calcium we shall speak in connection with rickets.

LITERATURE

- Brull, Mouriquand, Leulier, Weil, and Guillaumin: Le metabolisme du calcium. Congrès Français de médecine, xxi e Session, Liège, 1930.
- Dreyfuss: Ziegler's Beitr., 1926, lxxvi, 254. (Acid base equilibrium and calcification.)
- Greenwald: Jour. Biol. Chem., 1925, lxvi, 185; 1926, lxvii, lxviii. (Calcium and Phosphorus Excretion.)
- Holt, LaMer, Chown: Jour. Biol. Chem., 1925, lxiv, 509. (Solubilities of Lime Salts.)
- Klotz: Jour. Exp. Med., 1906, viii, 322. (Calcification.)
- Robison and others: Biochemical Journal, 1923, xvii, 286; 1924, xviii; 1925, xix; 1926, xx. (Ferments in Ossification.)
- Schmidt, C. L. A., and Greenberg, D. M.: Physiol. Reviews, 1935, xv, 297.
- Stewart, C. P., and Percival, G. H.: Calcium metabolism, Physiol. Reviews, 1928, viii, 283.
- Verse: Ziegler's Beiträge, 1912, liii, 212. (Universal Calcification.)
- Wells: Arch. Int. Med., 1911, vii, 721. Harvey Lecture, 1910-11, 102. (Calcification and Ossification.)
- Various older reviews in Lubarsch and Ostertag's Ergebnisse: Aschoff, 1902, viii, 561; Ricker, 1896, iii, 1, 643; Schultze, 1910, xiv, 706.

DISTURBANCES IN THE METABOLISM OF IRON

Distribution of Iron in the Body.—The whole nature of the interchange of iron in the body is very imperfectly understood, although it is known to be of profound vital significance.

Iron exists in the body of an adult in the haemoglobin of the red corpuscles and in all the cells of other tissues. The amount contained in the blood is about 3 gm. That contained in invisible form in other cells has been estimated roughly at 1 to 3 gm.

It is similarly a constituent of the blood and tissues of other animals and of vegetable cells. Hence it enters into the human body in animal and vegetable food. The complex organic compounds are decomposed in the intestine in such a way that the iron is absorbed in the ionic form. Bunge's statement that it could be absorbed only when presented

in the form of the higher organic combination is rendered improbable by this fact, and further disproved by the familiar clinical experience of the effect of administering inorganic compounds in anæmias, and by the results of direct experiments which show the absorption of these compounds.

The ingested iron is absorbed in the duodenum and the upper part of the small intestine. As has been shown in cases of intestinal fistula, the chyme of the lower part of the ileum contains none. On the other hand, the excess is excreted into the colon and leaves the body with the faeces. By microchemical methods it may be demonstrated in the walls of the duodenum, and again in those of the colon, but not in the walls of the lower ileum.

The exact mechanism of absorption is not clearly known. Some is directly received by the epithelial cells and transferred later. Some appears to be carried into the tissue by leucocytes, or may possibly enter in association with lipoid droplets (A. B. Macallum). Part of it is thought to pass by way of the thoracic duct, but it may be assumed that the greater part enters by way of the portal vein and reaches the liver. We are equally ignorant of the exact mechanism of excretion, but in this respect iron seems to show analogies with calcium.

In the blood, iron is found in the *haemoglobin*, a combination of a very complex protein, globin, with haemochromogen or its oxidation product, haematin. Haematin ($C_{34}H_{34}N_4O_5Fe$, Abderhalden) may be decomposed into haematoporphyrin through the loss of its iron, and this in itself is a complex carbon compound containing pyrrol derivatives, and related to an analogous decomposition product of chlorophyll. Abderhalden points out that the formation of haemoglobin involves, therefore, the process of formation of haematin and its subsequent union with the highly specific globin, which, since all must start with the simplest building-stones which can pass the intestinal wall, leaves several points at which the production of the haemoglobin may be deranged.

The intermediary exchange of iron is beset with difficulties of interpretation. Red blood-corpuses are destroyed in the body, probably very largely by the spleen. The haemoglobin thus set free passes intact or partly decomposed from the spleen to the liver. Doubtless most of the iron absorbed from the intestine passes in the same way directly to the liver.

From the haematin separated from the globin iron is liberated in the liver, and the iron-free residue constitutes the bile-pigment, *bilirubin*, which is identical with *haematoiodin*.

The fate of the iron thus set free in the liver, and of that brought there from the intestines, has not been traced, but it is clear enough that it is somehow worked up into haemoglobin.

The iron of the tissues which is largely a constituent of the chromatin is tenaciously held by the cells and shared with the blood only in conditions of grave anæmia.

At birth the fœtus is rich in iron which was stored in its body from the mother, but during suckling very little iron is absorbed with the milk, which is extremely poor in that substance. Therefore, the iron content

is low at the end of the period of suckling, but rises rapidly when the infant begins to take other food than milk. M. B. Schmidt found that if the iron-free diet were continued in growing mice after the termination of suckling, they gradually became anaemic and were stunted in their growth. The offspring of such mice were studied through several generations, throughout which the feeding was continuously "iron free." If, now, iron were given to one of a litter of such meagre, anaemic mice, it quickly outgrew the control brother, and as quickly acquired a high percentage of haemoglobin and a nearly normal blood count, showing that the manufacture of haemoglobin had been halted by the failure of the tissues to acquire and then set free sufficient iron, and that this matter was quickly set aright by the supply of inorganic iron. The rapid growth that ensues indicates the fundamental importance of iron. But recent work ably reviewed by Elvehjem, reveals the fact that copper is present in considerable quantities in lower animals and in plants and evidently plays a part in the human body. Its essential function seems to be in aiding the transformation of ingested iron into haemoglobin. It is necessary as a supplement to iron for haemoglobin formation in red-blooded animals, and it seems that in extreme anaemia the administration of a pure iron salt has little restorative effect, but with the addition of a minimal amount of copper, the new formation of red corpuscles with haemoglobin proceeds rapidly. The spleen appears to be the organ in which the blood-corpuscles, destroyed there or elsewhere, give up their iron to be carried to the liver. But this idea of the function of the spleen, which is regarded by Chevallier also as an organ of assimilation of iron, preserving and transferring it for the manufacture of haemoglobin, must be made to accord with the fact that the spleen is a great site of blood destruction, and the further fact that its extirpation has a beneficial effect in such severe anaemias as may occur in haemolytic jaundice.

The function of iron in the body is at least to be definitely associated with the transfer of oxygen, and probably more generally with the processes of oxidation of the tissues. Its rôle in connection with its presence in the chromatin of the cells is not so clear, but it seems to affect directly or indirectly the process of growth. As in the case of fats and lipoids, it is evident that the forms in which iron is active in carrying out its important functions are those in which it is invisible even with the aid of most microchemical reactions. When it becomes visible, it is because it is cast out of functional activity and lies scattered in the tissues in pigmented granules.

Much has been written recently concerning its relation to the process of calcification. It appeared from the work of Gierke and others that substances about to become the seat of a deposit of lime salts first absorbed a quantity of iron. Hueck opposed this on the ground that the microchemical reactions showing the presence of iron in calcified areas were due to impurities of fixing fluids, etc. He even suggested the test for iron in tissues soaked in a weak iron solution as a means of demonstrating the distribution of calcium. Noesske found that, while perfectly fresh bones and calcified tissues showed no iron, it was to be

demonstrated in those situations if the body had lain for some time. He, therefore, thought that in this interval iron had been absorbed from the adjacent tissues.

Sumita, Eliascheff, and others return to the original idea that iron is actually to be found as a forerunner of the deposition of calcium in tissues examined when perfectly fresh after every precaution has been observed to avoid the objection that calcified material eagerly absorbs iron from the most dilute solution. Sprunt found an incrustation of elastic tissue fibres with calcium and with iron, while Gigon, in studying a lung supposed to contain a similar combination of lime and iron, as shown by microchemical methods, found by analysis no calcium, but much iron in association with sodium salts. The results are very contradictory, but there is, at least, much evidence that iron and calcium are deposited together, although it is not so clear as to which is the pioneer. We have found that in every area of pathological calcification there is a narrow boundary line of demonstrable iron just as there is in the line of ossification and beneath the periosteum in growing bone. Further, that the addition of an extremely minute trace of iron promotes precipitation in a mixture of calcium salts and phosphates in solution so dilute that without it the fluid remains clear. It seems probable that in the growing bone the iron is present in some such combination as that in haemoglobin which does not give the Prussian blue reaction, since it requires long fixation in formalin before this combination is dissociated so that the iron fraction responds to the test, but there is no reason to suppose that iron is merely absorbed from impurities in fixing fluids.

Two definite affections may be mentioned here as examples of disturbances in the metabolism of iron, the others, which appear to be rather more incidental processes, leading to local accumulations of iron-containing pigment, being discussed elsewhere.

Chlorosis.—Young girls frequently develop a peculiar greenish pallor with great weakness, perversion of appetite, digestive disturbances, and constipation. The blood shows a nearly normal number of red corpuscles, which, however, are very pale, so that the haemoglobin index may be extremely low. The disease is readily cured or even passes away itself with improvement in the state of the digestive organs, so that little is known with regard to its pathological anatomy. It is influenced by purgatives, and in a most remarkable way by the administration of iron in any form. Whether the inorganic iron thus given actually forms the material for the new production of haemoglobin, or stimulates its production by liberating the supply of combined iron from the tissues, remains uncertain. Nor do we know whether the defect in the formation of haemoglobin is due to the inadequate absorption of iron or to some difficulty in its combination with haematoporphyrin to form haematin, or finally to lack of the necessary globin. Chlorosis has practically disappeared in the last few years and Dr. Welch suggests that it is the result of the modern fashions in dress. Exposure to sunlight appears to promote in the most extraordinary way the metabolism and the oxidative activities of iron.

Hæmochromatosis.—A disease described by Hanot and Chauffard, and named by v. Recklinghausen, in which an extraordinary deposition



Fig. 54.—Hæmochromatosis. Pigmentation of liver.

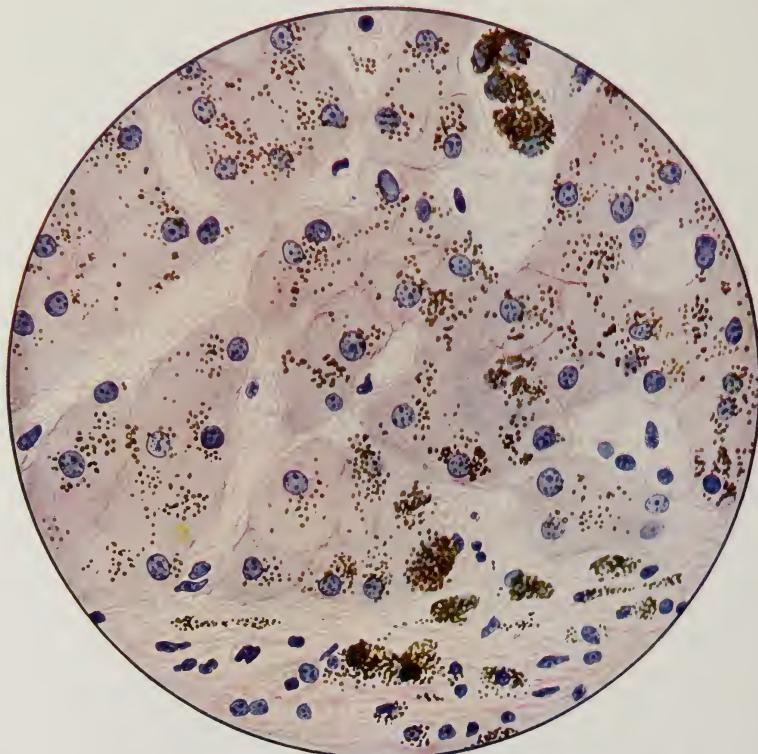


Fig. 55.—Hæmochromatosis. Pigment deposit in tissues of the liver.

of iron-containing pigment (hemosiderin), together with other pigment (haemofuscin) which contains no iron, is found in practically all the

organs, including the skin. It is often associated with cirrhosis of the liver and pancreas and with diabetes, hence the name, "bronzed diabetes," which is appropriate in many cases.

The skin is of a dusky bronze hue, and in sections the pigment may be demonstrated by its giving the Prussian-blue reaction. The liver, pancreas, kidneys, lymph-glands, heart muscle, etc., are found to be of a bright, chestnut-brown color, and show microscopically astounding collections of pigment in clumps and granules (Fig. 54). The pigment lies chiefly in phagocytic cells, such as Kupffer's cells of the endothelium of the liver, but it is also lodged in the connective tissue and in the liver-cells themselves (Fig. 55). In the other organs it has a corresponding position—apparently its presence as a foreign body leads to much new-growth of encapsulating fibrous tissue. Most of it can be stained blue with ferrocyanide and hydrochloric acid, but part of it remains brown and responds to no tests for iron (haemofuscin).

There is no obvious anaemia, no especial evidence of wide-spread blood destruction, and no especial activity of the blood-forming organs to repair a destruction of blood which would, of course, occur to any one as the probable source of so much iron-containing pigment.

Here the disturbance of iron metabolism must occur at some other point. In sharp contrast with chlorosis, in which it appears that absorption of iron or its combination into haemoglobin is deranged, there is found an adequate haemoglobin production, little or no blood destruction, but at the same time an overwhelming accumulation of hemosiderin. There is no marked retention of iron as determined by investigation of the intake and excretion. Indeed, the studies of Howard and Stevens and of McClure show perhaps a slight negative balance in the case of iron, but no marked general disturbance of metabolism. Various theories as to the nature of this disease have been suggested, but without being generally accepted. Mallory in a recent publication looks upon it as the effect of copper poisoning, and has discovered copper in the tissues of such persons who were found to have been drinking liquors distilled from copper vessels. Hurst similarly produced a pigmentation of tissues with haemofuscin in animals poisoned slowly with copper sulphate.

LITERATURE

- Abderhalden: Lehrb. d. physiol. Chemie, 1909, 491.
 Elvehjem, C. A.: Significance of Copper in Iron Metabolism, Physiol. Reviews, 1935, xv, 471.
 Gierke: Virch. Arch., 1902, clxvii, 318.
 Howard, C. P., Stevens, F. A.: Arch. Int. Med., 1917, xx, 897.
 Hurst: Arch. Pathology, 1926, i, 204.
 Macallum, A. B.: Jour. Physiol., 1894, xvi, 268. Proc. Roy. Soc., 1891, 1, 277.
 Mallory: Amer. Jour. Pathology, 1925, i, 117; 1931, vii, 351.
 McClure, C. W.: Arch. Int. Med., 1918, xxii, 610.
 Opie: Jour. Exp. Med., 1899, iv, 279.
 Schmidt, M. B.: Verh. Dtsch. Path. Gesellsch., 1912, xv, 91.
 Sheldon: Hæmochromatosis, Oxford Press, 1935. Lancet, Nov. 10, 1934, p. 1031.
 Sprunt, T. P.: "Hæmochromatosis," Arch. Int. Med., 1911, viii, 75.

DISTURBANCES OF PIGMENT METABOLISM.

Pathological disturbances of metabolism are by no means limited to proteins, carbohydrates, and fats, but involve irregularities in the formation and distribution of many other substances which ordinarily serve a normal function. Were we better informed, it would be most logical to discuss each of these according to its chemical nature and relations, but we know so little that we can hardly escape from the temptation to group them according to some striking peculiar feature. It is for this reason alone that we discuss in one chapter pigments which are often hardly related, except through the fact that they are colored.

Most of these pigments serve important purposes, and very little of their history concerns pathology except when, like the slag heap that indicates the activity of a smelter, they show by their accumulation the presence of some unusual activity in the body. Ordinarily, enough of the coloring-matter of the skin or hair is produced to confer on the animal those colors which are the beauty of the animate world, and which serve so well in the protection and even in the propagation of each individual's life. Or they are concerned in the interior of the body with the mechanisms for carrying oxygen to the tissues and in the production of bile, and an exquisite economy is observed in their use and the maintenance of their proper proportions. Only when something disturbs these mechanisms do we find the pigments or disjointed by-products in their formation accumulated somewhere in excess, or, on the other hand, lost to the body to such a degree that it lacks its normal colors.

Certain colored substances are formed in the body and elaborated to typical forms, although we may meet, too, with less complex materials which are destined to be built up into these type forms or are the results of their decomposition. These are endogenous pigments. Beside these there are foreign materials—colored particles breathed into the lungs or taken into the stomach or through the skin, or fluids which impregnate the body with colored deposits, and these are called exogenous pigments.

ENDOGENOUS PIGMENTS

Of these, several kinds are met with, the principal ones being those which are especially produced to color the skin, and hair and eyes, usually grouped as the melanins, those which are directly or indirectly derived from the haemoglobin of the blood, and those which are somehow associated with fat-like substances and come from the wear and tear and breaking down of the tissue-cells.

1. **Melanins.**—The melanins may assume various colors, but are usually dark brownish or black. Their enormous variety and the ways in which they normally occur more abundantly in those races exposed to sun and wind, their abundance largely dependent upon hereditary powers of the cells, their rapid appearance in the form of tan and freckles in response to exposure—all these things are hardly our concern, but belong to the field of physiology. Still the study of their abnormal production and distribution may throw some light upon their normal origin. The question of the origin and mode of formation of melanins

is an exceedingly complex one and even yet very imperfectly answered. It is impossible to discuss the chemical side of it intelligently here, and the student must be referred to such analyses as those of Bloch, Oberndorfer or Fürth. In general, it seems that cyclic complexes are split off from the protein molecule and these often in combination with sulphur and iron-holding constituents are converted into melanin by oxidative ferments. Melanins generally contain sulphur, but are not obviously iron-containing and are not derived from the pigments of the blood. Tyrosin has been most commonly mentioned as a substance upon which



Fig. 56.—Melanotic sarcoma. Secondary nodules in liver.

an oxidizing ferment may work, but other substances are also suggested. Bloch found that dioxyphenylalanin (abbreviated to dopa, in speaking of the dopa reaction) could be used to demonstrate the presence of an oxydase in the epithelium of the skin and in leucocytes and myelocytes. This is a substance closely related to adrenalin and in the case of the bronzing in Addison's disease it is suggested that because the adrenals are destroyed and adrenalin is no longer elaborated there, its mother substance is converted by the oxydase ferment in the skin into a brown pigment.

It has been shown that the oxydase ferment exists in the epidermal cells of the skin, but not in the cells of the cutis, although they may take up pigment formed in the epidermis. Further, it is found that it is absent in the skin and hair of albinos and in leucoderma patches and the white areas in vitiligo. White hair is that which grows without the oxidative ferment. Exposure of the skin to sunlight and artificial light of high actinic power seems to increase this ferment, which is naturally present in great abundance in the skin of negroes. The oxydase has also been found in the tissue of melanotic tumors.

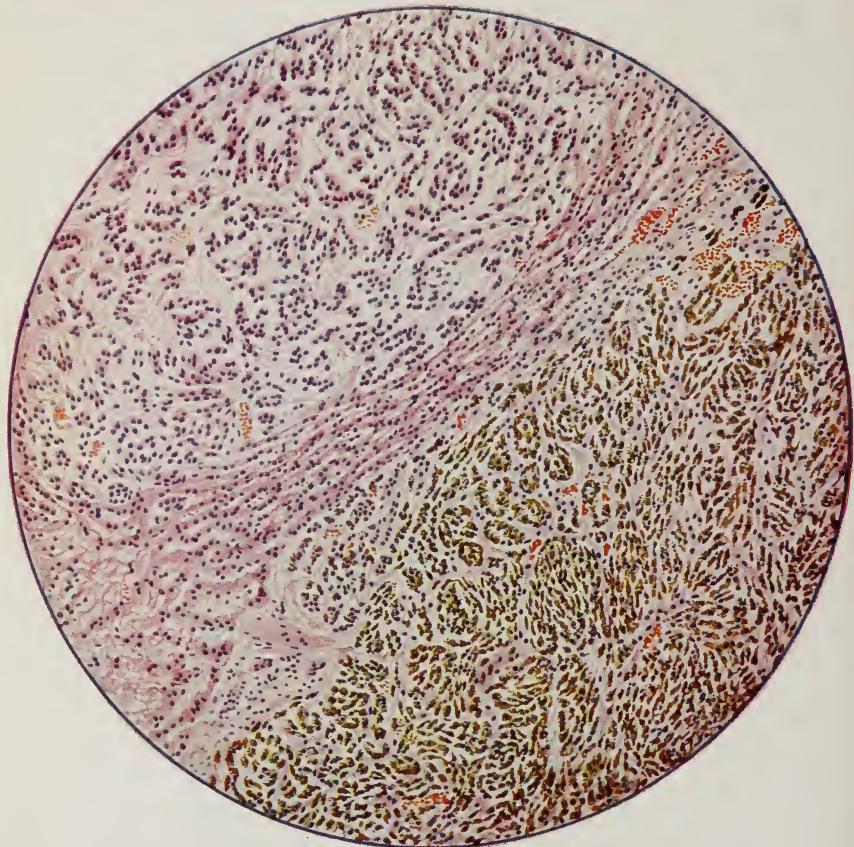


Fig. 57.—Pigmented cells of melanotic sarcoma in contrast with others not pigmented. Pressure atrophy of the liver.

But while it seems clear that the ferment is essential, the nature of the substances upon which it acts is not clearly defined.

Since dioxyphenylalanin produces a black pigment under its influence, it is suggested that they may be somehow structurally related to that, but there is still the sulphur to be accounted for.

Except in a few cases, we are not at all well informed with regard to the abnormal development of melanins in the skin. There are pigmentations which are doubtless only accentuations of the normal, and occur

chiefly in the most pigmented areas of the body, such as the chloasma of tuberculosis and of pregnancy, in which brownish flecks appear on the face and body, and the areolæ of the nipples, axillæ, etc., become more deeply colored. Probably, too, in the healing of many destructive skin diseases, and in the area about an old healing ulcer, increase of melanin produces part of the brown coloration, although, especially in the latter instance, blood-pigment plays a part.

The most striking example of the massive production of melanin is seen in the so-called melanotic tumors, which usually spring from the skin or from the pigmented tissues of the eye. Such tumors, which in their early and apparently innocent stages are known as moles or pigmented nævi (Fig. 601), seem to be derived from the melanoblasts, inasmuch as their metastatic nodules continue to form melanin, which could not be expected of mere pigment-carrying cells, the chromatophores. The weight of evidence in the prolonged strife as to their sarcomatous or carcinomatous nature is apparently with those who hold that they are really of epithelial origin. Growing with extreme rapidity and invading the most distant parts of the body, arid of pigment, these tumor-cells continue to manufacture such quantities of coloring-matter that not only is the mass itself coal black (Figs. 56, 604), but the pigment is carried away and appears in the urine either as such or in a modified, colorless form, which turns again on exposure, or when an oxidizing substance is added, to pigment which stains the urine black. No one seems to have followed very precisely the wandering of this pigment, although it is known that melanins injected into the circulation of an animal become decolorized by the reducing action of the tissues, only to blacken again when they are oxidized.

Ochronosis is a rather rare condition in which a brown or blackish pigment, probably allied to the melanins, is deposited especially in the cartilages and ligaments, but also in the aorta and sometimes in the kidneys. The patient becomes conspicuous on account of the bluish color that shimmers through the skin, where, as in the nose and ears, the pigmented cartilages are near the surface. It is due to metabolic disturbances often accompanied by alkapttonuria, or to the introduction of small quantities of such a substance as carbolic acid, as in the prolonged treatment of an ulcer with that antiseptic. Poulsen thinks that the pigment is produced by the action of such a ferment as tyrosinase upon tyrosin or homogentisic acid, or upon derivatives of the phenol introduced by the surgical dressings.

The malarial parasite, while still within the red blood-corpusele, produces particles of a shining, brownish-black pigment at the expense of the hæmoglobin-containing cell. This is probably derived directly from the hæmoglobin, although it is iron-free and by most authors regarded as a form of melanin. The remainder of the hæmoglobin dissipated in the plasma after the parasite breaks out of the cell forms an iron-containing pigment. Spleen, liver, and other organs become so laden with a combination of these pigments as to be quite blackened (Figs. 461 and 462).

Of the second group of endogenous pigments, those derived from

the blood, we may distinguish several forms. The source of all is haematin, which, in combination with a globin, forms haemoglobin, and it is after the haemoglobin has been set free from its suspension in the corpuscle that the decomposition may take place. Many things, ranging from distilled water through a series of organic or inorganic poisons to the most subtly modified blood-sera, may act as haemolytic substances capable of disintegrating the red corpuscles and setting free the haemoglobin. If it be thus set free in large amounts in the general circulation, it may be excreted through the kidneys, producing the so-called haemoglobinuria. This is not an uncommon accompaniment of malaria in some countries (black-water fever), and there has been much discussion as to whether it is caused by the malaria or the quinine given to cure it.

Another form occurs in paroxysmal attacks in certain predisposed persons whose red corpuscles seem very fragile and liberate the haemoglobin on the slightest injury. Even the mere exposure to cold produces an excretion of haemoglobin, and it has been found that this is because the haemolytic substances present can combine and act only at a low temperature. The kidneys become loaded with clumps of a yellowish material which seems to have come through the glomeruli and lodged in the tubules. In a similar way poisoning with chlorates produces the excretion of a modified haemoglobin, methaemoglobin, and that with sulphon and allied poisons causes the appearance of iron-free haematoporphyrin.

Some bacteria have the power of causing hemolysis, and in general infections, where the blood becomes filled with these bacteria, there is much destruction of red corpuscles. After death the laked blood stains the tissues so that at autopsy the walls of the heart and the linings of the blood-vessels are of a dull red color. Through the walls of the superficial veins this color may diffuse to such an extent that one sees a network of purplish bands shimmering through the skin. Nor is this cadaveric staining exclusively the effect of such general infections, for in any body which has lain some time after death the tissues which are in contact with large accumulations of blood are stained deep red. It is not particularly a pathological phenomenon, but one which might confuse the unwary.

2. Pigments Arising From the Decomposition of Hæmoglobin.—Ordinarily, although, as we know, the red corpuscles circulate intact only a relatively short time, so that in every hour millions of them fall to pieces, there is no noticeable coloring of the blood-plasma with haemoglobin. Nor is the haemoglobin excreted from the body in the urine—instead, it is taken up by various cells and converted into different sorts of yellowish-brown pigment. Of these, one is bilirubin, which is the coloring-matter of the bile, an iron-free substance ($C_{16}H_{18}N_2O_2$) which is apparently formed chiefly by the activity of the Kupffer cells and secreted into the bile ducts by the liver cells. Of this we shall speak in connection with jaundice. When a large haemorrhage occurs in the tissues or in a body cavity, we often find, especially in the interior of the mass, a reddish-brown pigment in granules or in rhombic or needle-shaped crystals. This was called haematoidin by Virchow and

was thought to be formed essentially in the absence of living cells. It is now known to be identical with bilirubin, and Rich has shown that it is formed in living cells in crystalline form both in living animals and in tissue cultures. It may become conspicuous in the center of a haemorrhage or infarct when the cell that formed it dies and disappears.

More abundantly formed by the same phagocytic wandering cells is the amorphous yellowish-brown, iron-containing hæmosiderin. To this we can give no formula, for it is merely a mixture of pigments in which iron exists in a most accessible form, so that its presence may be readily shown by the application of the Prussian-blue reaction. Hæmosiderin is the common blood-pigment which results upon any small extravasation of blood into the tissues, in so far as that blood is not immediately reabsorbed as such. Bilirubin is probably there too, but

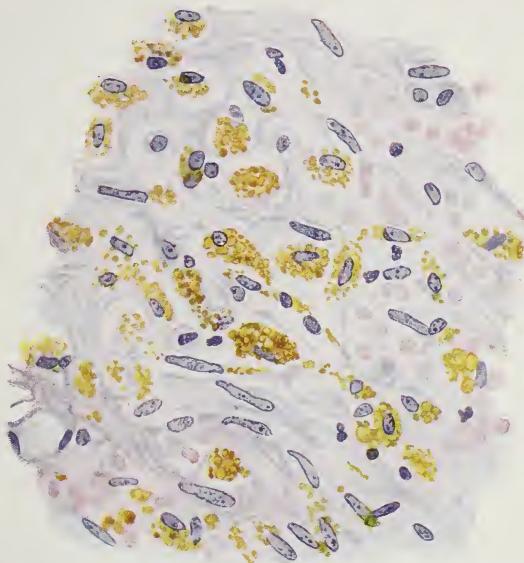


Fig. 58.—Hæmosiderin in phagocytic cells near an organizing thrombus.

is not visible except when it occurs in crystalline or amorphous form. Thus in every sort of wound and bruise, in every sort of inflammation in which red corpuscles escape from the vessels, in purpura, in scurvy, and in every other disease where there are ecchymoses or more extensive haemorrhages into the tissues, or about the stings of insects or reptiles, hæmosiderin may be found after some days. When the poison is of a haemolytic character, and, in fact, in any condition in which blood or the coloring-matter of blood escapes into direct contact with the tissues, there may be formed in the phagocytic cells yellow or yellowish-brown, shapeless granules of this pigment (Fig. 58).

A few common examples may illustrate the mode of occurrence of this pigment. In old insane persons, especially, perhaps, those forms of insanity arising from syphilis and chronic alcoholism with arterio-

sclerosis, one may find lining the dura mater a thick, blood-stained membrane which will peel off in thin layers and which, on being washed free of blood, proves to have an ochre or orange-yellow color. This so-called chronic haemorrhagic pachymeningitis may be the result of a single hemorrhage, but is usually produced by something, perhaps itself a small haemorrhage, which causes the formation of a thin layer of vascular granulation tissue from the capillaries of which new hemorrhages occur and cause the growth of a new layer of tissue. In the wandering cells which pervade this tissue hæmosiderin in granules which give the yellow color to the whole. A quite similar rusty-brown membrane may be found in hemorrhagic hydrocele sacs where the tunica vaginalis testis has long been inflamed. Sometimes a hemorrhagic infarction of the lung may heal, and the area, once turgid with crumbling red corpuscles, is found shrunken and firm with scar tissue and of the color of a mass of iron rust. In the interior much of the pigment may

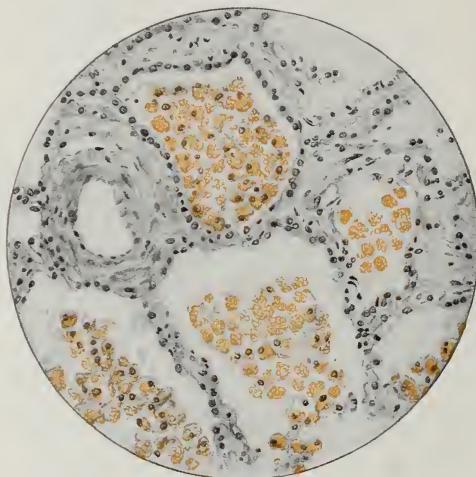


Fig. 59.—Heart-failure cells in the lung. Chronic passive congestion.

be the iron-free hæmatoidin, but that in the more marginal portions is found to stain blue with ferrocyanide and hydrochloric acid, and to be made up of amorphous granules inclosed in cells which are often fairly bursting with their load of pigment. Again, when the mitral valve is contracted so that blood does not readily escape from the lungs, we may find them distinctly brown on section. A piece of such a lung washed free of blood and dipped in ferrocyanide of potassium and then in weak hydrochloric acid becomes bright blue, and we find that this is because blood-corpuscles have for months oozed into the alveolar cavities, and have there given up their haemoglobin, which is converted by the phagocytes into hæmosiderin. Microscopically, these cells are seen, swollen with yellow granules, lying in the alveoli or in the sputum which has been coughed up from the lung. Their dependence upon this chain of events has given them the name "heart-failure cells" (Fig. 59).

Arnold finds that many of the iron-staining granules are due to the assimilation of fluid iron-holding material by the specific granules of the cell protoplasm, and not to mere engulfing of hæmosiderin granules by phagocytic cells, and Neumann states, too, that in the heart-failure cells the pigment masses often have a coal-black central point and are really formed by the incrustation of particles of soot by the iron-containing hæmosiderin.

Not in all cases is the formation of hæmosiderin such a local process, however, for there are many forms of general anaemia in which the

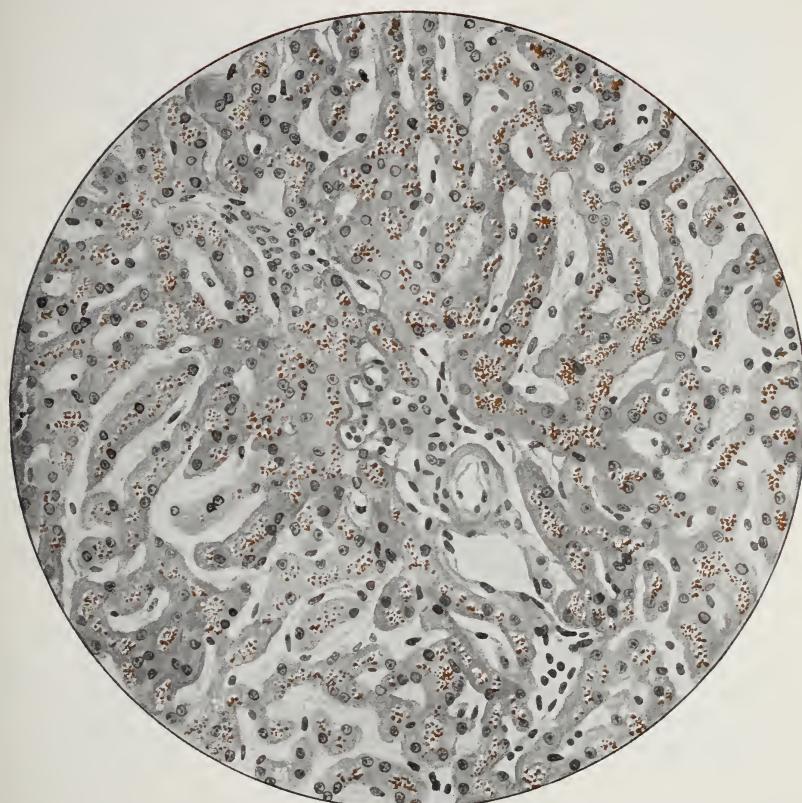


Fig. 60.—Hæmosiderin granules in the liver-cells and endothelium. Pernicious anaemia.

destruction of the red corpuscles, usually by some unrecognized agency, sets free continuously a great excess of haemoglobin into the circulating blood. This may cause the production of an excess of bile-pigment or it may result in a wide-spread deposition of hæmosiderin in the cells of many organs. In the so-called pernicious anaemia, of whose true nature we are ignorant, the cells of the liver and often of the cortex of the kidney, spleen, etc., become laden with haemosiderin in fine granules (Fig. 60).

In haemochromatosis, a disease of which mention has already been made, there is an even greater deposition of haemosiderin and of another iron-free pigment, haemofuscin, without any extensive destruction of red corpuscles.

We know that such pigment is transported from one part of the body to the other, and transferred from cell to cell, and that much of it reaches the bone-marrow, where it must be thought of as furnishing, according to the economical scheme, the iron-rich material for the formation of new haemoglobin by the erythroblasts, but that step in the process is far from clear. When there has arisen in any way a deposit of haemosiderin in the tissue of the intestinal wall or in the liver and spleen, decomposition of the body after death or even the excessive formation of hydrogen sulphide in the intestine or in the infected peritoneum may give rise to the formation of black iron sulphide throughout the superficial layers of the tissue. This is pseudomelanosis.

3. The third group of endogenous pigments may be more briefly dismissed, since we know little to tell of them. Nevertheless, we may probably look forward to learning some day that their significance is greater than we have thought. These are the yellowish granules which are found in many organs, such as the seminal vesicles, heart muscle, ganglion-cells, and probably also the interstitial cells of the testes and the cells of the corpus luteum and adrenal. They give something of the characteristic color to the organ, and in some cases this color is intensified when the cells of the organ waste away. It seems that the pigments are in some instances produced from the cell protoplasm in the process of wasting, wherefore Lubarsch and Sehrt call them "wear and tear pigments." Others have loosely called them lipochromes, but they do not give the reactions which have been set forth for the "true" lipochromes, such as have been found in plants and are found in fats, and perhaps in the lutein cells of animals. Their distinctive feature is that they are in a sense colored lipoids and stain brightly with Sudan and other fat stains. Perhaps the best example of their accumulation in gross is seen in the wasted, shrunken heart of old or cachectic people (brown atrophy of the heart). There the muscle has a chestnut-brown color, and microscopically the spaces at the ends of the nucleus in the narrow, thread-like muscle-fibre are filled with brown granules which are shining and red after staining with Sudan. Of course, they are normally there, but they are vastly more abundant in the brown, atrophic heart (Fig. 30).

Jaundice.—The occurrence of a yellow or green or even deep bronze pigmentation of the skin and exposed mucosae, together with the excretion of bile-stained urine, has long been known as jaundice or icterus. With the appearance of jaundice the patient is usually depressed, his pulse is slowed, and his skin itches. The urine, when the jaundice is intense enough, becomes brownish-green and gives a green froth. The coagulation of the blood becomes slowed, and surgeons hesitate to operate upon jaundiced persons lest they bleed to death.

It is essential to realize that bilirubin, the pigment of the bile, is identical with haematoidin which, as has been said, is formed when

vitamin K

blood-corpuses are destroyed in the tissues. It has always been thought that bile-pigment is formed by the liver-cells, but recently it has been shown that even when the liver is extirpated (Mann), it continues to be formed and to appear in the blood-plasma. Briefly, the result of most painstaking studies has shown that while its source is the hemoglobin of the red corpuscles, it can be formed by those tissues especially in which the large specialized phagocytic cells (reticuloendothelial system) are most abundant. This is true of the spleen, bone-marrow, many other tissues, and perhaps particularly of the liver.

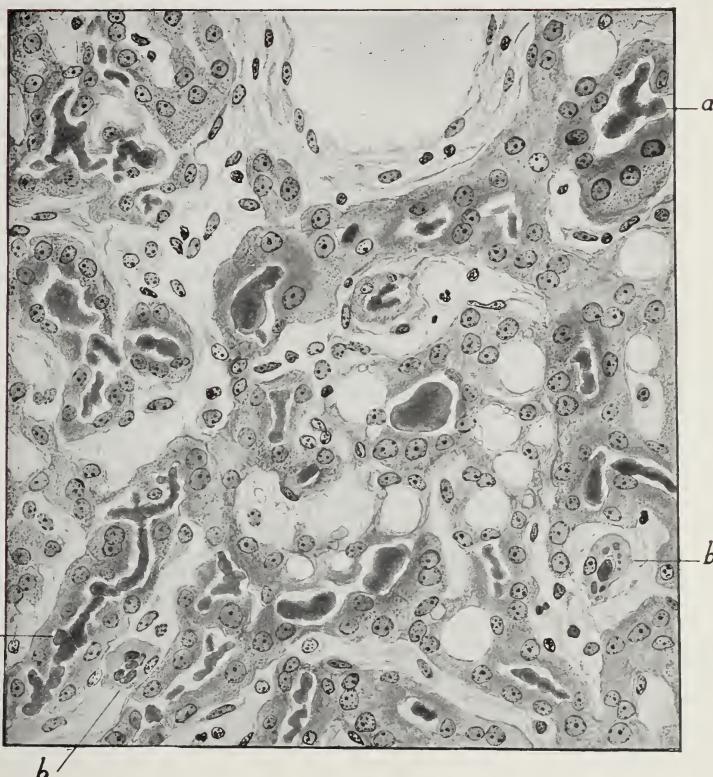


Fig. 61.—Bile-canaliculi in jaundice plugged with bile-pigment (*a*, *a*). Phagocytic cells in capillaries containing similar plugs of bile-pigment (*b*, *b*).

itself, in which the Kupffer cells of the sinuses are the abundant representatives of this group. McFee has emphasized this possibility, and Rich has shown, in the tissues and most clearly in culture, that such cells and no others take up the disintegrating red corpuscles, and later form in their own bodies bilirubin which may appear there in crystalline form, but is doubtless normally discharged in solution into the plasma.

How the bile-salts are formed and secreted, and how cholesterin appears in the bile remains obscure, but these are processes which may be dissociated, and the French have particularly emphasized their sepa-

ration in some forms of jaundice so that, while the pigment is retained, salts and cholesterin may be normally secreted. All this is, of course, very different from the old ideas of jaundice, and the student should consult the reviews of McNee and Rich for the evidence upon which such statements are based, and contrast them with the older reviews of Stadelmann, Eppinger, and others. The liver-cells are left with no part in bile-pigment formation except that of secreting it into the bile-ducts.

The van den Bergh reaction allows us to distinguish, in the blood, bilirubin which has been formed in the tissues and never as yet has passed through the liver cells, from that which has been secreted into the bile canaliculi and mixed with bile-salts and cholesterin. The latter gives the direct reaction while the former will not give it directly, but only after the addition of bile-salts or cholesterin or even alcohol—the so-called indirect reaction.

It is possible, therefore, to distinguish conditions in which bilirubin accumulates primarily in the blood from those in which it extravasates from the bile canaliculi into the lymphatics and thence into the blood. Rich distinguishes retention jaundice and regurgitation jaundice—perhaps better called extravasation jaundice. The retention jaundice is found in those conditions in which great blood destruction is accompanied by reduction in the secretory power of the liver cells. This reduction is usually the effect of the anoxæmia which follows the destruction of red corpuscles in the various forms of anaemia, by whatever haemolytic agent they are produced, or of the analogous anoxæmia which comes from the slow motion and imperfect oxygenation of the blood in chronic passive congestion. Experiment has shown that inadequate oxygen supply causes the shrinkage and even necrosis of the liver cells about the efferent vein in each lobule, apparently as the result of a special sensitiveness of these cells as compared with the midzonal or periportal cells.

It is of course essential that the secretory power of the liver for bilirubin should be greatly impaired while increased bilirubin formation occurs in the blood, if the tissues are to show the jaundiced hue, because ordinarily the liver has a very great reserve power in this direction. So it is that retention jaundice, even in the type conditions mentioned by Rich, such as pernicious anaemia, malaria, chronic passive congestion, etc., is slight except in extreme cases. In such retention jaundice the blood shows an increased indirect van den Bergh reaction, stools and urine contain increased amounts of urobilin which is formed in the intestine by reduction of bilirubin.

The second form of jaundice which results from extravasation of the bile from the canaliculi into the blood, does so either because the outflow of bile into the intestine is mechanically obstructed, or because the liver cells which form the walls of the canaliculi and direct the bile into the larger bile-ducts are necrotic and disintegrated, so that the whole bile including bile-salts, cholesterin, etc., escapes into the blood in the intra-lobular sinuses. Thus it gives the direct van den Bergh reaction in the blood, it fails to reach the intestine in normal quantity and the stools and urine contain less urobilin, but on the other hand the urine contains such bilirubin as has been secreted with bile-salts into the bile-

ducts, because only that type of bilirubin which gives the direct van den Bergh reaction can be excreted through the kidney.

Many forms of mechanical obstruction of the large bile-ducks might be mentioned, such as gall-stones in the common duct, tumors filling or compressing it and even bacterial infections of the ducts which are associated with the formation of abscesses about their branches. It is obvious that the obstruction of a branch of the hepatic duct will not produce any extreme retention of bile, and that obstruction of the cystic duct would merely interfere with the function of the gall-bladder which is a reservoir, while the bile from the liver could still pass through the common duct into the duodenum.

A tumor of the pancreas, or of the stomach, or of the papilla of Vater may obstruct the flow of bile through the common duct, and at the other extreme, numerous tumors in the liver may compress so many branches of the hepatic ducts as to cause jaundice. While in the cases in which obstruction is produced far down in the common duct by the pressure of a tumor the gall-duct and gall-bladder are found dilated and thinned out, the reverse is true when the obstruction arises from the impaction of gall-stones which have long lain in the gall-bladder or in the branches of the hepatic ducts. Then one finds the ducts roughened and thickened and the gall-bladder contracted and thick walled (Courvoisier's law).

The extreme destruction of liver cells which, in the absence of mechanical obstruction of the large bile-ducts, still allows the extravasation of bile into the blood-stream may sometimes result from the action of poisons such as the arsenicals which are used in the treatment of syphilis. This is practically like the so-called acute yellow atrophy of the liver, of which some cases without recognizable cause still occur. Chloroform, carbon tetrachloride, and various other substances can produce similar, but usually slighter destruction, and the poisons of yellow fever and Weil's disease, affecting as they do the midzonal cells of each lobule, cause their characteristic deep jaundice in this way.

Catarrhal jaundice, so-called, seems to belong to this group, since the direct test for bilirubin in the blood is obtained, but all the cases recover and the anatomical changes are unknown.

For a full discussion of the pathogenesis of jaundice the student is referred to the paper of Rich, Johns Hopkins Hospital Bulletin, 1930, xlvii, 338.

EXOGENOUS PIGMENTS

These are nearly always relatively simple substances, which get into the body in some way and color the tissues. Most common are those found in the various dust diseases, or konioses, in which the lungs become loaded with the particles which are breathed in by those who ply a dusty trade. The miller fills his lungs with flour, the smoker with soot, the coal-miner with coal-dust (*anthracosis*), the grinder with metallic dust (*siderosis*) or with the dust from cut stone (*chalcosis*), and so on. These should be called *pneumonokonioses*, and their variety is as the variety of dusts. The most common is the ordinary, practically universal

anthracosis, which is found in every one and every animal of sufficiently advanced age, especially if they live in a city. The pigment is sometimes in discrete patches, collected along the interlobar septa, but when it is very abundant, as in the coal-miner, it fills almost all the tissues of the lung. Such lungs are often very hard on account of the constant attempt at encapsulation of the pigment in scar tissue, and some pigments are so irritating and require so dense a capsule that the lung tissue becomes almost stony (Fig. 62).

The nature of the coal-pigment has been disputed, and it probably is a mixture of soot and a great variety of insoluble particles, but

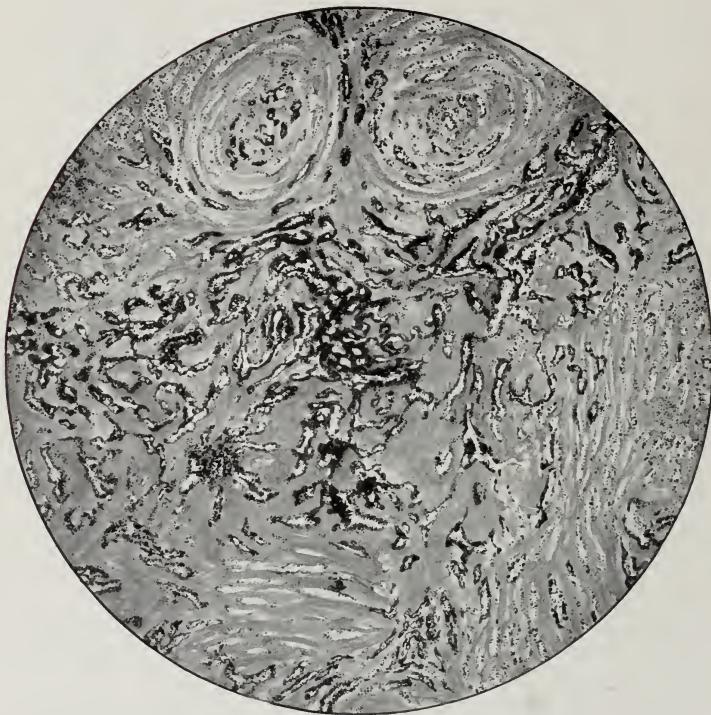


Fig. 62.—Anthracosis of bronchial lymph-gland. Hyaline alteration of gland tissue.

Traube was able to show in some lungs, doubtless those of actual coal-miners, that the granules were really fragments of carbonized coniferous plants, as could be seen from the characteristic bordered pits of the cells which had persisted throughout. Engulfed by phagocytic cells in the alveoli, or even in the free state, these particles gain entrance to the lymphatics of the lungs, and are carried, probably with frequent interruptions and transfers to other phagocytic cells, to the bronchial lymph-glands, which are blackened and indurated by their presence. These glands are often found adherent to the pulmonary veins in such an intimate way that there may arise an actual transfer of pigment to the vein-wall, or even a hole in the wall through which pigment is swept

into the blood-stream. This may explain the occasional presence of coal-pigment in the abdominal lymph-glands or in the spleen and liver, for it has been found that little if any of the dirt and colored matter taken into the intestine passes through the walls into the lymph-glands.

Metallic dust may be inhaled, and colored substances derived from it distributed in the tissues. Most striking is the rusty pigmentation of phagocytic cells about a needle or any other iron particle which has long been embedded in the tissue. These cells look almost as if they had actually gnawed off particles of the metal and carried it away. The same thing is true of the silver sutures used by some surgeons and left in the tissue. Years afterward they may be recognized by a gray cloud about them, which is found to be due to the presence of swarms of

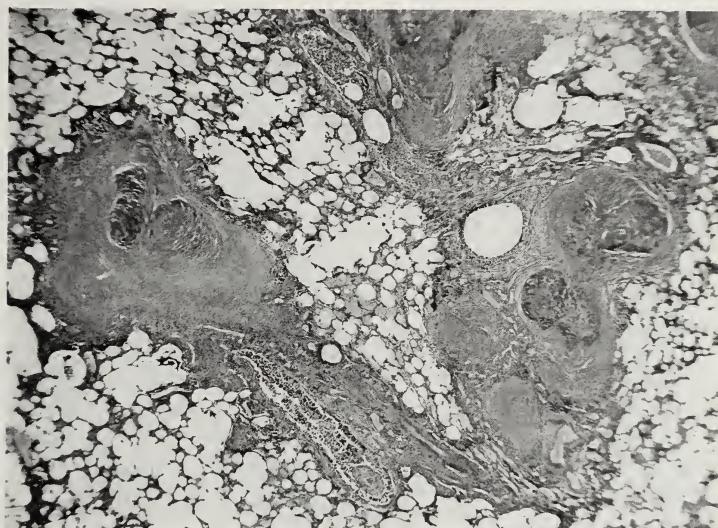


Fig. 63.—Silicosis. Dense hyaline scarred nodules in the lung.

branching cells loaded with fine particles of blackish silver. The long-continued administration of any silver salt by mouth, as was once the habit in the treatment of epilepsy, gastric disturbances, etc., often led insidiously to the production of argyria, in which the skin, connective tissues, and the framework of various organs assumed a leaden color from the fine deposit of what is probably a silver albuminate. Any one who has ever seen one of these victims can never forget the ghastly gray-blue color of his face and hands.

Much stress has been laid recently upon the changes in the lung produced by the inhalation of dusts containing silica crystals, the so-called silicosis. Sharply defined nodules of fibrous tissue and whorled islets of hyaline material appear especially in the angles of the bronchioles which become narrowed. This seems to predispose to tuberculous infection.

LITERATURE

- An excellent discussion of melanins is given in O. Fürth, Lehrb. de Physiol. u. Pathol. Chemie., 1926, i, 339, but the most comprehensive review of pathological pigments is that of S. Oberndorfer, Lubarsch and Ostertag, 1921, xix, 2, 47.
- Barron: Bilirubinæmia. Medicine, 1931, x, 77.
- Eppinger: Die Hepatolineal Erkrankungen. Enzyklopædie der Klinischen Medizin, Berlin, 1920.
- Gardner: Jour. Amer. Med. Assoc., 1934, ciii, 743.
- Garin: Revue de la Tuberculose, 1934, ii, 801.
- Gettler and others: Argyria, Amer. Jour. Path., 1927, iii, 631.
- König: Abnutzungs pigment. Ziegler's Beitr., 1926, lxxv, 181.
- McNee: Quart. Jour. Med., 1923, xvi, 390.
- Poulsen: Ziegler's Beitr., 1910, xlvi, 348 (ochronosis).
- Rich: Physiol. Reviews, 1925, v, 182; Bull. Johns Hopkins Hosp., 1930, xlvi, 338.
- Simson: Jour. Path. and Bact., 1935, xl, 37.
- Soffer: Medicine, 1935, xiv, 185.
- Stadelmann: Ikterus, Stuttgart, 1891.

CHAPTER IX

DEFENCES OF THE BODY AGAINST INJURY

Immediate and late reactions to injury. Inflammation, fever, immunity production, and repair. Inflammation an elaborate mechanism to combat injury. Details of vascular and phagocytic phenomena. The wandering cells.

Reactions to Injury.—We may say without hesitation, except perhaps in the case of tumors of whose origin we are ignorant, that the underlying cause of every abnormal change in the body is some sort of injury. Often we may see the direct effects of such injuries, but in many cases they are confused with the efforts of the body to annul or repair the hurt.

In the course of ages, through the action of external agencies, the human body has been elaborated to its present form, which is marvelous in its perfect adaptation in every detail to its uses. Variations from this standard in some respects are compatible with life so long as they are not too extreme, although they may handicap the individual in his struggle for existence. Why such a form should have been developed involves broader questions than we can consider here. The same questions arise in connection with every other species, and it is a matter of interest to the palaeontologist and the general biologist that, once established, such creatures should go on transmitting through ages all the details of their structure to their offspring, and that individuals should possess the inherent tendency to maintain that form and to return to it as they recover from maiming and distorting injuries. So great is this tendency in the lower orders of animals and in plants that if only a fragment of the body is left it can reconstruct the whole. Even in man, such is the tenacity with which the standard is adhered to that within the life of the individual great strides are made to return to the normal when tissues and organs have been disarranged.

It seems, however, that there are two distinct chains of events, the first being the perfection of a structure and form adapted to the environment, but subject to extremely slow variations, which maintain this adaptation and are hereditary and stamp the species. The second group of phenomena is subservient or auxiliary to this, and consists in the development of protective mechanisms which guard the life of the individual. But one cannot so sharply classify and divide these things, for they overlap. Mechanisms which protect the individual form some of the characters of the species, and the repairing of a wound in the individual is in great degree guided by the hereditary tendency toward the form characteristic of the species and independent of the momentary action of the environment.

It is this group of hereditary and gradually perfected mechanisms for defence that we must discuss. Of these, some are quite simple and obvious in their character. The body is covered with a relatively im-

pervious skin, further protected in places by hair and nails. It is true that, compared with a turtle or a rhinoceros, we are defenceless in that regard, but ordinarily our need is perhaps not so great. Our respiratory tract is lined with cilia, which keep dust out of the lungs, aided by sneezing or coughing when necessary. Irritating substances are ejected from the stomach by vomiting. Wounds are warded off by all sorts of reflex muscular movements, and so on. All these, in so far as they are functional, have become or were always involuntary processes tending toward the projection of the body from injury.

But still injuries occur from mechanical, physical, or chemical causes, and from the invasion of living plant or animal parasites, and these injuries, which generally imply the destruction of some of the tissue, call into activity several kinds of reactions or responses which have been elaborated through ages of natural selection and bequeathed to their offspring by those whom they have helped to survive. They are of several types, and appear to be rather independent of one another, for some injuries call out one, some another, but most often they all come in combination or in succession. They are: Inflammation, fever, immunity production, repair.

Inflammation is a complicated vascular and cellular response, which follows almost immediately upon the injury, and is adapted, by bringing much blood to the spot and pouring out its elements upon the injured tissues, to prevent the extension of the injury, hold in check the injurious agent, or even destroy it. Through the agency of some of the cells which are brought in, and in other more purely mechanical ways, it is also important in clearing away the débris of injured or dead tissue and preparing the way for the process of repair.

Fever is another complex response through which, by certain changes in the heat-regulating mechanisms, the temperature of the body is raised chiefly through the saving of heat. It is thought that this is bound up with—

Immunity production, a response to certain types of injury which quietly and slowly forms substances specifically adapted to annul and prevent the inroads of that particular injurious agent. Sometimes this power remains inherent in the tissues for life.

Repair is the new formation of tissue to replace that which was destroyed. It may be local, in which case the repair is often a kind of patching with tissue of a different sort. Or it may occur in addition at a distance from the point of injury, and consist in the new formation of the sort of tissue which was destroyed in such a way as to make up for the deficiency which its loss occasioned. Then it is often called compensatory hyperplasia.

Repair must, therefore, not be confused with inflammation nor regarded as a part of it. It is true that the result of the local tissue growth is not always what we should regard as the ideal outcome of an attempt at healing. Awkward scars or an altogether excessive mass of fibrous tissue may be produced which may even interfere seriously with the function of the organ and be entirely out of proportion with what would seem necessary for the repair of the actual gap first pro-

duced by the injury. Usually this is because the injurious agent persists and repeatedly frustrates healing by injuring the repairing tissue itself, so that layer after layer of this new tissue is laid down and consolidated into a firm scar. Possibly this might not be so to such an extent were it not for the inflammatory outpouring of fibrin which it has become the habit of this mechanism to replace by fibrous tissue, rather than to remove in any other way.

It is a mechanism like the others which seems to have been perfected through long generations toward a rather complex end, for not only does it repair gaps in the tissue, but it is protective in the sense that it brings about the encapsulation of any noxious material and prevents its further influence upon the neighboring tissues. While we are familiar with its ordinary course, and can even prophesy what will happen in a given case, we are not so well informed as to the exact mechanism which impels these cells to grow. If, therefore, we speak of the impulse to repair, or disturbance in the equilibrium of tissues, or, on the other hand, of chemical or mechanical stimuli acting directly upon the cell and causing its proliferation, we are using vague terms, all of which may possibly have the same meaning.

This reaction, like the others, is imperfect, and may produce unsatisfactory or even harmful results; but if the person survives, there is set at work a remodeling process through which, in time, much is done toward restoring the tissues to the normal standard. This involves other mechanisms which obliterate blood-vessels in one place and form them in another, rarefy and fret away tissue at one point or strengthen it at another. Seldom does any one live long enough to have this completed, but we find evidence at autopsy that it has been at work.

INFLAMMATION

According to the definition of inflammation given above, it seems preferable to use this name for the immediate protective and defensive reactions to an injury. It is a complex phenomenon, elaborated to a certain degree of perfection in which the blood-vessels with their contents and the wandering cells from adjoining regions play the greatest parts. Its aim seems to be the prevention of further injury by antagonizing the injurious agent, and this must be thought to include the solution and removal of foreign materials (which may be the dead cells themselves) because such material is in itself a cause of injury.

The removal of foreign material or of cellular débris may take place, as in the desquamation of the epidermis or the bursting of an abscess by mechanical means, which hardly form part of the inflammatory reaction, so that perhaps this process of cleaning up the field so that repair may occur may be regarded as incidental to the main aim of combating the injury. At any rate, the reaction seems to be quite distinct from the process of repair. It is confusing, however, that inflammation, cleansing of the site of injury, and repair commonly overlap and proceed together inextricably mingled in the same area. One might construct a simile in which the fire department, hurrying to a

burning house, represents the inflammation, although often long before the fire is extinguished workmen are found carrying away the charred timbers and enthusiastic carpenters are rebuilding wherever they can approach near enough. If this combination of activities be carried on for a long time, it is easy to foretell a curious distorted building as the result of the carpenters' efforts. But would any one say that it was the fire that had directly stirred the carpenters to work?

We must discriminate between the direct effect of the injurious agent upon the tissues and the inflammatory reaction. This direct effect may be the killing of some of the cells, with further injury not sufficient to cause death, diminishing as one passes away from the point at which the destructive agent impinged upon the tissue. Sometimes the injury is hardly visible, although it stirs up an intense inflammation, but generally it is necessary that at least a few cells be killed, that this may result. Extensive injuries which cause metabolic disturbances in the cells may arouse no inflammatory reaction at all; cells may gradually waste away from disease or malnutrition or from pressure, as in a hydronephrotic kidney, and there is little or no inflammation; but let a few cells die and coagulate into what is virtually a foreign body, or introduce any foreign body, and an inflammatory reaction appears at once. This reaction is not attuned to all sorts of injuries, nor even necessarily to the most severe, for a man may have his leg cut off by the surgeon and the wound will heal with evidences of an inflammation which is directed toward the annihilation of the few dying cells which happen to have been cut in two in the line of incision, quite regardless of the more serious catastrophe that the man had lost his leg. Or a vein may be opened aseptically and an animal bled nearly to death; wonderful reparatory processes will occur in the distant bone-marrow to restore the blood, and fluid will pour from the tissues into the blood-vessels, but there will be no inflammation. Cauterize the wound, however, with a hot iron or with boiling oil, as as they did in the time of Paré, and the inflammatory reaction will appear in its full force. We are tempted to ask whether, after all, inflammation as a reaction responds only to the presence of dead cells, and their diffusible decomposition products, and whether, in the course of the development and elaboration of the reaction, this has evolved itself as the general signal for inflammation, but we know that we may greatly intensify the reaction by the use of some other more irritating substance to kill the cells.

Given the adequate injury, the inflammatory reaction begins with a red flush. It can be followed in any place near the skin, perhaps especially well, as Samuel pointed out, in such an object as the rabbit's ear, where the blood-vessels can be seen, but for the minute details it is best to study with the microscope such transparent tissue as the mesentery or tongue of the frog or the wing of the bat. If the tip of the rabbit's ear be painted with croton oil or dipped in hot water, the whole process comes on with a rush. First, after a momentary contraction, there is the widening of the arteries and veins, so that the blood courses through them very rapidly, and simultaneously the widening of

all the minute arterioles and venules in the affected area, so that channels come into view which were evidently completely collapsed before (Figs. 64 and 65). This much is commonly attained if, by compressing the veins or by cutting the sympathetic nerves, we cause the dilation of the vessels. But, in addition, in the inflamed ear, all the spaces between these visible widened channels become uniformly red. A needle passed through one of these spaces in the mechanically congested ear will draw no blood; but in the inflamed ear there is free bleeding from the puncture. Evidently, then, the capillaries are uni-



Fig. 64.—Portion of inflamed diaphragm cleared by Spalteholtz's method to show the abundant dilated blood-channels.

formly distended with blood. While this change takes place at first in the actually injured area, it soon spreads to the adjacent part of the ear, and finally even to its root or over the side of the head. The ear is much warmer than the other, because blood rushes through it so fast that it has the temperature of the interior of the body, and it is gone again before there is time to cool off. This lasts only a short time before the ear becomes swollen and the skin tense. If it be pinched, the impression of the finger remains for a time. It becomes

so thick and heavy that it hangs down, and its function must thereby be interfered with. Besides it is very tender and even spontaneously painful. At the least touch the animal jerks back as if burnt. Two or three days later the artery may be found contracted again to something near its normal size. In the injured area the redness persists, though it may be a darker, more violet color—the ear is cooler—blood seems to be passing through the vessels very slowly, and the swelling is gradually passing away. It may require ten or twelve days for all to

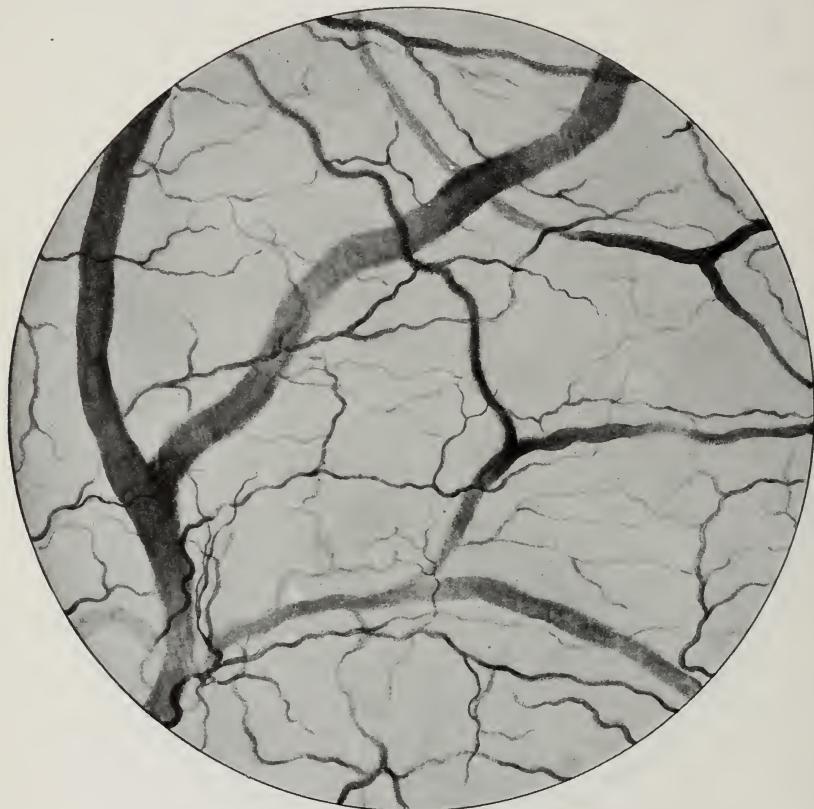


Fig. 65.—Portion of a normal diaphragm, showing in contrast relatively few visible blood-channels.

become normal again—the part which has actually been injured is the last to recover, and then usually with the loss of its surface epithelium, but even there the circulation finally returns to the normal, the epithelium is repaired, and the inflammation is over.

If a transparent tissue is selected, the whole process can be watched in its development. In the region where the tissue has been injured, and for some distance around it, the small blood-vessels are seen to widen. All the capillaries are stretched by the increased stream of blood, and contracted channels, which could not be seen before, reopen,

and the blood courses through areas which were quite pale before. The stream, pulsating in the arterioles and steady in the venules, now rushes through with vertiginous rapidity. Though we cannot see it, there is probably even at this stage some filtering-out of clear fluid from the vessels into the crevices of the surrounding tissue. After a time, although the stream-bed remains wide, the current slows down until one loses the impression of a homogeneous, yellowish-red fluid hurrying along, and it becomes possible to catch glimpses of the corpuscles as they pass. Throughout all this one can see that in the



Fig. 66.—Inflamed omentum showing outwandered leucocytes about a small vessel

venules, where there is no pulsation to disturb it, the arrangement of the corpuscles is peculiar in that they float in the centre of the stream, separated everywhere from the vein-wall by the clear plasma. With the slowing of the stream leucocytes begin to appear in this marginal stream and are rolled along the wall. They even seem to find the wall sticky, so that they adhere now and then, only to be turned over and dragged along by the rest. Still later some of them refuse to be dislodged, and one can see that they have fastened themselves to the wall by piercing it with a protoplasmic process which may even project a little way on the outside. Such a leucocyte soon becomes dumb-bell shaped, with

half its body outside the endothelial wall, the nucleus squeezing its way through the small hole forced by the protoplasm. It is not long before the whole cell escapes through this gap and wanders away among the fibres of the surrounding tissue. These are chiefly polymorphonuclear neutrophile leucocytes, which are the most numerous in the blood, and this is the process of active emigration which formed the crucial feature in Cohnheim's classical observation, and which is one of the most significant occurrences in the whole process of inflammation (Fig. 66).*

Along with the leucocytes, or behind them, red corpuscles escape passively to the outside, and during the whole time fluid has filtered through unobserved until now the cells and fibres of the tissue around



Fig. 67.—Acute diffuse inflammation. Tissue is oedematous and shows exudate of leucocytes and red corpuscles in a network of fibrin. Some mononuclear wandering cells are present.

the blood-vessel are spread apart widely by its great accumulation—the inflammatory oedema. Since this fluid is coagulable like the plasma of the blood, and since there are injured cells in the neighborhood to set free thrombokinase, there soon appears a delicate coagulum of fibrin stretching in fine filaments through the spaces forced open by the fluid (Figs. 67, 68, 69).

If the injury is extreme, the current of blood may come to a complete stop in some of the vessels, and there emigration of leucocytes

* Dr. W. Bulloch has pointed out that Waller anticipated Cohnheim in his "Microscopic observations on the perforation of the capillaries by the corpuscles of the blood, and on the origin of mucus and pus globules." London, Edinburgh, and Dublin Philosoph. Magazine and Jour. of Science, 1846, xxix, 397.

ceases. But in the others, although the corpuscles pass along very slowly, enough fresh blood seems to be brought to nourish the tissues.

The leucocytes and the fluid press toward the point where the tissues are most injured and surround those cells. If bacteria are present, the leucocytes may swallow them unless they have diffused around themselves too strong a poison. Then it seems impossible for the leucocytes to approach without being killed, perhaps because in order to do this they have to pass through dead tissue around the bacteria where they receive no oxygen. It is almost like firemen who are

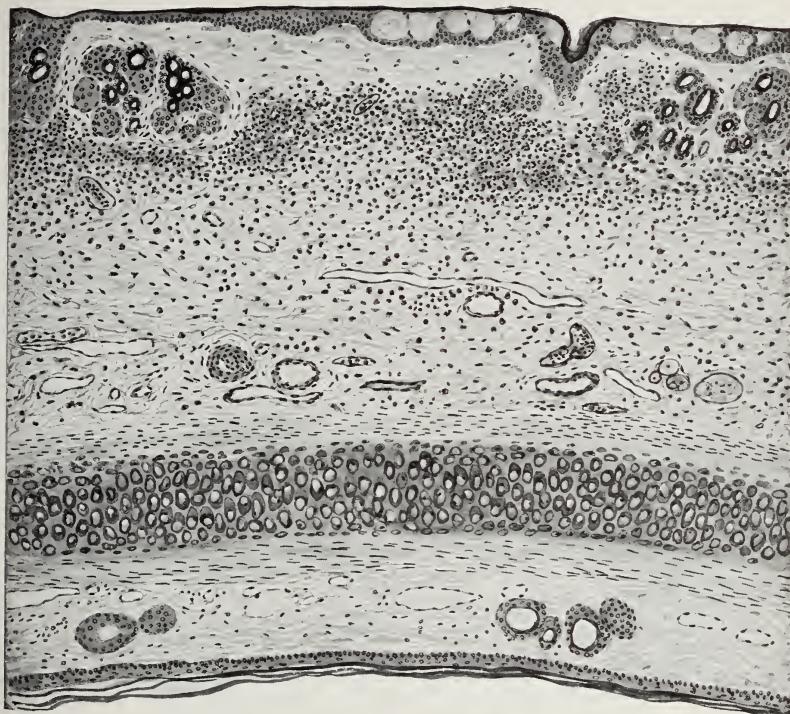


Fig. 68.—Inflamed rabbit's ear showing blisters in the skin and inflammatory infiltration of the subcutaneous tissue.

checked by the smoke, but keep on rushing in past the dead bodies of those who preceded them.

Finally, as a rule, if the injury is not enough to cause the death of the animal, the bacteria are overcome. This is effected by the continued action of the fluid and the leucocytes in ways which we shall discuss. Of if there have been no bacteria, the dead tissue is permeated by the exuded fluid and invaded by the leucocytes.

After this the process becomes an effort to clean up the débris. Partly by self-digestion, partly through digestion by the leucocytes, the dead cells and fibres are liquefied or reduced to a fine granular fluid and absorbed through the walls of the lymphatics. The dead bodies

of leucocytes suffer the same fate, and those which remain alive aid by carrying particles through the walls of the lymphatics, where they are swept along into the next lymph-gland. There any such particles or dead cells are exposed to the digestive action of the cells of the lymph-gland.

Thus the area is cleared of débris; the blood-vessels gradually return to their normal calibre, their walls again become normal and contract, and the circulation resumes its normal rate. Naturally gaps are

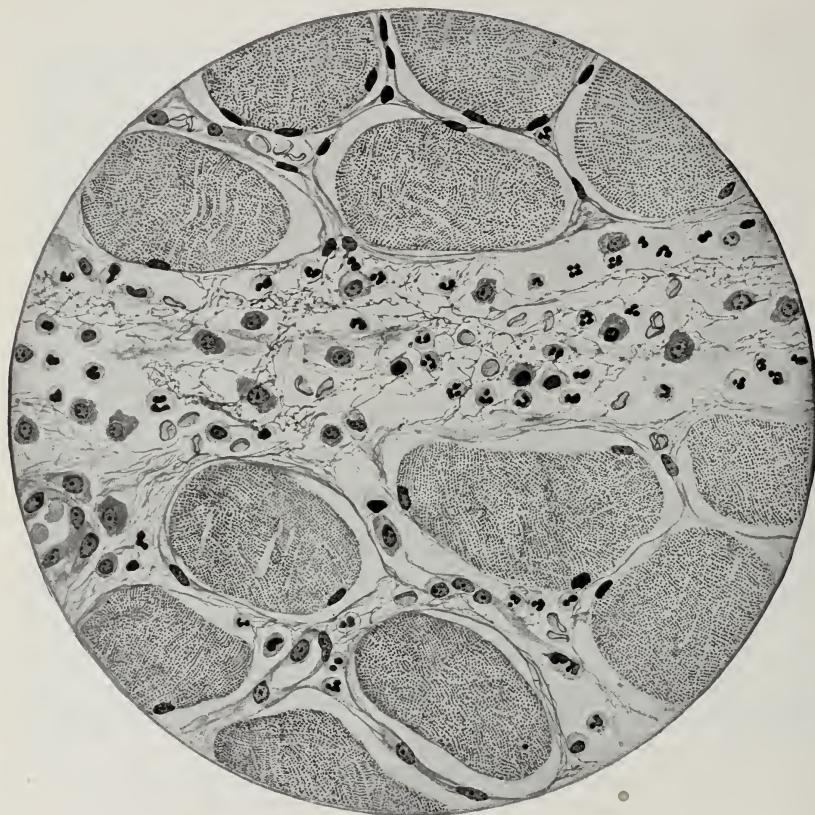


Fig. 69.—Acute myositis. Diffuse acute inflammation with mononuclear wandering cells as well as leucocytes, red corpuscles, and fibrin.

left in the tissue where cells have died and been removed, but the repair of these gaps will form another chapter.

It is seen from this that inflammation is really a complex but well-rounded mechanism, designed chiefly to pour over injurious substances and dead tissue a fluid and cells rich in neutralizing materials and digestive ferment, which tend to quench the action of the injuring agent and to liquefy the débris for removal. From this point of view it seems a purposeful and beneficial reaction.

Probably every inflammation is accompanied by some general dis-

turbance, such as fever, of which we shall have more to say later. When the injury is intense enough, poison may be absorbed from the injurious agent or even from the dead tissue to affect the nervous system and other organs and to cause disturbance of their functions, and what we know as illness. Even the fever itself may bring along with it disturbances in function. In all cases, too, there is likely to be a change in the blood in general, consisting in a great increase in the number of leucocytes. This leucocytosis is a convenient index of the existence of an obscure inflammation, and results from the great over-production of the cells of the bone-marrow and their liberation into the blood.

While the inflammatory reaction may thus happily succeed in overcoming the injury and restoring the cleansed area to a condition in which it is ready for repair, it is not always so. The injurious agent may persist, as in the case of bacterial infections, or it may be frequently repeated, in the case of physical or chemical injuries, so that a smouldering fire is kept up for a long time. The persistent reaction, which is then often spoken of as chronic inflammation, comes to differ from that which is quickly finished, chiefly in that, among the wandering cells which appear in the tissue, there arrive swarms of mononuclear forms which are slow to move, being attracted chiefly by dead tissue or other substances unlike those which draw the neutrophile leucocytes. The congestion of the vessels and the œdema may subside, being kept up chiefly along the frontier. Most confusing, however, is the fact that, if so much time is occupied, reparatory processes appear and are closely interwoven with those of defensive character. The mononuclear cells emigrate in small numbers with the polymorphonuclears in the acuter forms, but now they come in such numbers that one cannot escape the idea that many of them wander in from the crevices of the adjacent tissue or are even formed *in situ* by multiplication of those which first appear. They assume many forms, and many of them grow to a great size as they move about, swallowing up particles of dead tissue or even whole cells which have been injured. When the area is finally and permanently rid of the injurious substance, and when all the débris of dead tissue is cleared up, these cells in their turn slip away into the spaces of the tissue or into the lymphatics and disappear into distant parts of the body.

With this bare outline of the inflammatory process we may pass to the discussion of some of the underlying principles.

The Widening of the Vessels.—The widening of the blood-vessels is probably due to complete paralysis of their walls, at any rate in the actually inflamed areas. Klemensiewicz, who holds this idea, showed that the vessels of the web of the frog's foot could be made to contract by electrical stimulation of the medulla or of the vessels themselves, but if the foot were inflamed, no such stimulation affected them in the least. Section of the sympathetic fibres to a part allows of a temporary great dilatation of the vessels. In the rabbit's ear section of the auricular nerves, on the contrary, causes their contraction. Sensory stimulation will reflexly cause vascular engorgement, but while all

these conditions may be produced first, and will thereupon modify the course of an inflammation set up in that region, they are quite different from the changes in the vessels which inflammation entails, and which cannot be greatly altered by section or stimulation of nerves when it is once well developed. Inflammation in a rabbit's ear flushed by section of the sympathetic proceeds more rapidly and intensely than in a normal ear, and inflammation in a rabbit's ear rendered anaemic by section of the auricular nerves goes on imperfectly, so that in the end the injured ear becomes necrotic and drops off. But, after all, these are only superimposed influences, and, as we have shown, inflammation runs its course, complete in each detail, in a limb which has been amputated and then reunited by vascular suture, so that there can be no possibility of the existence of any nervous connection with the central nervous system. Bruce confirmed this and ascribed the vascular widening to an "axone reflex," by which he meant that sensory stimuli were transferred to efferent vasomotor fibres without reaching the cord or brain. He found, however, that if the nerves be allowed to degenerate no such arterial hyperæmia occurred. Breslauer confirmed this, and stated that local but not general anaesthesia abolished the initial hyperæmia ordinarily produced by the application of an irritant. Lubarsch and his students find that in limbs deprived of their nerves or locally anaesthetized, the early stages of inflammation are retarded and perhaps diminished in intensity, but that the further course is lengthened and more severe. General anaesthesia has only a slight effect in delaying oedema, but not the hyperæmia. The nervous system has at most a regulating influence, but does not control inflammation.

The experiments of Dale and others on shock have shown that it is probable that the paralysis of the capillaries, which is responsible for that condition, is due to poisoning by some substance resembling or identical with histamine derived from injured tissue. If the mangling of muscle or the bruising of intestines can allow the diffusion of enough of this poison to paralyze capillaries over the whole body, it seems probable that the local injury of tissue may liberate enough of the same material to poison and paralyze the capillaries in the area which becomes inflamed. Dr. Abel shows that practically every tissue is capable of producing histamine in consequence of injury; indeed, that it can be extracted from normal tissue. Rich showed that histamine applied to the blood-vessels of the omentum does cause their dilatation, but Bloom found that it produced no emigration of leukocytes. One may surmise, therefore, that here we deal with two quite separate processes.

The Changes in the Rate of Flow.—The stream in any given stream-bed ordinarily runs more slowly when it reaches a widened stretch, but here, where there is a choice of channels, it is more influenced by the friction against the wall, and consequently runs through these widened vessels at a rate more nearly approaching that in the larger vessels than before. It is for this reason that the part feels hot—not that there is any appreciable amount of heat produced by increased metabolism

in the inflamed area, but merely because, in a superficial tissue, the blood, when coursing normally, has time to cool, while now there is no such opportunity and the temperature of the part approaches that of the interior of the body. Probably we could determine no difference in temperature between an inflamed loop of intestine and a normal one in the same person.

The slowing of the stream and the passing out of the leucocytes into the marginal or plasma zone are much harder to explain. One is practically compelled to think that there is a change in the endothelial lining of the vessel of such a character that it becomes rough or sticky, and thus offers more friction to the passage of the blood-stream. Some have thought that the blood itself becomes thickened by the loss of fluid through the vessel walls, and that this increased viscosity might explain the sluggish stream, but there is no convincing evidence that the venous blood from an inflamed area has any perceptibly greater viscosity than the arterial blood.

Indeed, the observations upon the slowing of the stream have usually been made upon such an object as the exposed mesentery of the frog, where the minute vessels could be examined microscopically, and end, as a rule, in complete stagnation of the blood from the intensity of the injury, so that I have been disposed to question the occurrence of such slowing in a more protected tissue. Schlarowsky and others have shown that any suspended particles passing in a stream of fluid through a tube are governed by a centripetal force which keeps them in the axis of the stream, but that, with slowing of the stream, this force is relaxed, and first the lighter, then the heavier, particles are allowed to approach the periphery. Apparently this would explain the marginal position of the leucocytes as the stream slows, but it does not touch upon their adhering to the wall and finally penetrating it. Nor does it throw any light upon their increasing abundance in the whole circulating blood, for which two things quite different causes must be sought.

Chemiotaxis and Phagocytosis.—It has been observed, in watching free swimming amœbæ and other unicellular or even multinucleated organisms which are mobile and jelly-like (*myxomycetes*), that their movements are largely influenced by changes in their surroundings, or even more definitely by physical or chemical stimuli. Of special interest is their behavior toward soluble substances, some of which attract, while others repel, them. One of the *myxomycetes*, for example, which grows on tanbark, will move actively along a moist surface toward a drop of an extract of that bark, while it will move just as actively away from a solution of glucose or of some salt. Nevertheless, it can be accustomed to these latter things so as to be attracted rather than repelled by them. This is an example of chemiotaxis, or the stimulation to motion by a chemical substance, in the one case positive, in the other negative. Attempts have been made (A. B. Macallum and others) to explain this activity as due to alterations in the surface tension of the protoplasmic mass, and apparently this is the true basis, although it becomes complicated when we come to explain how the

response changes as the amoeboid organism accustoms itself to a repellent substance and is finally attracted by it. Probably a similar explanation will hold good for the tactile irritability which is evident in those amoebae or other cells which come in contact with some insoluble particle. In such a case the protoplasm flows around the particle and encloses it completely unless it is too large, when it spreads itself over the mass as far as possible.

This is the process of phagocytosis in its beginning, and both it and chemiotaxis are things which can be closely simulated by non-living substances. Thus a drop of chloroform in water will stretch itself along a thread of shellac brought against it, and, dissolving it as it goes, keep moving along the thread until it is saturated.

All of this applies equally well to the mobile cells of the body, particularly to the leucocytes, and Metchnikoff especially has laid great stress upon the fundamental rôle which it plays in inflammation, for while in lower forms these mobile mesenchymal cells form the means of defence, arriving at the point of injury by their own motility, in vertebrates there is added a convenient blood-vascular system, with its rapid current, which brings the leucocytes to the injured area and then slows up so that they may emigrate through its walls and reach the spot. Were it not for this slowing and the roughening and stickiness of the endothelium in that region, the leucocytes would all be swept by without any chance of reaching the place where the injury occurred.

Many ideas have been expressed as to the reason for the passage of the leucocytes through the wall, but it seems that the weight of evidence is in favor of their active penetration between the cells in response to the attraction of some diffusible soluble substance which is either the injurious agent itself or produced by its destructive action on the cells of the tissue. It is so evident that dead tissue killed by any mechanical means or by being deprived of its blood supply, as in the case of an infarction, can act in this way to attract the leucocytes, that in every case it must play a part. Experimentally it has been shown that extracts of dead cells are positively chemiotactic. Nevertheless, the leucocytes appear in so much greater number when bacteria or some chemical irritant cause the inflammation that unquestionably these poisonous substances themselves have a powerful influence.

All forms of leucocytes are not equally attracted by each substance, and indeed some things actually repel one form while attracting another. Thus while in most inflammations the polymorphonuclear neutrophile cells are prompt to respond in great numbers, cells of the type of the large mononuclear phagocyte are most abundant in the inflamed areas in typhoid fever and even in tuberculosis. So, too, in the lesions produced by many animal parasites, such as the trichina, the polymorphonuclear eosinophile cells appear in great numbers. It is not clear that any bacteria exercise a definitely repellent action on the neutrophile leucocyte, although it seems that this may be so in typhoid fever.

Leucocytosis.—How the impulse is sent to the bone-marrow, when there is a localized infection, to call forth the storm-like discharge of new leucocytes into the blood, is not very clear. Certainly far more

are formed and liberated than could possibly be accounted for by any dearth in the circulating blood caused by their departure from the blood-vessels, and it seems necessary to believe that some chemical substance circulating in the blood causes this great hyperplasia. If one reflects that a leucocytosis of 30,000 to 40,000 per cubic millimetre is not unusual, the colossal number of new leucocytes quickly formed and thrown into circulation becomes a matter of wonder.

The Wandering Cells.—It is clear that, in the adult animal, certain cells cling together and remain in a definite order to form a stable tissue which we recognize instantly and surely and expect to find always in its own appointed place. We are convinced of the specific character of the cells which make up such an organ as the liver and expect neither to find liver-cells in the kidney nor to find them giving rise to kidney-cells or thyroid-cells when they multiply. But the anatomist, knowing exactly what cells are proper to the structure of each organ, is never surprised to find other cells lying loose in the crevices of that tissue, and recognizes them as wandering cells not particularly at home anywhere, although they seem to have some favorite haunts. They are like the white cells of the blood and have the same powers of independent motility and phagocytosis. In the circulation they are hurried along, but in the interstices of the tissues they wander at leisure and pick up particles which attract them. There it is easy to recognize them by their sharp outline, the independence of attachment to other cells and, if they have not been allowed to grow chilled and retracted into a round form, by their pseudopods.

Of course their movements are relatively slow, but when they are photographed in a cinematographic film, at intervals of perhaps a minute, and then thrown on the screen at a rapid rate, as was done in the marvelous films of Dr. Carrell, Dr. Lewis and Dr. Canti, one acquires a completely new impression of cells. There the connective-tissue cells grow out majestically and smoothly from the margin of the field (which really represents a culture of tissues and cells *in vitro*), crossing and interlacing until a firm new structure is formed. Among these cells one may see others of quite different aspect worming their way with no thought of building. Arrived at the margin where they escape from the entanglement of these more serious fibroblasts, they show their true characters. Some are polymorphonuclear leucocytes and they hop about within a limited area in a sort of ecstatic frenzy, evidently throwing out and retracting pseudopods at a great rate. Then there are lymphocytes which move humbly, like slugs crawling only a little way with head to the ground. But also there are macrophages which reach out great arms, perhaps in two or more directions, and at the end of these arms there is a flourish of clear protoplasm with outflung streamers that wave and search about for whatever can be seized or else the whole advancing margin of the cell flows out and comes back like a wave, sucking in any particle that comes in its way. If only we could see all cells in this way many difficulties would disappear. It is evident though, even without this revealing glimpse, that in the adult human being there are several kinds of mobile cells which

have special characters and functions which mark them out as perfectly distinct and recognizable individuals in the community. They are known by their size and the form of their nucleus, by their staining properties and the sort of granules they contain, by their movements, by the kind of things that stimulate and attract them, by their ability to absorb into their bodies granules or various chemical substances, and perhaps especially by the different ferments they produce.

But, although such individuals are recognized, no one seems content to say that each is merely the descendant of a long line of quite similar ancestors, as we would in the case of the cells of the liver or the in-

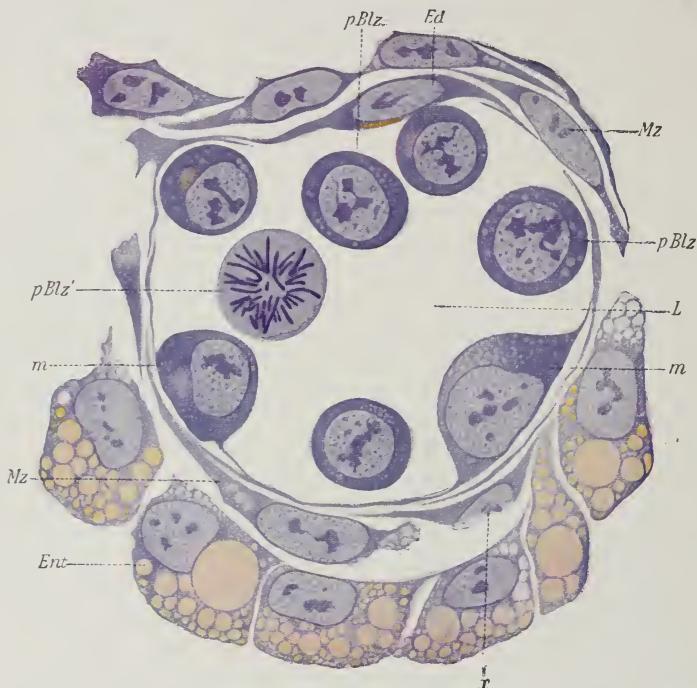


Fig. 70.—Early development of wandering cells in embryonic tissue (Maximow). Cross-section of a vessel of the area vasculosa with primitive blood-cells (*p. Blz*) in the lumen. Rounding off of endothelial cells (*m*) and their conversion into blood-cells; *Mz*, mesenchyme cells; *Ed*, endothelium.

testinal epithelium. Instead, there is an unceasing effort to trace their origin from some other sort of cell. This is partly because some of them, such as the red corpuscles and the neutrophile and eosinophile leucocytes, seem to be cells which are at the end of their course of development and specialization, and no longer able to divide and multiply into others like themselves, so that they must have ancestors of a different sort. Indeed, everyone agrees (and this is always a dangerous expression) that red corpuscles are directly derived from nucleated red cells, which do not come into the circulation, and that the leucocytes are directly derived from myelocytes. After that, however, all

is vague, and we do not venture to say that the other wandering cells cannot propagate their kind by division. The other difficulty is that all these cells are so ubiquitous and move about so much that it is hard to discover where they are produced. There is no such trouble about the cells of the liver or the spermatozoa—everyone knows exactly where to look for their new formation. It is true that it is pretty obvious that under ordinary conditions the bone-marrow is concerned in the production of red corpuscles and leucocytes, but if some tumor should spread so as to occupy most of the bone-marrow, blood formation would appear in the most unexpected places throughout the body. It is as though normally the formation of red corpuscles and leucocytes were finally assigned to the bone-marrow merely as a matter of economy in organization, for in the embryo it can be seen going on everywhere.

As to the mononuclear cells which have not so obviously run their course of development, there is greater difficulty. They are everywhere scattered loosely, or in small but recognizable accumulations, or even forming a regular tissue, but no one can say with certainty where lymphocytes are formed, nor where the larger mononuclear phagocytic cells especially arise. Every imaginable conception has been put forward and each has had its vogue. The distinctive characters of all these cells have become clearer in recent years, but the welter of theory about their origin and relations still prevails. Staining of dried smears or sections promised much, vital staining roused new hopes, culture of cells *in vitro* so that their activities and development may be traced, is in favor now, but still obscurities remain.

The cells concerned are about as follows: In the normal circulating blood beside the red corpuscles and the platelets (the latter supposed to be derivatives of the megalocaryocytes of the bone-marrow) there are several types of leucocytes. Of these the polymorphonuclear neutrophile leucocytes are most numerous and from 60 to 70 per cent of all the white cells. They are larger than red corpuscles, very active in their movements, with a nucleus usually in lobules united by narrow threads and cytoplasm which contains abundant minute neutrophile granules. Similar in form are the polymorphonuclear eosinophile leucocytes with large shining granules, which stain brightly with eosin. These are far less numerous and form not more than 1 per cent. Still less numerous are those of the same general conformation whose cytoplasm contains basophilic granules. Beside these there are lymphocytes which are sometimes smaller than red corpuscles, sluggish in motion with relatively large, round, deeply stained nucleus and no conspicuous granules in the scanty cytoplasm. Larger cells of similar character are called large lymphocytes. Another type, with large, rounded or indented vesicular nucleus and cytoplasm in which granules hardly appear by ordinary stains, but in which mitochondria and vitally staining granules can be found, are monocytes. These are actively motile phagocytes when they emigrate into the tissues. All of these cells can pass through the walls of the vessels and appear in the interstices of the tissues.

Outside the circulation in the tissues one finds ordinarily few stranded red corpuscles, except as the result of haemorrhage or in inflamed tissues. Once out of the stream they end in disintegration. The fate of leucocytes which emigrate from the vessels, is less certain, for they may wander back again into the stream. But the polymorphonuclear neutrophiles and eosinophiles are not ordinarily found in the meshes of the normal tissues.

It is far otherwise with the mononuclear cells which are so abundant there. Lymphoid cells generally regarded as identical with the lymphocytes of the circulation are found wandering in many places. They are also generally regarded as identical with the cells which make up the denser tissue of the lymph-nodes, the Peyer's patches, Malpighian bodies of the spleen, etc., and are supposed to be formed in these situations. Larger pale cells are clustered in the middle of each of such lymphoid nodules, and it was Flemming's idea that these large cells produced the lymphoid cells. It is very uncertain, however, and the large cells look rather more like phagocytes and become conspicuously increased in the course of infections, but never seem to produce lymphocytes.

It is most difficult to determine the standing of these large mononuclear phagocytic cells which are distributed in the tissues, partly in some recognized relation but largely as free wandering cells. Even yet after a great deal of study with the most ingenious methods, there is no agreement as to their origin or their interrelations. They have been given many different names, such as *histiocytes*, *clasmacyte*, *macrophage*, *reticulo-endothelial cell*, *adventitial cell*, *rhagiocrine cell*, *endothelial leucocytes*, *polyblast*, etc. We have ourselves hitherto called them mononuclear wandering cells and since this is quite non-committal we may go on with it but the terms histiocyte and macrophage are also used.

There are several groups of authors who hold different views as to the origin and relations of these cells which views may be followed in the huge literature on the subject, but no one seems to regard them as an independent type of cell constantly reproduced and originating from an ancestral cell of the mesenchyme, distinct from those which give rise to the other well recognized cells of the bone-marrow and blood, although this might seem the most reasonable idea. Briefly, Mallory and others derive them from endothelial cells. Naegeli, Piney and others relate them to myeloblasts. Maximow is sure that they develop from lymphocytes, Aschoff and Kiyono from reticulum cells and endothelium which they combine into the reticulo-endothelial system; Sabin, Doan and Cunningham by supra-vital stains separate sharply monocytes which occur in the tissues and also in the blood from clasmacytes because monocytes have a circle of granules in the cytoplasm near the nucleus, which stain red with neutral red, while clasmacytes have no such specific character. Naegeli finds that the monocytes give the oxidase reaction and have fine neutrophile granules which brings them close to the myeloid type rather than to the lymphocytes which have no oxidase reaction. Bloom, following Maximow, insists

that monocytes and lymphocytes both show the circle of red stained particles and ignores the difference in oxidase reaction. Lewis sees no real distinction between clasmatoctyes and monocytes which Sabin and coworkers derive respectively from endothelium and reticular cells, and prefers to bring them together as one type. It seems that he really tends to go back to the very earliest stages in the mesenchyme for the origin of such mononuclear wandering cells, or macrophages.

It is well known that they abound in the tissues and are actively mobile so that they hasten to a place where their services are needed. They are abundant in the spleen, in lymph nodes, in the walls of the digestive tract and in the omentum and about blood vessels everywhere



Fig. 71.—Lymph-gland showing phagocytic wandering cells in the lymph-sinuses.

and bronchi, and even in the septal tissues in the lung. It seems that cells identified with these by practically everyone are suspended or anchored within the endothelial lining of the blood sinuses of the liver. These are the Kupffer cells. Probably similar cells with similar anchorage are those which cross the peripheral sinuses in the lymph nodes and there are many quite analogous cells in the meshes of the tissue between the sinuses in the splenic pulp. Whether the actual lining cells of these blood sinuses of the spleen are, in part, of this character is questionable but it seems quite probable. At any rate, the outstanding character of this group of cells which we prefer to think of as a single type and derived from some remote ancestor in the mesenchyme, is their mobility with their phagocytic activity and apparently their important

rôle in relation with immunity and the protection of the body. In this connection the student should read the Harvey Lecture of Gay.

From the morphological point of view it is well to point out the distinctive features of such cells as they occur in different places. The monocyte in the circulating blood is a cell much larger than a lymphocyte with cytoplasm slightly basophilic, a nucleus usually bent on itself, not very deeply stained with very faint cytoplasmic granulations, sometimes showing the oxidase reaction and often enclosing fragments of red corpuscles or other outside material. Outside the circulation the same cell or its close relative is generally described as rather larger, with more active phagocytic nature, with perhaps paler cytoplasm and with no specific arrangement of neutral red staining granules. The Kupffer cells have long processes which suspend them along the walls of the liver sinuses. In the spleen one can in sections distinguish in the pulp large pale cells of irregular outline, loaded with phagocytized fragments, from other cells with more deeply stained nucleus and cytoplasm. It appears that these latter cells are derivatives of the lymphocytes from the Malpighian bodies, as Rich has recently demonstrated in artificial immune reactions.

Gay demonstrated the activity of the macrophages by irritating the pleura with an injection of aleuronat which brought them in great numbers to the subpleural tissues on that side after which he injected bacteria into the opposite pleura which brought them at once across to that side where they were actively protective.

These are, according to Gay, the cells which really confer protection by their presence rather than the polymorphonuclear neutrophiles which hurry so quickly to the point of infection.

The macrophages were studied by Metchnikoff who realized that they are little apt to phagocytise such bacteria as Streptococci and Pneumococci but do take up tubercle bacilli and some protozoa or fungi. They act vigorously as phagocytes for foreign substances and indeed one method of recognizing them is to inject into the blood stream carmine, India ink or some dye which then marks out brilliantly Kupffer cells and mononuclear phagocytes wherever they are normally lodged. It is interesting, as shown by Brickner and others, that in such animals the colored material is concentrated in the organs and tissues mentioned as the chief habitat of these cells while brain, heart muscles, etc., remain perfectly uncolored: The cells engulf foreign particles or partially surround them, if they are too large. Indeed, the cell itself increases in size to a great degree under such stimulus and with multiplication of nuclei becomes a giant cell, often then completely enclosing the foreign particle. It will be pointed out later that the tendency to engulf tubercle bacilli observed by Metchnikoff has led to the recognition of the fact that the epithelioid cells and giant cells of tubercles are derived from the monocytes or macrophages in the tissue. All of this can be made much clearer by reference to illustrations, if good ones can be made. The student is especially referred to the illustrations in Maximow's papers and in the histology of Maximow

and Bloom; also to the plates in the paper of Clough on "Monocytic Leukaemia," and the papers of Bloom and of Lang.

Lewis and his co-workers by the use of cultures of cells, seem however to have shown clearly, just as Maximow believed, that all the forms and sizes depend upon the age of the cell and its opportunity to stuff itself with foreign material and grow. Every stage up to the formation of huge giant-cells can be observed in these cultures, and the growth of a small mononuclear cell into a giant protoplasmic mass actually followed.

It is our impression that the endothelial cells which line the blood- and lymph-channels are limited to the fulfilment of that function. We have no evidence that they ever act as phagocytes, although foreign materials or phagocytic cells may adhere to them. Nor have we any convincing evidence that, once differentiated to the proper function, they ever divide the form wandering cells of any sort. Whether the formation of red corpuscles and leucocytes in the bone-marrow is ultimately dependent upon endothelial cells is open to grave doubt, in spite of the perfectly definite statements of so many writers. Always at the last stand they merely assume that endothelial cells must have been the source of the new cells. It seems more reasonable to suppose—although it is no great help—that at a very early stage in embryonic development ancestral cells were established for each of the types found in the adult, and that these, although inconspicuously lodged throughout the body, are still producing each its own type of cell. It does not seem reasonable to suppose that such cells would first undergo differentiation into endothelial cells or even angioblasts, which must then turn about and organize the ancestry for a whole series of different races of cells.

The explanations of the interrelations of these cells are so new and so little applied in human pathology that it may be excusable for a time to speak of all the large, phagocytic, mononuclear cells of the tissues simply as mononuclear wandering cells.

Among them there occurs one peculiar form which is probably derived from the lymphocyte through a modification of its nucleus and protoplasm. This is the so-called *plasma cell* described by Unna, which occurs normally in the intestinal mucosa and elsewhere and appears in great numbers in many forms of long-standing subacute inflammatory reactions (Fig. 74). Tuberculous granulation tissue and gonorrhreal salpingitis afford examples of such conditions. The cells are rather larger than lymphocytes—somewhat amœboid, but in fixed preparations they usually assume a rounded or oval form, with the nucleus eccentrically placed, generally at one end of the cell. The nucleus, whose chromatin is in coarse masses, is surrounded by a pale halo, while the remaining protoplasm takes a bluish stain with ordinary nuclear dyes. Such cells, which may be regarded as a type slightly differentiated from the rest of the tribe of mononuclear wandering cells, are conspicuous because they are so constant in their form. They are not commonly phagocytic, but probably active in producing a digestive ferment.

The mere fact that all these cells take up in their nuclei or proto-

plasm or in their granules certain stains in a specific way does not, after all, afford us much information as to their true character. It would be more important to determine something as to their function.

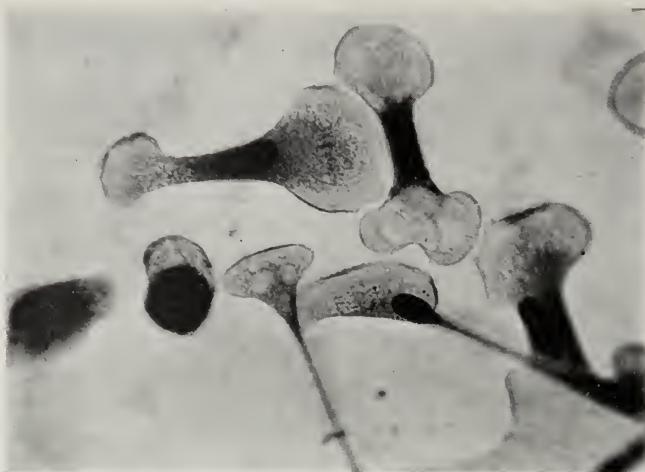


Fig. 72.—Monocytes from culture *in vitro* photographed while alive.

Metchnikoff, in his studies of inflammation and immunity, has been at great pains to show the analogy between the activities of the wandering cells of the body and those of amœbæ or other amœboid, simple,

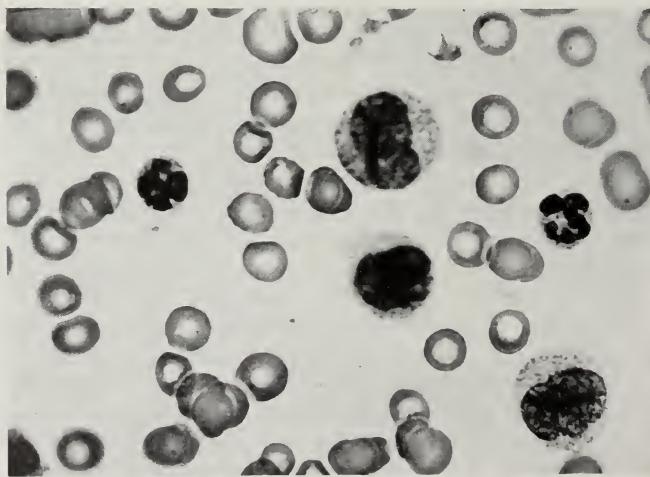


Fig. 73.—Monocytes in blood smear contrasting with polymorphonuclear leucocytes.

protoplasmic organisms. These latter swallow up bacteria and other substances, and by the aid of fermenters or cytases digest them. These fermenters, he says, are also present in the wandering cells of the body, and differ according to the type of cell, the small neutrophile leucocyte

possessing a so-called microcytase, while the mononuclear cells or macrophages, which eschew bacteria, except such as the tubercle and

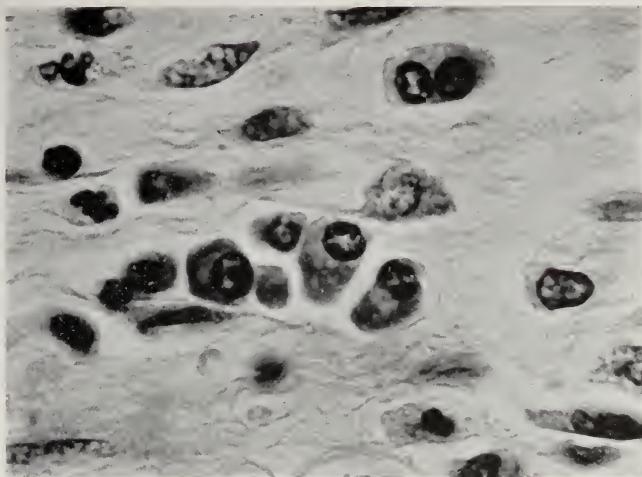


Fig. 74.—Cell infiltration in tissue lining a sinus leading from an old osteomyelitic abscess. In the centre are several plasma cells. About them are fibroblasts and three or four polymorphonuclear leucocytes.

leprosy bacilli, and digest with avidity cell débris, carry out their digestive processes by the aid of another ferment which he calls macrocytase.

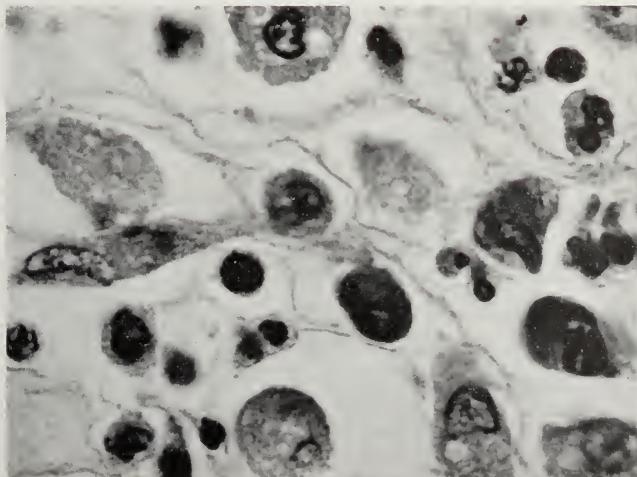


Fig. 75.—From the same tissue as Fig. 74. Macrophages, lymphoid cells, and polymorphonuclear leucocytes with fibroblasts and two plasma cells.

Many writers have recognized the power of certain tissues to digest themselves *in vitro* (autolysis), and have observed that the neutrophile

leucocytes produce a strong proteolytic ferment capable of digesting fibrin, gelatin, etc. Most of them, however, according to Wiens, have denied the production of a ferment by lymphoid cells. Opie has cleared the matter up very well by finding that the ferments of different cells require for their activity different reactions. He states that the polymorphonuclear neutrophile leucocytes and their ancestral granulated cells produce a trypsin-like ferment which acts best in an alkaline or neutral medium to digest proteins. Its action is often combated by an anti-enzyme, which is present in the plasma of the blood and in other body fluids. It is resistant to heat up to 70° or 75° C., and is therefore quite different from the complement of the serum, which is destroyed at 55° C. When formed in great concentration in a focal area of inflammation, the enzyme far outstrips the neutralizing anti-enzyme, and brings about the liquefaction of dead tissue, as in the case of an abscess. When in the presence of a great exudation of fluid, as in the pleural cavity, its action may be held in check. This proteolytic ferment Opie calls leucoprotease. Contrary to the results of other workers, he finds that, if the correctly feeble acid reaction be offered, the mononuclear cells also show the formation of a proteolytic ferment which is more like pepsin in its character, although it is unable to act in so strong an acid as is favorable to pepsin. This ferment, which he calls lymphoprotease, is produced in the lymph-nodes and in all accumulations of lymphoid cells, and of the various types of larger wandering mononuclear phagocytic cells which go to form Metchnikoff's group of macrophages.

While these ferments are evidently used inside the cell in the case of the particles which have been ingested, it seems certain that, in the formation of pus, as in the abscess, they are diffused from the bodies of the disintegrating leucocytes, and in the free fluid effect the solution of the adjacent injured and dead tissue. This function of the wandering cells is, of course, of immediate importance in connection with their task of cleaning up the injured area to prepare it for repair. While the proteases thus produced are active in the solution of undesirable material, their unbridled action might be detrimental. As a matter of fact, it is shown by Jobling and Petersen that the anti-ferment known to be present in the serum and to restrict the action of the ferment is a recognizable chemical substance, usually a soap or other combination of an unsaturated fatty acid. It is possible to remove or decompose this substance or to saturate the fatty acid with iodine and thus release the ferment to its full activity. The presence of excess of such soaps in the tubercle bacilli seems to be the cause of the delay of liquefaction of tissue brought to necrosis by those bacilli. Opie, however, points out that these experiments refer to leucoprotease, which is probably not concerned in the absorption of a tubercle or gumma. It is seen from this that we are at the beginning of our knowledge of the activities of the wandering cells. What other ferments they produce has been as yet only imperfectly studied, although we have evidence that others, such as oxydases, are produced by some of them, and there are surely more.

Pain in Inflammation.—Doubtless the cause of pain in inflamed tissues is different in various parts of the body, for in certain confined places it is not hard to imagine that the accumulation of exudate stretching sensitive tissues would cause suffering, which might be relieved, as is so often the case, by an incision which allows the exudate to escape. Still it has been objected that pressure and tension on the nerve-endings are not sufficient to cause pain, since local anaesthesia can generally be produced by injecting some indifferent solution into the tissues until they are distended. Therefore it has been thought that the poisons which caused the inflammation also irritate the nerve-endings. Possibly this is so, but an inflamed area following a burn is as painful as one resulting from bacterial infection, and in sunburn no pain is felt during the injury, but only when the inflammation is at its height. Possibly the hyperæmia itself renders the sensory nerves hyperexcitable, as seems to be true in the case of non-inflammatory hyperæmias.

LITERATURE

- Bloom: Archiv f. exp. Zellforsch., 1928, v, 271; Folia Haematalogica, 1928, xxxvii, 1, 63.
- Brickner: Bull. Johns Hopkins Hosp., 1927, xl, 90.
- Danchakoff: Anat. Hefte, 1908, xxxvii, 473. Anat. Record, 1916, x, 397, 483. Amer. Jour. Anat., 1916, xx, 255; 1918, xxiv, 1, 127.
- Doan and Wiseman: Ann. Int. Med., 1934, viii, 383.
- Ehrlich: Germinal centres (secondary nodules) in lymphoid tissue, Amer. Jour. Anat., 1929, xlvi, 347; Ziegler's Beiträge, 1931, lxxxvi, 287.
- Gay: Harvey Lecture, 1931; Jour. Amer. Med. Assoc., 1931, xcvi, 1193; Jour. Exp. Med., 1930, lii, 95.
- Jobling and Petersen: Jour. Exp. Med., 1914, xix, 293, etc.
- Lang: Ztschr. f. Mikr. Anat. Forsch., 1926, iv, 417.
- Lewis, M. R. and W. H.: Carnegie Inst. Contrib. to Embryol., 1926, xviii, 95.
- Lewis, W. H.: Harvey Lecture, 1925-26, xxi, 77.
- Lubarsch, Rössle, and others: Verh. Dtsch. path. Gesellsch., 1923, xix, 3. (Review of inflammation.)
- Marchand: Verh. Dtsch. path. Gesellsch., 1914, xvi, 5. (Lymphocytes.) Virchow's Archiv, 1921, cxxxiv, 245. Handb. d. Allg. Pathologie, Krehl and Marchand, 1924, iv, 1, 78. (This is the best recent article on the whole subject of Inflammation.)
- Maximow and Bloom: Textbook of Histology, Saunders, Phila., 1934.
- Metchnikoff: Lectures on the Comparative Pathology of Inflammation, 1893.
- Opie: Harvey Lectures, 1919, 192. Physiological Reviews, 1922, ii, 552.
- Rich: Jour. Exp. Med., 1921, xxxiv, 287. (Capillaries in histamine shock.)
- Sabin: Physiological Reviews, 1922, ii, 38; Bull. Johns Hopkins Hosp., 1923, xxxiv, 277.
- Sabin, Cunningham and Doan: Carnegie Inst. Contrib. to Embryol., 1925, xvi, 125, 227; Jour. Exp. Med., 1927, xlvi, 627, 645.
- Weidenreich: Arch. f. mikr. Anat., 1909, lxxiii, 793. (Literature.)
- The student should particularly consult the papers of Maximow with regard to the cells concerned in inflammation and the repair of tissue, as follows:
- Maximow: Ziegler's Beiträge, Suppl. 5, 1902; 1905, xxxviii; 1907, xli; 1929, lxxxii, 1; Arch. f. mikr. Anat., 1906, lxvii; 1909, lxxiii; 1910, lxxvi; 1922, xcvi, 494; Physiological Reviews, 1924, iv, 533. See especially Bindegewebe und Blutbildende Gewebe, Handb. d. Mikr. Anat. des Menschen, Möllendorf, 1927, ii, 232-583; Archiv f. exp. Zellforschung, 1928, v, 169. Cultures of blood-leucocytes.

CHAPTER X

DEFENCES OF THE BODY (Continued)

Fever. *General nature of the reaction. Its chemical characters and relation to immunity.*

Immunity. *Nature of injurious agents. Types of resistance. Artificial immunity. Anaphylaxis; allergy. Asthma.*

FEVER

General Nature of the Reaction.—It is common knowledge that fever is likely to accompany inflammation, and, as in the case of inflammation, the efforts of physicians and healers of all sorts have been directed toward cutting it short on the idea that it in itself is the harmful process. Only in the last decades has it become vaguely appreciated that there is real evidence that fever, on the contrary, is a reaction elaborated to a considerable degree of perfection, which aids in the defence of the body against the advance of an injurious agent by facilitating the production of the substances which are formed in the body to neutralize poisons or kill bacteria.

From this point of view it would seem, to say the least, short sighted to give a patient in fever an antipyretic drug which will cut short the febrile reaction.

Fever is a reaction which seems to be carried out under the control of the nervous system, and especially of the vasomotor mechanisms which have to do with heat regulation, the most striking feature of which is the elevation of the temperature of the body above the normal. This is not the result of an excessive heat-production, although there is a moderate increase in the production of heat, but rather of the retention of an undue proportion of the heat produced. In the course of fever the body gives off more heat than it normally would at rest, but not nearly so much as it would during active exercise. Indeed, the heat-production during exercise may be increased 200 or 300 per cent., but such is the accuracy of adjustment of heat loss to this increase that the temperature of the body remains normal. During fever, on the other hand, the production of heat is increased only 20 or 40 per cent., but the dissipation of heat is not proportional, and therefore the temperature rises. Heat is given off, but, as Liebermeister has said, the regulating mechanism is altered to react for a different standard of body temperature. It is tuned up to a higher pitch, so that it begins to allow of the escape of heat only at a higher level, just as we might screw up the thermoregulator of a thermostat so that its temperature would stand at 40° instead of 35° C.

The regulating mechanism is found in the vasomotor apparatus of the vessels of the skin, in the secretory activities of the sweat-glands, in the respiration (especially in the dog, which cools itself by panting), in shivering, and partly, in human beings, in conscious changes in the clothing. A striking instance of the coördinated working of all

these arrangements is seen in a chill, which is so frequent an accompaniment of toxic or bacterial injuries with inflammation. The superficial vessels of the skin are contracted so that little blood is carried to that radiating surface. The skin is pale or livid. The sweat-glands stop secreting, so that the cooling effect of evaporation of the sweat is held in abeyance; the smooth muscles in the skin contract and pull it into gooseflesh; the person feels cold, cowers together, covers himself heavily with blankets, and shivers violently, thus turning stored-up energy into heat. Every available mechanism is brought into play to stop the dissipation of heat and to warm up the body, and in spite of the sensation of cold, the temperature of the interior is at its highest during the chill!

Later, when chemical processes are under way to produce the moderate excess of heat which is observed in fever, these contractions of the cutaneous vessels, etc., are no longer kept up, and the skin may be flushed and even moist, but still the balance is so adjusted that a little less heat is dissipated than is produced—enough, at least, to keep the temperature above the normal.

Chemical Characters of Fever.—Naturally, since fever is a process concerned with heat-production, the most painstaking efforts have been made to ascertain its nature by the study of the changes in metabolism during febrile diseases, but so varied and complex are the conditions that it can hardly be said that the results have brought out any very definite and characteristic changes peculiar to fever as such, and independent of the direct effect of the underlying cause. It is generally agreed that oxidation is increased over that found in the normal individual at rest, but it is not so certain that it is qualitatively altered. From a study of the excretion of nitrogen, together with a comparison of the amounts of carbon dioxide and oxygen in the expired air, it has been thought that the increased oxidation affects especially the nitrogenous or protein constituents of the body, and indeed not so much the labile or circulating proteins as those which actually form part of the living tissue. It is known that the store of carbohydrates is rapidly depleted, but it was thought until recently that the other ordinary fuel used in the production of heat energy—the fat—was relatively little encroached upon. Now May, Grafe, Coleman and Shaffer, and others state that in fever, too, the fats form a particularly important source of heat, and that if sufficient carbohydrate and fat be supplied to the febrile patient the waste of body proteins may be prevented. Indeed, Grafe thinks that this attack on the living tissues which was traditionally emphasized as the most typical feature of febrile metabolism, is due altogether to inanition, and that qualitatively the febrile metabolism need not differ greatly from the normal.

It has been found that the cells of the tuber cinereum especially send out the impulses for temperature regulation, and Freund and Grafe show that when the lower cervical region of the spinal cord is interrupted, all influence upon the temperature regulation of the body is lost. The animal becomes poikilothermic, like a frog, but reacts to external cold by increasing its oxidative processes, and that not in the

consumption of carbohydrates or fats, but of proteins. No fever can be produced in such animals but the suggestion is made that fever, when it appears in an intact animal, is due to stimulation of that heat-regulating mechanism which is lost to these animals in which the spinal cord and sympathetic nerves have been cut. The regulatory mechanism is disordered, however, and works uncertainly and irregularly, and is not merely keyed up to a higher pitch as Liebermeister would have it.

In many fevers, especially in pneumonia, there is a curious retention of sodium chloride, which is then excreted in great amounts after the fever is over. Water may be retained in the same way. The metabolism of other inorganic substances may suffer alteration in this way or that as well, but, on the whole, it is difficult, if not impossible, to put one's finger on any of these changes and say that this is characteristic of the metabolism of fever.

In all these studies little attention has been devoted to the anatomical changes in the disease, so that it is not surprising that there are discordant results. If there is extensive destruction of tissue produced by the poisons of bacteria, or if great quantities of leucocytes appear in the tissues and are broken down, digested, and absorbed, as in pneumonia, there must be changes in the nitrogen output. It is difficult, too, to estimate what part of the increased oxidation is due to the heightened temperature itself, quite aside from any other cause, for it has been shown that artificial overheating produces an increased oxidation.

But aside from the mere existence of dead tissue which can be used as fuel and appear in the excreta, and the later result that heightened temperature facilities further burning, there must be some original cause for the intensification of the oxidation process, even if it prove that it is not qualitatively but only quantitatively altered.

Relation to Immunity.—So closely has attention been concentrated on the questions of disturbances in metabolism that the biological significance of fever has been somewhat neglected, but Rolly and Meltzer, Loewy and Richter, Fukuhara, and others have published results which show it in a clearer light. They found that if animals were artificially kept at a high temperature in a thermostat room, they were able to develop a much more effective defence against intoxication and infection than those left outside at ordinary temperatures. Briefly, Rolly and Meltzer showed that the high temperature itself had probably no injurious influence on the growth of bacteria in the body. Further, that if a fatal dose of bacteria or of a toxin be given, no special difference could be observed between heated and unheated animals. But this sort of infection, by the sudden introduction of enormous quantities of bacteria or of a toxin hardly occurs in nature. Instead, a few bacteria get into the tissues and then gradually increase in number, or in their growth produce an increasing amount of toxin, so that time is given for the appearance of a defensive reaction. If, now, the experiment be arranged in the same way, small doses of bacteria or toxin being injected at intervals, the heated animals showed a great advantage over the controls. They lived longer, and many of them survived doses which inevitably killed the control animals.

When they studied the details of these experiments more carefully, they found that it was not that the high temperature merely prevented the growth of bacteria—it might do so in test-tubes, but in the body the bacteria grow well enough at febrile temperatures. Phagocytosis proved difficult to compare in the two sets of animals, but *in vitro* they found that it was increased by temperatures ranging even up to 41° C., so that probably the conditions for its development are improved by high temperatures in animals. When they studied the formation of specific antibodies, however, they found a great difference. Antitoxin they did not investigate, but agglutinins and bacteriolytic substances were produced far more quickly and in much greater amounts than in the control animals.

New as these results are, they seem to open the way to a more fruitful study of fever and to confirm the somewhat vaguely expressed idea that it is in a way analogous to the vascular reaction in inflammation in that it is the process which facilitates the more essential activities of the phagocytes and the production of defensive chemical substances in the body.

But still more recent discussions of fever seem to lay little stress on this aspect of the matter. Instead, they are concerned more especially with the mechanism of nervous control and with the character of the chemical substances which excite this nervous mechanism to the production of the disturbance of heat regulation which we have described. In brief, it appears that destruction or interruption of the hypothalamic region of the mid-brain throws out of function the regulatory mechanism, so that the warm-blooded animal becomes poikilothermic and makes no response to the usual causes of fever. This merely means that the vasomotor and other changes ordinarily set in motion by the "heat-regulating centre" are absent because their connection with the brain is interrupted. As to the nature of the regulating centers nothing is yet known.

In anaphylactic shock the temperature falls suddenly, but if the dose of antigen is too small to produce this collapse, it results in fever. Friedberger, Leschke, and others show that with minute doses of "anaphylatoxin" it is possible to produce a febrile rise in temperature at will, but it remains to be seen whether there is one substance responsible for this or many. One gains the impression that it is the product of injury of cells and consequent decomposition of protein which stimulates the heat-controlling centres. In this sense the fever may still be purposeful, although it is less easy to discover any active character than formerly seemed to be the case. Antipyretics and baths may do good, not so much by allaying the fever as by calming the excitement of the rest of the brain.

LITERATURE

- DuBois, E.: Basal Metabolism in Fever. *Jour. Amer. Med. Assoc.*, 1921, lxxvii, 352.
Barker's Endocrinology and Metabolism, 1922, iv, 95.
Freund, H.: Wärmeregulation u. Fieber. *Ergebn. d. innere Med. u. Kinderh.*, 1922, xxii, 79; *Dtsch. Med. Woch.*, 1922, xlvi, 81.
Grafe, E.: Stoffwechsel u. Fieber. *Ergebn. d. Physiol.*, 1923, xxi, 2 Abt.; *Klin. Woch.*, 1923, ii, 1005.

Krehl: Krehl and Marchand, Handb. d. Allg. Pathologie, 1924, iv, 1, 1.

MacCallum: Arch. Int. Med., 1908-09, ii, 569.

Meyer, H. H.; Krehl, Schittenhelm, Friedberger, Grafe, Leschke: Verh. Congr. f. Innere Medizin, xxx, 1913, 15-80.

Rolly and Meltzer: Dtseh. Arch. f. klin. Med., 1908, xciv, 335.

Welch: Cartwright Lectures, Boston Med. and Surg. Jour., 1888, cxviii, 333, 361, 413.

IMMUNITY

Nature of Injurious Agents.—The body may be regarded as a kind of tube with thick walls, into which there extend cavities open to the exterior. These cavities, as well as the lumen of the digestive tract, with all its diverticula, are outside the body, and poisonous fluids or bacteria can exert their influence only when they pass through the lining membranes into the real interior. An injury to the lining membrane, often produced by the bacteria themselves, exposes the interior of the body, just as in the case of an abrasion of the skin, to invasion, but many poisons can be absorbed without such cell destruction.

These surfaces then constitute the *portals of entry* of all the injurious agencies from the outer world, whether in the form of inanimate poisons or live creatures which can live and multiply in the interior of the body, to its detriment. Sometimes entry is immediate, but it is well known that the outer and lining surfaces of the body may and do swarm with living creatures, many of which are permanently innocent, while others are only waiting an opportunity when the guard is weakened to force their way through the walls and attack the vital organs inside.

Externally the impermeability of the skin acts as a defence, while in the case of the lining membranes, fluid secretions tend to wash away noxious materials or annul their effects, in which they are often aided by phagocytic cells. So in the conjunctiva bacteria are quickly washed down into the tear-duct; in the upper respiratory tract ciliated cells wave back every kind of particle, and from all the adenoid apparatus leucocytes are ready to emerge on alarm. In the biliary ducts, as in the genito-urinary organs, bacteria are kept in check by the stream of fluid, often aided by valvular arrangements to close the channels, which washes away the bacteria and cleans the lining surfaces. Nevertheless, all these defences are often overcome. Through the skin the attack may be successful not only by way of ordinary wounds, but by the agency of biting insects and other animals, or even in the case of some worm larvae by their own penetrating force. Through the mucosae entrance is forced by the destructive action of the organisms themselves, though this is often aided by mechanical factors which protract their contact with these tissues or by the failure of the phagocyte guard from the interior. Thus the upper intestine and the bladder, which normally keep themselves practically free of bacteria, quickly become perfect hotbeds for their growth if an obstruction prevents the escape of the intestinal contents or the urine.

Aside from mechanical or physical injury, the body suffers from the effects of destructive chemical substances which may be wholly derived from the inorganic or inanimate world, or may be produced in some way by living beings. Indeed, the greatest danger comes from the latter

when, as is so often the case, these living beings establish themselves in the body or on its surface and manufacture their poisons on the spot.

A word should be said here about the rather obscure question of their interfering with the well-being of their host by the mere abstraction of the materials necessary for its nutrition and metabolism. Possibly this may occur in the case of some of the larger parasites: they may drain away the blood or, as in the case of malaria, eat out the blood-cells, but probably even in the most obvious of such cases the greatest harm is done by the poisons which these creatures produce. On the other hand, Dibbelt has lately maintained that in the fulminant bacterial infections which kill in a few hours, death is not due to the formation of poisons, but rather to the wholesale withdrawal of oxygen from the tissues. Such a result might be comparable to that in cyanide poisoning, in which metabolism is brought to a standstill by the stoppage of oxidation processes.

Of all the living parasites which thus insinuate themselves into the body, only a few, such as the diphtheria and tetanus bacilli, have been shown to produce a soluble, diffusible poison or toxin which, by itself circulating through the organs, can cause the symptoms of the disease. Such bacteria can, therefore, live and grow, even in a very small spot in the tissues, and yet diffuse enough poison to kill the animal. Practically all the rest, whether animal or vegetable, fail to do this, although they cause the most intense and frequently fatal diseases. The fluids of animals dying of these diseases will not cause the disease in other animals if the parasites are filtered out, and the fluids in which they have grown are found not to contain any appreciable amount of poison. Still, if their bodies are ground up, a poisonous material or *endotoxin* may often be found mixed with their body proteins in the extract made from the débris. How they produce the disease is, therefore, very difficult to learn, and generally we are content with the idea that they become harmful only when they die and are broken up in the tissues, liberating their endotoxin. The recent work of Mrs. Parker seems to show, however, that other organisms, such as the staphylococcus, really produce toxins, but they are so easily destroyed that we have failed to find them. Properly protected they are capable of causing extreme injuries and can be neutralized by an antitoxin.

Types of Resistance.—Poisons very similar to those produced by bacterial and animal parasites are secreted by venomous animals and plants, or may be extracted from them. Indeed, it is quite difficult to draw any sharp line of demarcation in the long series of poisons beginning with the simple inorganic substances, and passing by way of the complex synthetic compounds to the highly intricate combinations, of whose nature we are generally ignorant, which we find in the toxins and toxalbumins and other protein substances which play such an important rôle in disease. In general, however, it is found, through the biological test, that it is only toward the complex, protein-like poisons that the body can elaborate special defensive substances. Even though the others may finally be tolerated, it is through some other mechanism. Thus it is well known that through long habit animals or human beings

may become able to swallow doses of such poisons as arsenic, morphine, etc., which would be far more than enough to kill an ordinary being, but our ideas as to how this tolerance is produced are very vague. Certainly no substance is produced in the body which will neutralize the poison, and it seems that it must be due to some change in the metabolism of the cells themselves.

There is, even without any such gradual case-hardening, a natural insusceptibility on the part of some animals to injury from certain poisons; thus an almost unlimited quantity of the most intensely active tetanus toxin, a milligram of which would kill thousands of mice, can be injected into a scorpion or an alligator without producing the slightest malaise, and a long time later it may be found still lodged in the tissues. Certain animals are equally resistant to invasion by bacteria which can produce the most deadly disease in others, apparently because those bacteria find in the tissues, conditions which do not allow them to multiply, while closely related bacteria which have through generations of adaptation accepted those conditions invade rapidly. In this case the adaptation seems to be on the part of the bacteria, although it is quite possible that through long survival an animal species may become resistant to bacteria which formerly invaded and produced disease. Race immunity is doubtless an example of this kind, and race susceptibility illustrates its opposite. The South Sea islanders succumbed in thousands to measles or more probably to a secondary bacterial infection stirred to great virulence by association with the virus, as has been observed in great epidemics. This, however, was no example of race immunity or susceptibility but merely that measles had never existed there so that none were immune. The sailors who brought it, together with the secondary infection, doubtless suffered as severely, while those who had had measles before would not harbor the combined injurious agents.

Children in our countries sicken with so-called children's diseases but are usually protected from the serious secondary bacterial infection.

In all the ills produced by living invaders there exists a struggle for supremacy—even for existence—between the host and the parasite, in which the stronger prevails and in which defences are developed not only by the host, but by the invader as well. It is doubtless through this that the bacteria accustom themselves in passing from the body of one animal to another to the action of the defensive reactions of the host, and become thereby more virulent. This is made evident in some cases by the appearance, under these circumstances, of capsules which are formed in the bacillus of anthrax, the pneumococcus, etc., as they grow in the animal body, but not in cultures. The capsulated forms become less susceptible to phagocytosis and it is even stated that infection can occur only when capsules are formed. Danysz found that bacteria in culture may be accustomed gradually to the presence of arsenic, so that they finally grow in relatively strong solutions and in the course of this adaptation acquire a capsule. Indeed, it is clearly shown that certain protozoa, the trypanosomes, may, like the Styrian arsenic-eaters, become so used to arsenic that they live on unhurt in the body through

a continued bombardment with the new synthetic arsenic compounds, if only they have managed to survive the first doses.

We know so little about the defences of the parasite, however, that at present we must exemplify the principles by reference to those of the host. We realize that, normally, animals have well-developed powers of defence, although these are efficient in such different degrees in different animals that we must surmise that they are not concerned in their full perfection on all at their creation, but have been gradually acquired through the survival of those best provided, who in turn bequeathed them to their offspring. These defences may guard against simple poisoning or against the inroads of living parasites, and we shall see that they do not lack in variety to correspond with these different forms of injury. Already we have found that certain general mechanisms, inflammation, and fever, have been developed alike in all animals, but we have been forced in both instances to recognize the fact that these reactions are merely auxiliary mechanisms designed to bring into play to the greatest advantage, and in the most opportune concentration during sudden emergencies, other more profound and more subtle processes, phagocytosis, and the chemical neutralization of poisons which we admit as the essential agents of defence.

For a time there were those who maintained that the activity of the phagocytes constituted practically the whole defensive armament, while others, enthusiastic over their new discoveries, were just as sure that the neutralizing substances in the body fluids were all-important. But now a reconciliation of these cellular and humoral doctrines has been effected, because it has been shown that they are very largely inter-dependent, phagocytosis depending upon the presence of auxiliary substances in the plasma (opsonins) while in turn the leucocytes are important in producing other defensive fluid substances.

Artificial Immunity.—From time immemorial it has been known that a person who has had smallpox, or typhoid fever, or yellow fever, or any one of a host of diseases can hardly have another attack of the same disease: he is immune. On the other hand, there are certain diseases, such as pneumonia, erysipelas, furunculosis, etc., which seem to predispose to a repetition. While we are yet far from clear as to the reasons for this latter fact, we have learned a great deal about the security conferred by the immunizing sort of diseases. It is not necessary that the illness should be severe to give this lasting protection, and, recognizing this, it was the habit, many years ago, to court mild attacks of such a deadly disease as smallpox in order to be safe in the midst of an epidemic where the disease was severe. This was the beginning of man's intentional use of artificial methods of providing immunity, a plan which, under the influence of the phenomenally intelligent studies of such men as Pasteur, Ehrlich, and von Behring, has extended until it promises now to become the very most important practical achievement of medicine. It has proved possible to devise methods by which security from parasitic disease can be attained without risking any serious preparatory illness, and to intensify the strength of this defence until it is almost absolutely unassailable. Further, instead of thus producing

an active immunity by making the person go through an imitation of the disease himself, it is possible by introducing the causative factor of the disease in a weakened or sterilized form into some animal, to produce in its tissues or in its blood the reaction products of immunity, so that by transferring these to the body of the patient a *passive* immunity is conferred which may even stop the disease already in progress.

Several methods are thus in common use: (1) The parasites in full virulence, but in very minute doses, are administered so that the animal finally overcomes and recovers from a mild attack of the real disease; (2) the same thing is accomplished by a larger dose of weakened, attenuated, or non-virulent parasites; (3) dead bacteria or virus are used in place of the living, and produce a feebler but similar immunity; (4) the isolated poisons of the parasites are injected in gradually increasing doses so that the power is developed to neutralize the poisons, or (5) from such an animal this neutralizing power is transferred to another which thus, without effort, becomes immune.

For this book a discussion of all the phenomena of immunity as worked out in such great detail in recent years, is not desirable, and the student is referred to books on immunity such as that of Zinsser.

But while cytolytic and bacteriolytic substances, agglutinins, precipitins, antitoxins, etc., may be dismissed in this way, it is important to refer at least to such changed reactions as affect and modify actively the pathological alterations of the tissues which we must study.

Allergy and Anaphylaxis.—Since the work of von Pirquet, Arthus and others, much attention has been devoted to the peculiar reaction of the body following upon the introduction of a second dose of a protein into the body of an animal already sensitized by a previous injection. Such sensitization results only when the protein has been introduced parenterally, that is, directly into the blood or tissues, and not by way of the digestive tract. If the same protein be injected into the blood-stream after sensitization the reaction differs in various animals; in some such as the guinea-pig there follows extreme contraction of the bronchial muculature and overdistention of the lung with imprisoned air, upon which death quickly follows. In others there is vasomotor paralysis, inefficient contraction of the heart, dyspnœa, oedema of the skin, diminution of the coagulability of the blood, etc. Death may occur in these conditions too, and such results are known as anaphylactic shock. Tragic results from the inadvertent injection into the vein of large doses of diphtheria antitoxin in horse serum in patients who had previously been sensitized by a similar dose, led to the idea that such a person could be desensitized by preliminary small doses and thus saved from any serious injury when a large dose was given.

Von Pirquet used the term allergy to mean a changed reaction of the tissues, implying that an antigen-antibody combination underlay it. An example is found in the case of a bland or harmless protein such as egg-white, a later injection of which into the skin produces necrosis of the tissue with a slough and ulcer formation in the midst of an area of intense inflammation—the so-called Arthus phenomenon.

A quite similar sensitization is brought about by infection with the

tubercle bacillus which produces in a short time such hypersensitization that the existence of the infection may be recognized by injecting a small dose of tuberculin (a protein extract of the bacilli) into the skin. In a normal animal, never exposed to tuberculous infection, the injection produces no visible change, but in an animal already infected with tuberculosis there appears a local swelling and reddening and ultimately, if the dose is large enough, necrosis and sloughing. So too necrosis results in the internal organs in previously infected animals if the bacteria reach them and, being broken up, liberate their protein in contact with the sensitized cells.

Rich has shown that immunized animals which are also hypersensitive to the protein of the infecting organism, can be desensitized and are still quite as resistant to infection as before. Sensitization is a change in the cells, possibly due to the accumulation upon their surfaces of an antibody which brings about the death of the cells when the sensitizing protein reaches them. Some of this antibody may circulate in the plasma but in bacterial infection there may be only traces there, and it is not sufficient to suppose that a poison is produced by the interaction of the bacterial protein and the circulating antibody, for a mixture of the plasma of a sensitized animal with the sensitizing protein has no effect on a normal animal. On the other hand, the cells of a sensitized animal in tissue culture are killed, even in the absence of its own plasma, by the addition to the medium of the sensitizing protein, while normal cells are unaffected. Nor has the allergic reaction anything to do with the immediate fixation of the invading bacilli *in situ*. Bacteria are agglutinated and made to adhere locally to the tissues by the agglutinating antibody, and this happens in the complete absence of the allergic reaction. Hence it is clear that the inflammation of the allergic reaction is not, as has been supposed by some authors, the cause of the fixation of bacteria or protein at the point of entrance. Further, the fixation is complete before any sign of inflammation appears.

This state of allergy is extremely variable in one individual from day to day in the course of a progressive infection, being abolished as in the case of the desensitization in anaphylaxis by a new dose and built up again later so that it becomes necessary, if we are to compare the effects of various injections, to know exactly what was the state of hypersusceptibility at the moment each was given. Its study must be important in every infectious disease, but we are only at its threshold yet and attention has been more especially directed to the effort to understand the changing effects of introducing foreign sera at intervals, and to the peculiar phenomena of food idiosyncrasies, hay-fever, asthma, etc., all of which are closely related. These are discussed at great length in the immunological literature (Longcope, Harvey Lecture, 1915-1916, Series xi, Jour. Exp. Med., 1918, xxvii, 341; Duke, Allergy, Asthma, etc., St. Louis, 1925). Most authors tend to regard the violent destructive effects and the intense reaction as the effect of some poisonous substance produced by the antigen-antibody combination (anaphylatoxin) or by the decomposition of protein and think of it as purely deleterious to the animal, and, indeed, it is hard to feel

differently when one observes the great destruction of tissue and the extreme illness of such an animal or person, often ending in death, which is apparently greatly hastened by this violent response to new infection or the mechanical spread of the old.

LITERATURE

- Only general reviews which give further literature references are cited.
- Aschoff: Ehrlich's Seitenketten-Theorie, Jena, 1902. (*Ztschr. f. allg. Physiol.*, 1902, i.)
- Besredka: Kraus and Levaditi, *Handbuch d. Immunitätsforschung: Anaphylaxie*.
Biedl and Kraus: *Ibid.*, 255.
- Ehrlich: *Gesammelte Arbeiten*, Berlin, 1904.
- Friedberger and many others: Kolle u. Wassermann, *Handbuch der Bakteriologie*.
- Gay: *Arch. Path.*, 1926, i, 847; *Jour. Immunol.*, 1923, viii, 1.
- Krause and Willis: *Trans. Nat. Tuber. Assoc.*, 1924, xx, 277.
- Metchnikoff, E.: *Immunité dans les maladies infectieuses*, Paris, 1901. Lubarsch-Ostertag *Ergeb.*, 1896, i, 298.
- Opie, E. L.: *Jour. Immunol.*, 1924, ix, 231; *Jour. Exp. Med.*, 1924, xxxix, 659.
- Rich and McCordock: *Bull. Johns Hopkins Hosp.*, 1929, xliv, 273.
- Rich: *Arch. Int. Med.*, 1929, xliii, 691; *Bull. Johns Hopkins Hosp.*, 1930, xlvii, 189; 1933, lii, 203. *Trans. III Internat. Pediatric Congress, Acta Pædiatrica*, 1933, xvi.
- Sobernheim: Krehl u. Marchand, *Handb. d. allg. Pathol.*, 1908, i, 417.
- Wassermann, A.: Volkmann's *klin. Vortr.*, 1902, No. 331 (Chir. No. 94).
- Consult especially,
- Zinsser: *Infection and Immunity*, New York, 3rd ed., 1923; *Arch. Int. Med.*, 1915, xvi, 223. (*Anaphylaxis*.)

Asthma.—Asthma, or as it is sometimes called, bronchial asthma, is a peculiar condition lasting over years, in which there occur spasmodic attacks during which respiration is greatly embarrassed. Inspiration becomes very difficult and until the sudden relief that comes with a paroxysm of coughing, there is disturbance of the circulation.

The cause of this condition is not in all cases clear, and there are several theories as to its nature, but in most cases it is evident that an anaphylactic condition exists with sensitization to some protein substance whether of animal or vegetable origin. That this may be due to the parenteral introduction of some substance such as pollen, or dust, or from something in the food, is generally agreed, but in some instances it seems to be due to the presence of bacteria. This may be associated with abnormal conditions in the nose and nasal sinuses but it is clear that the pathological changes in the lungs are not directly caused by bacteria in the way familiar in bronchitis or pneumonia. In addition, many authors feel that some disturbance of equilibrium in the function of the vagus and sympathetic nerves may play a part.

Death as a direct result of asthma is not so rare as was once thought and at autopsy the lungs are found to show an extreme emphysema. The bronchi and bronchioles are thickened and contain moulds of thick mucus. In a case studied recently these presented a remarkable appearance since they projected a little way from the cut ends of the bronchi and could be seized with forceps and pulled far out without breaking. Such was their elasticity that when released they would snap back again into the bronchus. These on section (Fig. 76) show

the typical spiral arrangement of layers of thick mucus around a central filament of denser mucus described first by Curschmann and known from their appearance in the sputum as *Curschmann's spirals*. Sometimes they contain also the so-called Charcot-Leyden crystals, but always they are rich in eosinophile cells. The walls of the bronchioles

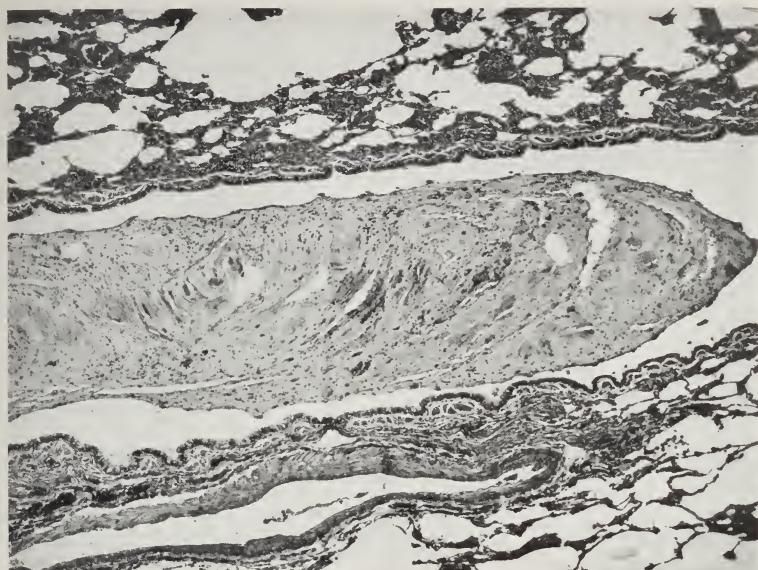


Fig. 76.—Asthma. Curschmann's spiral in a bronchiole.

are swollen and thickened and the lining cells evidently active in the secretion of mucus. Eosinophiles are present throughout these walls and even in the neighboring tissue but there is no appearance of inflammation such as would be caused by bacteria.

LITERATURE

- Bergstrand, Hilding: Acta Pathol. et Microbiol. Scandinav., 1928, v, 251.
Brown, T. R. (Charcot-Leyden crystals): Philadelphia Med. Jour., 1898.
Hoesslin: Dtsch. Med. Woch., 1934, lx, 1801.
Huber and Koessler: Arch. Int. Med., 1922, xxx, 689.
Rolleston and Freeman: Proc. Roy. Soc. Med., 1935, xxviii, 247.
Vallery-Radot and Claude: La Pratique Méd. Illustrée, Paris, 1932.
Walker, J. Chandler: Jour. Med. Research, 1917, xxx, 487.

CHAPTER XI

DEFENCES OF THE BODY (Continued)

New-growth of tissue. General characters. Influence of various agencies on growth. Growth stimuli.

NEW-GROWTH OF TISSUE AND REPAIR

WE ARE very ill informed with regard to the principles which underlie the growth of tissues, and any discussion of them soon leads us to a point beyond which we cannot go without invoking the deceptive aid of such expressions as vital force, inherent vitality, etc. There have been many efforts to explain the manifestations of life on a chemical or physical basis, but while they explain very well what happens, they leave us with little notion of what the real spark is which starts the setting free of energy, whether its result be a functioning of the cell as we see in a muscular contraction or the division of one cell into two.

We do know well enough that new-growth of tissue occurs when tissue is destroyed. Much of this compensatory new formation may take place somewhere quite far away from the point of injury, but at any rate there is a local patching which, when the tissue destroyed is a highly specialized one, is usually carried out by the ubiquitous connective tissue. The patch is, therefore, not likely to be of the same dignity as the original tissue, and serves mainly to reëstablish continuity.

Since injury often excites the inflammatory reaction also, the two may become inextricably entangled, so that there has long been confusion with regard to "inflammatory new-growth." This is especially true when, on account of the persistent repetition of the injury, the inflammatory reaction continues for a long time, and attempts at healing are repeatedly partly frustrated. But the most intense inflammatory reaction may occur with hardly any new-growth of tissue, as in pneumonia, and, on the other hand, regeneration and repair sometimes take place with no visible signs of inflammation. The two processes seem distinct in their causes, in their aims, and in the cells which participate, so that though they occur together they should not be confused. If we reflect upon this, even though we meet with difficult and questionable cases, we must realize that that process which we call inflammation consists essentially in the flooding of the injured tissues, by special mechanisms, with an excess of wandering cells and the fluids of the blood which tend to neutralize the injurious agent and clear away the débris and then to fade away and disappear, having taken no part in new formation of tissue. Repair, on the other hand, is the new formation, from neighboring cells, of a more or less complex, permanent, and coherent tissue which takes the place of that which was lost.

It seems not unreasonable to suppose that the warmth and good blood-supply which are so characteristic of inflammation might favor this process of repair, or even that the irritant itself, when it becomes

diluted in its extension into the tissue, may act as a stimulant to cell growth. The conception of "inflammatory new-growth" or "productive inflammation" must depend upon this last possibility, and there will arise occasion to discuss it further. For a long time there was doubt as to the rôle of the many kinds of wandering cells which appear in old areas of inflammation, and as long as they were thought to be able to give rise to connective tissue, the influence of inflammation on new-growth seemed very great. Now, however, since Maximow and others have shown their rather specialized wandering character, and it is admitted only grudgingly that they have any part in tissue formation, the matter becomes clearer and we have to deal with wandering cells as concerned with inflammation and fixed tissue cells with repair.

Nowhere, however, could there be a more convincing instance of the effect of a chemical stimulant acting to excite a rapid new-growth of tissue than in the case of the sudden phenomenal proliferation of leucocytes in the bone-marrow, and the flooding of the blood with these cells when some bacterial poison is absorbed from an area of inflammation.

We must ask ourselves what are the causes which lead to the growth of tissue in general, and the new-growth of tissue in particular, and we find that, while we have some information concerning those things which influence growth, we are reduced to theories when we attempt to explain the actual causes. Underlying it all we must recognize one essential thing which distinguishes a live cell from a dead one, namely, the ability to absorb and assimilate nutritive substances, building them up into its own protoplasm, and then, by the exercise of a certain amount of energy, to divide its nucleus and protoplasm in such a way as to form two new cells in place of the old one. Given this power, which we cannot explain, we may as well go on to discuss the conditions and influences which guide this growth, and which are directly chemical or physical in their nature.

The materials for growth must be supplied, and are precisely selected by the cell in quantities to suit its metabolic processes. Water, protein, carbohydrate, and fatty substances, inorganic materials, and oxygen are absorbed, and carbon dioxide with various other substances, elaborated or excreted by the cell, are given off. We realize that growth is inhibited by faulty nutrition or by an inadequate blood-supply, and that the healing of a wound is slow and imperfect in those whose metabolism is impaired by old age or illness. The idea that increased activity in growth is brought about by an excessively rapid and abundant blood-supply has long been held, and there is some evidence in its favor. A rabbit's ear kept flushed with blood by the section of the sympathetic nerves is said to grow more rapidly than the other, and to outstrip it, while conversely it is well known that rapidly growing tissue makes its appearance with an excessive provision for blood-supply in the form of numerous wide capillaries which disappear when the tissue becomes mature. Still, the situations in which we may study the effect of an excessive blood-supply in comparison with an adequate one are generally complicated, and give us little light on the subject.

When tissue is grown artificially in a hanging drop of blood-plasma, all these influences come most clearly to view, and it is quickly apparent that growth stops at once when the supply of nutriment contained in the drop of plasma becomes insufficient. The effect of warmth is most apparent there also, and it can be shown that, whereas at very low temperatures growth does not occur at all, it begins and increases slowly in rate as the temperature is raised until, at a certain point, it finds the optimum conditions. Higher temperatures than this are unfavorable, and growth becomes slower and slower until a point is reached at which it is completely inhibited. In living animals this can be demonstrated to some extent, inasmuch as the ear of a rabbit kept warmer than normal for a long time is said to grow so that it becomes larger than the other ear, which has not been so treated.

In this last instance, as in the case of the influence of the nervous system, it is difficult to decide which of several things may be the real cause of the growth, for in such a rabbit's ear the warmth tends to widen the blood-vessels and thus bring increased supplies of nutrition to the part. Indeed, it is somewhat doubtful whether the nervous system has any direct influence over growth, even though we speak so confidently of trophic nerves. For while an extremity which has been paralyzed fails to grow as the normal one does, this may well be due to its inactivity and the consequent diminution of the blood-supply.

Mechanical influences play a considerable part in determining growth, although it is well known that in plants at least a force can be exerted by growing tissues far greater than that which might ordinarily be used to interfere with their growth. Here again there enter the complicating factors of interference with nutrition and light, which are most powerful to disturb growth, for while a tree growing in a crevice can split a rock and roots can lift up pavements, one may apply a relatively slight pressure so as to cut off nutrition and light, and growth will be blocked.

Continuous pressure applied to organs or extremities in the animal body interferes with their growth or causes the cells to atrophy and disappear, as we see in the deformed livers of those who lace tightly and in the misshapen skulls of those Indians who bind the heads of their children. But intermittent pressure, as that of a shoe which pinches, tends rather to cause an excessive callous growth of epidermis. We might multiply examples of the growth of tissue in response to various sorts of mechanical tensions and strains, a growth which forms the basis of the wonderful adaptation to function so generally observed when tissues or organs are subjected to changed conditions. Thus the arching lamellæ of bone which are precisely calculated to meet the strain at the upper end of the femur are, after a time, rearranged to suit the new conditions with equal mechanical perfection when the bone has healed after a fracture.

Probably few persons who survive an extensive injury, and in whom this process of readjustment to new conditions is going on, live long enough to allow it to be quite perfected, but there are frequently found in such persons the most extraordinary adaptations.

It is only in those tissues which have to do with movement and support, however, that the inciting cause of the new-growth of tissue is chiefly mechanical, and it must be remembered that in other organs whose function is not of a mechanical nature other influences are at work to bring about the readjusting new-growth. A good example of the mechanical type is seen in the establishment of a collateral circulation when an important vein or artery has been obstructed. Numbers of channels which were previously insignificant become large,



Fig. 77.—Fibroblasts growing into a thrombus.

thick-walled vessels and give passage to the pressing stream of blood in a roundabout way, so that it may rejoin the original channel beyond the obstruction. A remarkable instance of this which showed a complete obstruction of the superior vena cava is described by Osler.* A bulky mass of new vascular channels was so formed as to convey the blood from the upper part of the body over a long detour to the heart (Fig. 9).

* Johns Hopkins Hospital Bulletin, 1903, xiv, 169.

Obstructions placed before tissues which act mechanically in such a way as to make it difficult for them to carry on their function nearly always cause a growth of the tissue, so that it becomes stronger and forces the barrier. This is seen in the heart and in all those muscular structures, such as the intestine and the bladder, whose duty it is to move their contents by contraction. Above a tumor which obstructs the colon the wall becomes enormously thick and powerful, and so does the wall of the bladder when, through the enlargement of the prostate, urine is evacuated with difficulty.



Fig. 78.—Characteristic growth of connective tissue cultivated *in vitro*. There are many mitotic figures.

In the repair that follows a loss of substance these mechanical influences are not quite so plain, but they undoubtedly play a part. New tissue is formed hurriedly and in great quantities to replace that which was lost, and although at first it seems to grow in a somewhat disorderly way, it quickly shows an adaptation to its purpose. All this is probably guided, at least in part, by the influence of the solid materials with which the cells come in contact, for while the young connective-tissue cells and blood-vessels can grow by themselves and form an even swelling tissue, the more usual and natural way for them is to grow upward into a network of fibrin filaments along which they creep

and which, in turn, they dissolve and destroy (Fig. 77). Epithelium grows and spreads out on a surface when that is offered, but scarcely penetrates into a feltwork of fibrin. These are differences in the "inherent vital characters" of these cells, for when isolated from all connection with the body and growing in the hanging drop of plasma, they show the same peculiarities in their growth; connective-tissue cells sprout out in every direction so long as they may follow the course of a filament of fibrin. Epithelium grows in a sheet, just as it tends to do on the surface of a healing wound (Figs. 79, 80).



Fig. 79.—Characteristic growth of epithelium in culture.

Even the simplest of these forms of tissue proliferation can hardly be ascribed directly to any mechanical influence, but it is clear that the cells in their growth are guided and directed to some extent in this way. There must be remembered always the underlying tendency of the living cell to assimilate food materials, increase its substance, and divide.

Functional Equilibrium.—Is there then some stimulus from without which accentuates this tendency, or is the tendency merely allowed full play by the withdrawal of some restraining influence? This has been

the subject of debate for many years, for while Virchow held that there exist actual growth stimuli which might indeed act through the injury or destruction of certain cells, Weigert declared that cells grew because the mutual resistance of the tissues was set aside, the equilibrium disturbed, and, as John Hunter before him had thought, the cells grew impelled by the loss of the physiological limitations which one tissue element opposes to another. John Hunter had spoken of the stimulus of incompleteness; Weigert regarded the tissue growth which occurs with inflammation not as the result of a stimulus, but only as the con-



Fig. 80.—Epithelium and connective tissue growing side by side in a culture made from the intestine of an embryo.

sequence of the tissue defect. According to him, it was quite unproved that there is any direct idiopathic stimulus.

The existence of a certain equilibrium among tissues, and the remarkable effects of its disturbance, have long been recognized, but this equilibrium cannot be looked upon as a merely mechanical one. Nor is it to be explained on any simple chemical basis. We are perhaps nearest to the truth if we say that it rests chiefly upon a balance between the functional activities of different tissues. If, in the functioning of a cell, certain material is consumed, the cell makes this up by its assimilative processes. If functional activity is maintained at an ex-

treme, so is the assimilation, and the cell even increases its size and functional power, or, after accumulating an excess of cell material, divides into two cells, so that the function is better maintained (hypertrophy; hyperplasia). But no mechanical or chemical disturbance in the body will give more than a motive for this. The process itself depends on that inherited power of growth by which the cell adjusts itself to the new conditions.

When they reach maturity, the bodies of any one kind of animal have, as we know, a characteristic form and a recognized average size, but a good deal of variation from the standard is still compatible with life. Within the body the interrelation of organs seems to be much more precisely calculated, just as the works of a watch must be calculated throughout, although the case may have any form. It seems probable that there may even be an actual numerical relationship between the cells of different organs, so that a disturbance of this balance is felt if cells are destroyed in one. It is known, of course, that each organ is able to put forth in an emergency a vastly greater functional activity, since it has a reserve power which constitutes its margin of safety, but this effort is felt at once and shortly leads to the multiplication of the cells and the increase of the functional power. This is true whether the emergency results from the destruction of some of the cells or the increase in the demand upon the organ.

This is the functional equilibrium of the tissues which is maintained very precisely by the increase and reduction of the various functional units. But there is also a mechanical equilibrium. The tissues grow in certain arrangements, and the organs assume certain normal forms which are the result of the action of various tensions and strains not always easy to recognize or calculate, and the end-result is the recognized normal body form. It requires a very extensive disarrangement of the tissues to obliterate the trend of these tensions and strains and allow the body to heal into any unusual or inappropriate form. Usually, if time is given, the healing of any moderate injury goes far toward restoring the normal body form and thus the mechanical equilibrium.

When an injury is such as to unbalance for a time this mechanical equilibrium, there occurs a new formation of tissue to replace that which was lost, and in time the original mechanical conditions may be well restored and the body form reinstated, but it would be rash to state that this was carried out solely because the mechanical equilibrium was disturbed or that the cells grew because pressure relations were altered on one side or the other. There is always the other factor to be considered, namely, that the loss of tissue, even when it is merely supporting tissue, involves an unbalancing of the functional equilibrium, so that the growth occurs also to reinstate that. However, even with these two reasons it is difficult to explain the purposeful methodical growth of tissue which so precisely accomplishes the healing of a wound, but in its detail, in which fibrin plays a part, guiding the direction of growth of the new cells so that they stretch across from one side of the wound to the other, a plan is doubtless being carried out which has

become a routine after a long process of evolution, and is now merely the common means, regardless of the reason for growth.

That the unbalancing of the mechanical equilibrium can hardly be considered the main reason for the new-growth of tissue becomes clear when we consider cases in which it can be practically eliminated. When, for example, some poison kills a part of the liver-cells in each lobule of that organ, multiplication of the remaining cells occurs while the bodies of the dead cells are still in position and little change in the pressure relations can have arisen. So, too, on the removal of one kidney, or even when its function is annulled by obstruction of the ureter so that it becomes atrophied or enlarged into a sac of fluid, growth occurs in the other kidney until it is able to do easily the work of both (Fig. 81). These are examples of the results of an unbalancing of the functional equilibrium which seems, upon due consideration, to be the most important factor in this question of new-growth.

Influence of Nutrition.—In general, growth of tissue is much influenced by the character of the food, and in the lack of certain constituents may be greatly retarded. Not only are actual materials necessary for the normal production of new tissue, but stimuli to growth, which are ill-understood, but which seem to come from some of the organs of internal secretion, are necessary. Besides these which have very special effects, such physical influences as light, especially light-rays of certain wave-lengths, play an extremely important rôle in promoting some part of growth. And still further, there are peculiar substances—vitamins—present in minute quantities in foods which are also absolutely necessary to maintain proper growth. Some of them have already been isolated in chemical purity and it is possible that they act in conjunction with other things such as light-rays, but without them growth and function and even the structure of tissues go wrong.

These three (internal secretions, physical influences and vitamins) will be discussed in detail in later chapters.

Active Stimuli to Growth.—Still the question remains whether there exist means by which growth can be directly and actively stimulated. The great difficulty in answering this question lies in our being unable to eliminate the factors of the unbalancing of the mechanical and the functional equilibrium by the injury which these stimuli cause in the cells, and for this reason we may await with interest the results of systematic experiments with the application of such supposed stimuli to tissue growing *in vitro* where mechanical conditions can be controlled and functional demands reduced to a minimum. Further, in those frequent cases in the animal body in which the very excess of the new tissue produced seems to argue the existence of some special stimulus to growth, we must eliminate the possibility that this new tissue may represent the accumulated product of repeated attempts at repair, each of which has been partly frustrated by a new injury, so that even the repairing tissue is injured and responds in an attempt to repair itself. It is readily seen that this process, kept up for a long time, would end in the formation of a great quantity of scar tissue, or, at the margin of a chronic ulcer, of a greatly thickened and irregular epithelial growth.

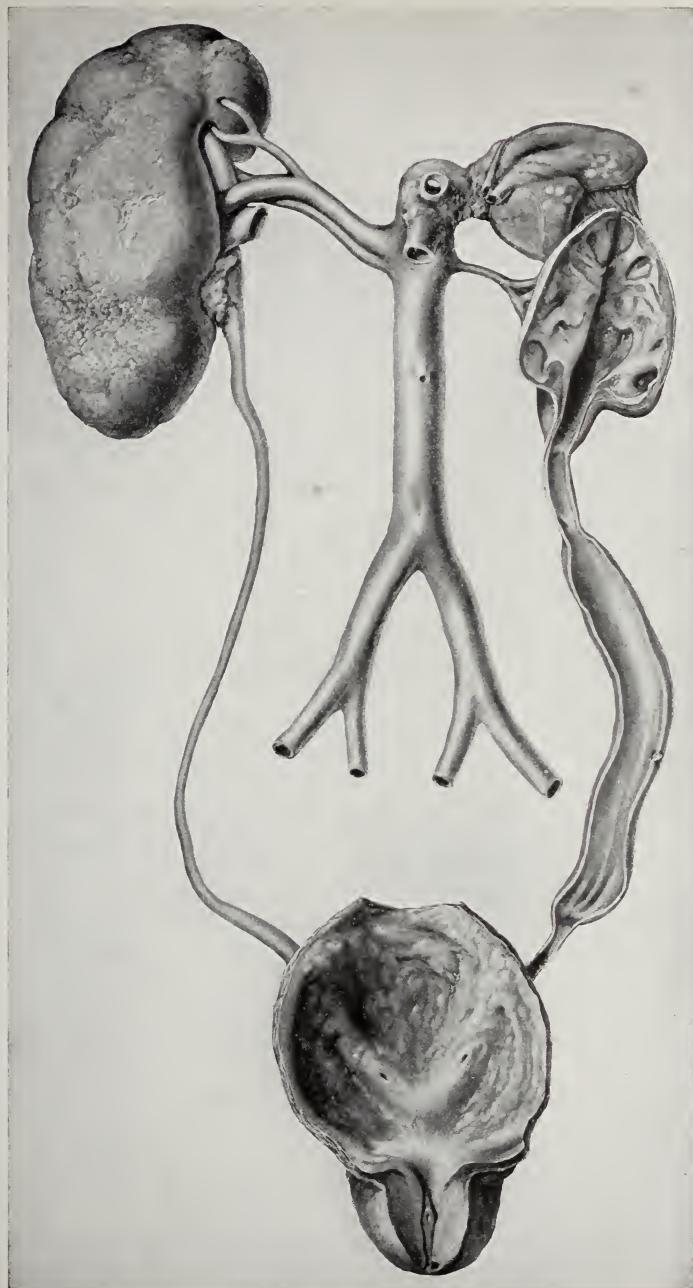


Fig. 81.—Atrophy of left kidney following obstruction of the ureter. Corresponding enlargement of the opposite kidney.

But in the present state of our knowledge it is impossible to deny the existence of direct stimuli to tissue growth, although it seems that this facile explanation ought to be used perhaps a little less freely than is done in most text-books. There are certain substances, such as the stains Sudan III and scarlet red, which, when injected into the tissues, provoke an extraordinary growth of epithelium, cartilage, etc., which in some cases finally looks almost like a tumor. Similar results have been obtained with skatol, indol, etc., and even with ether water. It is not quite clear how these substances act nor what part is played by the injury they produce in the tissues, but the new-growth is far in excess of what would be needed for repair. They are all soluble in lipoid substances, and it is possible that their effect is due to their attacking the lipoid membrane, which is supposed to envelop each cell, thus exposing the cell to outward influences from which it has been protected. This is somewhat allied to Loeb's methods of stirring up artificial or parthenogenetic development in unfertilized egg-cells, for in that process he emphasizes the importance of lipolytic substances in their action upon the envelope of the cell. In that case, however, the segmentation which is started is rather a process of the development of a cell endowed with great energy of growth, while in the mature cell the latent potential energy must be converted into an active form and greatly intensified.

Very vague, too, are our notions about the substances which cause the sudden new-growth of tissue at the onset of puberty, and especially those which produce the remarkable changes in the breasts and other organs in pregnancy. Doubtless these are chemical substances which circulate in the blood, as has been shown in the case of those malformed twins which, being fused together, have a common circulation, and in whom pregnancy in one affects the organs of the other (Blazicek sisters, one of whom became pregnant, after which the breasts of both secreted milk).

Other instances in which the increased or perverted activities of the organs of internal secretion are followed by a great overgrowth of all or a part of the tissues are well known (gigantism, acromegaly), and, on the other hand, the extreme stunting of growth from the failure of these secretions is equally well known (myxoëdema, cretinism, etc.). There are conditions, too, such as the pulmonary osteo-arthropathy of Marie, in which the absorption of poisonous material from the widened and infected bronchi produces a great overgrowth of the extremities—actually a sort of gigantism.

Infections and Foreign Bodies.—Of daily interest in regard to the new-growth of tissue is the influence of infections and of foreign bodies, among which may be classed dead tissue and fibrin.

Many infections lead to inflammatory reaction without necessarily resulting in any great destruction of tissue or any very evident reparatory process. But this is doubtless partly dependent upon the situation of the infection, for while the pneumococcus may produce a pneumonia which will disappear, leaving only a few gaps in the respiratory epithelium to be filled up by the neighboring cells, the same or-

ganisms in the pleura or pericardium are likely to produce an exudate the replacement of which by new tissue leads to the permanent binding together of those surfaces. Nevertheless, even there the adhesions may be slight or absent, and the extent of new formation of tissue appears to depend upon the extent of the injury.

The result of the destruction of tissue by bacteria seems to differ from that produced mechanically chiefly in that the bacteria persist after the repair has begun and repeat the injury. This is notoriously true of those resistant bacteria and animal parasites which remain lodged in the tissue for a very long time. It is true of the tubercle bacillus and of the Spirochæta pallida, which linger after completing their first injury to the tissue until they are encased in a nodule of new tissue, and then still longer, until, by their poisons, they cause the necrosis of the cells of that nodule, which is then replaced by a wall of cells a little further out. The first nodule seems far in excess of what was needed to repair the injury caused by the bacilli, and the question arises at once whether its abundant cells have not grown in direct response to a stimulus furnished by the bacillus. Probably so, but the matter is so complex in the animal body that it seems possible to decide it, if at all, only by recourse to experiments with isolated tissues growing *in vitro*.

All the factors which decide the inception of growth are at work when a portion of tissue is left dead and surrounded by living tissues in the organ, as in the case of an infarct. Scavenging leucocytes attempt to remove the coagulated material, but before they can make much impression on it the dead tissue is invaded and replaced by a new-growth of capillaries and connective tissue. The functional replacement occurs elsewhere, and at this point there is only a restoration of continuity and removal of the irritating foreign substance. Perhaps unbalancing of the mechanical equilibrium is important, but it seems that the presence of the fibrin-containing necrotic tissue offers a chemiotactic attraction which guides the growth of the invading blood-vessels, and it may be that it is really a chemical stimulus to growth. An exudate of fibrin on the surface of the peritoneum or pleura, where no unbalancing of mechanical or functional equilibrium can be caused by its presence, exerts the same influence on the underlying tissue and is quickly replaced by a new tissue. So, too, a clot in the course of the blood-stream, whether it obstructs the circulation or only lies on the wall of the heart.

Inert foreign bodies are attacked in the tissues by wandering cells of all sorts, just as the fibrin and dead cells are attacked and dissolved or surrounded; but they, too, soon find connective tissue and blood-vessels flowing in about them, so that they are quickly encapsulated or permeated by these cells. Indeed, there is hardly anything which sets up such an extraordinary new formation of cellular fibrous tissue as a suspension of foreign particles, such as the diatom shells which form the fine dust of silicious earth or kieselguhr (Podwyssotsky). Perfectly insoluble, these particles can hardly act through any chemical stimulus, nor do they appear to cause any great injury to the neighbor-

ing cells or disturb the mechanical equilibrium to any great degree. Perhaps it may be regarded as a tactile stimulus which causes cells to grow around them, much as they follow threads of fibrin or the surface of the cover-slip in cultures. Indeed, as Lambert has shown by the aid of lycopodium spores, the cells in a culture which surround foreign bodies are not those of the connective tissue, but the wandering cells. Nevertheless, in the body the actual fibroblasts appear in time, and form an outer capsule (Fig. 82).



Fig. 82.—Tubercle-like capsule formed around a lycopodium spore introduced into the liver through the portal vein.

The growth of tumors exemplifies in a singular way the stimulation of another tissue to growth. No matter what may eventually prove to be the reason for the unbridled growth of the tumor-cells themselves, we know that, standing as they do in close relation with connective tissue and blood-vessels, they stir up a growth in those structures which leads to the production of a most complicated and extensive organized stroma, which sometimes assumes forms totally unknown in the body

and reaches a bulk far greater than that of any new-growth formed in the process of repair.

Analogy Between Embryonic Growth and Pathological New Formation of Tissue.—The dividing cells, and more especially the products of division which appear in the course of the new formation of tissue, are often spoken of loosely as embryonic cells; the tissue has returned to the embryonic state, and the ontogenetic phases are being reproduced. This seems hardly justified, since these new cells do not really resume the character of embryonic cells, which have such a great potential energy pushing them to unfold and develop. On the contrary, they are merely young cells of the type which has reached maturity, and whose growth energy has been finally reduced to a point which leaves them able to maintain the integrity of the organ, but not to develop further into a still more highly specialized and mature tissue. Even in those situations in which normally there is a constant active production of cells, as in the Malpighian layers of the skin or in the bone-marrow, the cells are mature in the sense that they do not tend to develop further, but merely produce new ones of the same kind. Even the fact that these new cells become much modified does not affect this idea.

LITERATURE

Various papers of Harrison, Lambert, Hanes, Burrows, and others. Summarized, Trans. Cong. Amer. Phys. and Surg., 1913, ix, 63.
Rössle: Growth, Ergebni. d. allg. Path., 1917, xvii₂, 677; 1923; xx₂, 369.

CHAPTER XII

DEFENCES OF THE BODY (Continued)

Repair. Established character of tissues. Their early differentiation. Metaplasia. Regeneration as exemplified in the new formation of various tissue.

REPAIR

General Phenomena of Repair.—When the body has reached its mature form, cells are newly formed only in sufficient quantity to make up for those lost each day in the ordinary wear and tear. Since cells are being constantly rubbed off the surface of the skin, the lower layers are just as constantly occupied in producing new ones. Since the red corpuscles of the blood are short-lived cells, they are constantly manufactured anew in the bone-marrow. These processes are so gradual and inconspicuous that it is hard to be sure that they are going on. But if a piece of skin be scraped off, or a few ounces of blood allowed to escape, there suddenly occurs a far more vigorous new formation of cells in the skin or in the bone-marrow.

Every obvious new formation of tissue in the grown person seems to occur as a result, which we might predict, of some disturbance which impairs or renders inadequate the function of that tissue. It is a response so appropriate to the situation and carried out with such moderation and in a manner so eminently suitable to the supposed purpose of restoring the functional equilibrium of the body that it is hardly possible to doubt that it, like inflammation, must be a plan evolved and elaborated through ages of natural selection for the preservation of the species. It is complicated and makes use of subsidiary mechanical aids, as we shall see (such as the filling of the gap across which tissue is to grow with fibrin); but whatever the details may be, the process is nicely adjusted to the purpose, and is so constant that we can predict with absolute certainty what will happen in a given case.

This, as every one will recognize, constitutes a striking difference between the regenerative and reparatory growth of normal tissue and the growth of tumors, in which one cannot foretell with certainty what will happen or where the growth will end.

The embryo grows according to an inherited plan, almost entirely protected from outward influences until the body form is reached. Yet then, too, so profound is the impression of this plan, if part of an organ or tissue be destroyed, regeneration and repair take place in such a way as to further the original plan as much as possible. Indeed, the degree to which this repair may proceed is greater in the embryo than it is in mature life.

Specificity of Tissues.—An important factor governing the repair or regeneration of tissues lies in the established character of the tissues themselves. According to the plan of development of the animal, the

cells of each tissue assume at an early stage a specialized character which they retain tenaciously. When these cells divide and multiply after that, they breed true, as it were, and produce new cells which have the same form and function as themselves. This is the well-known specificity of tissues, which is pretty rigidly maintained in mature life. In the embryo we may, of course, pass back to stages where we can no longer recognize the character of the cell, and where we are unable, in the present state of our knowledge, to say that this cell is predestined to become a liver-cell and that a smooth muscle-fibre, for in reality the cells at that stage have not divided to the degree at which one of the daughter-cells takes one path while another follows a different one. They have not yet adopted their careers. But it is further clear that this is not only because we are unable to recognize their tendencies, but because, at a very early stage, these tendencies are not absolutely fixed. The original fertilized ovum forms by its segmentation the whole body, but after it has undergone its first division, each of those two segmentation spheres, if separated from the other, is capable of producing a perfect individual, as we so frequently see in those so-called single ovum twins which are of the same sex and remarkably alike in appearance. At later stages, when the segmentation has progressed much farther, the destruction of one or more of the segmentation spheres can be compensated by the adjacent cells, which assume their function, but there must come a stage, and that quite early, when such compensation can no longer be carried out; if, for example, all the formative material destined to produce the heart be destroyed, a monstrous foetus would be formed without a heart. We cannot say, however, when this specificity is established, nor whether it is at very different epochs in the development, for different tissues. In any case it is only when all the cells are destroyed that the production of that tissue is made impossible. If any of this formative material be left, the processes of cell multiplication in the embryo are so efficient that even that remnant may be able to reconstruct as much of the tissue as is necessary.

While we know that most tissues are so specialized that they can assume only one form and one function, and in dividing give rise to no other type of cell, we recognize somewhat different degrees in this specialization. We cannot imagine the case, for example, in which, through division and multiplication of liver-cells, there might be produced pancreas tissue, although these organs arise in the beginning in much the same way, but we are quite accustomed to observe the alteration of one type of connective tissue into another. Here the specificity appears to be less rigid, for while we know that ordinarily white fibrous connective tissue produces only that type in its growth, it may be greatly altered in character by metabolic changes or by such mechanical influences as oedema or the prolonged action of a tension in one direction. Mucoid or mucin-holding tissue apparently arises in one way, while loose connective tissue may become tendon-like in the other.

Adipose tissue is specific in its appearance, and especially in infants or emaciated persons, in which the tissue is not entirely distended with

oil-droplets, it can be seen in the form of lobules sharply marked out from the surrounding areolar tissue and supplied with a peculiar and abundant capillary circulation. Whether all fat, even in the most obese persons, is lodged in this special tissue only it is difficult to say with certainty.

It is in the complicated changes which go to the formation of bone that we see the most varied interrelations and modifications of connective-tissue structures. Both from cartilage and fibrous tissue, bone may be formed by the activities of certain specialized connective-tissue cells, the osteoblasts. In so far as bones are formed in the normal positions, we might believe that, at an early stage, this specialization of certain connective-tissue cells to the character of osteoblast formed the essential basis upon which bone formation is possible, but we are frequently confronted with the formation of perfectly typical bone in places, such as the wall of the aorta, where no osteoblasts could normally occur, but where areas of necrotic tissue had become encrusted with lime salts. It is for this reason that we must think that the specialization among connective-tissue cells is not so rigid as in more highly developed tissues, because it is obvious that in those cases some neighboring mesoblastic cells assume the function and form of osteoblasts, and then produce bone in the regular way.

Endothelial cells, both of the blood-vessels and of the lymphatic vessels, have a high degree of specificity marking them off from other types of mesoblastic cells, and yet it is precisely with regard to these cells that the most extraordinary powers of assuming other forms and functions have been described. They are said to be phagocytic, to produce almost every type of wandering cell, as well as red corpuscles, to produce connective-tissue and even to secrete fluids different from those in the blood-stream. I myself have never observed that they do anything except steadfastly form the lining wall of blood-vessel or lymph-vessel and in their growth and multiplication form new vessels of the same kind. Even in the spleen, where they are modified in form as the lining cells of the venous sinuses, one never sees them act as phagocytes, although the general statement is quite to the contrary. In the embryo they are said to form the cells of the blood and this is maintained for the bone-marrow in adult life, but even this seems doubtful. Even when a thrombus fills a vessel and becomes replaced by fibrous tissue, the endothelial cells confine their growth to the production of a new lining membrane which covers the clot and keeps the fluid blood from contact with it.

These examples have been cited to show, in a general way, the importance of the specificity of tissues and the different degree to which this holds good in different tissues. More will be said about it in connection with those more highly specialized structures in which it is held to far more strictly.

Metaplasia.—Metaplasia is a term rather loosely used to express the modification in form of a tissue so that it assumes the appearance familiar enough elsewhere but not in that position. Formerly such processes were thought to occur very frequently, and "the old master"

Virchow, did not hesitate to derive cancerous or epithelial tumors from a matrix of connective tissue, but now we realize that such a great leap is impossible and at most we refer to the change in form of cylindrical lining epithelium of a duct or bronchus into squamous or stratified epithelium as an example of metaplasia.

REGENERATION

Regeneration of lost parts occurs with great readiness in the lower and simpler animals, and it is well known that their life can continue after the most profound mutilations by the simple expedient of forming anew whatever is found to be lacking. Details of the extraordinary experimental studies of these phenomena may be read in the books of T. H. Morgan, J. Loeb, and many others. As has been stated, something of this power of regeneration prevails in the embryo of higher animals and man up to a certain stage of its development. It may be expressed once more by saying that the fertilized ovum and the first segmentation spheres are totipotent. The cells produced in the course of later segmentations are multipotent, but the cells of the differentiated tissue are highly specialized, as a rule, and potent to produce others of the same type only. Quantitatively also the power of regeneration diminishes with the advance of development and cell specificity, but even in the mature human individual the latent power of these specialized cells for regeneration is often astonishing. While we recognize this decrease in the versatility of the cell in so far as its offspring are concerned, we must also recognize a very great difference among the mature tissues in their power to regenerate themselves, for although such slightly specialized tissue elements as those of the ordinary connective tissue, the periosteum, the epidermis, etc., regenerate very rapidly and extensively, those which are more highly specialized, such as the central nervous system, heart muscle, and striated muscle in general, regenerate themselves hardly at all, and any gap made in their substance must be filled by some inferior tissue which can grow fast and restore the continuity quickly. It need hardly be said that the tissue most commonly employed is the ordinary fibrous tissue. Over and over again we find this principle exemplified. In the heart there may be energy enough to form new muscle tissue in time, but when an area is destroyed, it is healed by fibrous tissue and not by muscle.

Thus, owing to the different powers of regeneration shown by various tissues, local repair is carried out sometimes by the injured organ substance itself, but more often by an inferior material, such as connective tissue. But even though such patching may occur there is, with few exceptions, some attempt made there or elsewhere to restore the original specialized tissue unless it has been destroyed to the last cell. Before discussing this process of local repair we may pass in review the phenomena which appear in the case of each type of tissue.

Epithelium.—All sorts of epithelium possess a quite remarkable ability to grow again and make up for that which was lost. As is so well known to every one, the surface epidermis will quickly grow out to cover again any abrasion or to heal over the granulating surface of

an open wound (Fig. 83). This is so clearly visible in the case of a healing ulcer where the thin, pearly blue edges of the epidermis advance slowly from the margin toward the centre until the whole area is covered, that it seems strange that there could ever have been doubt as to the source of the epithelium. Yet for a long time it was questioned whether the epithelium might not be produced by the granulation tissue. More careful studies have shown, though, that the regeneration is strictly specific, and that all new epidermal cells are produced through division of those still alive about the margin of the wound. Apparently many of them move and stretch out to spread themselves over the uncovered area before any division occurs, because the karyokinetic figures are found a short distance back of the edge, and especially in the lower layers of cells. These less modified cells seem to take a greater part in the new formation than those which have progressed some way toward the keratinization, and have, therefore, lost

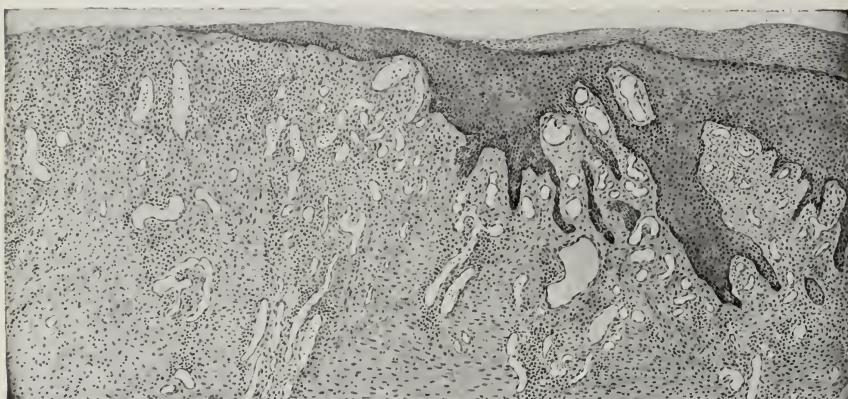


Fig. 83.—Growth of epithelium over a granulating surface. Irregular downgrowths of epithelium are an index of the delay in the healing.

to some extent or completely their power of division. Groups or masses of new cells are thus formed and furnish the material for the further spreading of the whole layer, but if, as is so often the case, that spreading is constantly prevented, they accumulate and extend downward in rapidly thickening and very irregular interpapillary growths (Fig. 83). It is generally stated that direct or amitotic division plays a great part in this new formation of epithelium, but this statement receives very little support from the direct observation of growing epithelium *in vitro*.

Since such a conclusion is dependent upon finding distorted or constricted nuclei, or upon the failure to find mitotic figures, it seems hardly convincing. No one can fail to accept the evidence concerning the growth by mitosis, but there seem to be very few instances in which the appearance of a cell with its nucleus constricted in the middle, and a corresponding constriction of the protoplasm, must be accepted as showing that two new cells of normal capacities are thus being formed. The appearance may so readily be due to pathological conditions, and the chance of abnormalities in the amount and arrangement of chromatin in the new cells is so

great, that I hesitate to accept the process of amitotic division as a normal method of reproduction and growth in the organs of the higher animals. Of course, we have abundant observations of this sort of division in simpler forms, and one may not deny its existence or its importance, but at least it seems clear that such a process should be more closely investigated rather than so unquestioningly accepted. If there is any truth in the theory of Hansemann that tumor growth may be imitated by the unequal or irregular separation of chromosomes in dividing cells, then amitotic division, where the separation of chromatin material into two nuclei is guided by no such precise mechanical process as in mitosis, may well be the source of such inequality.

The regeneration of surface epidermis produces a smooth layer of cells without any reformation of such specialized epidermal structures as sweat and sebaceous glands and hairs. Yet, as Minervini points out, the interpapillary downgrowths and the fine markings of the palm are formed again after years. Of course, if the abrasion be so superficial that these glands and hair-follicles are not completely destroyed, they



Fig. 84.—Compensatory hypertrophy of the lobules in a part of the liver after all the liver-cells have been destroyed in the other half.

may regenerate themselves from the remnants, and may also produce the less specialized surface epithelium.

The epithelium of the mucous surfaces behaves in exactly the same way, growing out from the edges to cover, with a smooth layer, the denuded area. Glands are regenerated from the epithelium which remains in their depths if they have not been completely destroyed. This is the common result in superficial ulcerations of the intestinal tract, and, indeed, one receives the impression that, even though the whole mucosa be destroyed over a small area of the intestine, as in the deep typhoid ulcers, it may be restored to a semblance of the original much more rapidly than in the case of the skin. After all, the production of crypts or villi is a rather simpler matter than the new formation of sweat and sebaceous glands and hair-follicles from the epidermis.

In the epithelial organs new specialized and perfect gland tissue is produced essentially by subdivision and multiplication of the remaining specialized cells. It is true that an elaborate effort toward their

regeneration is made by the less highly specialized cells which constitute the lining of the ducts. From the very fact that they are less highly specialized, and therefore more resistant, these cells survive in places where all the gland epithelium is destroyed, and remain alone in that area as a possible source for new gland tissue. They multiply, and the ducts bud out and ramify in all directions, but generally end in forming new connections with the gland tissue which remained alive after the injury, and whose duct connections may have been disarranged. Occasionally one may find, in a cirrhotic liver, a definite for-

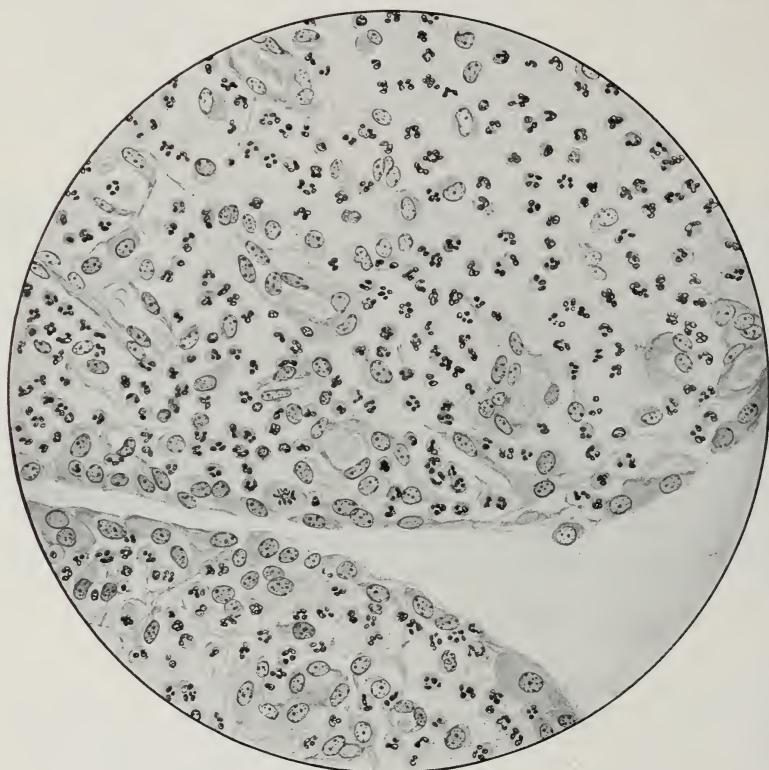


Fig. 85.—Granulation tissue lining a cavity showing endothelium-like flattening of the innermost cells.

mation of new specialized liver-cells at the end of a growing bile-duct (Fig. 163). The cells are seen to be fresh young liver-cells from their characteristic staining and their lack of pigment, but such things are rare and can play no very important part in the restitution of the functional liver tissue as compared with the profuse multiplication of the already differentiated liver-cells which remain in the fragments of the liver lobules which have not been destroyed.

In the kidney, in the same way, the increase in the specialized secreting cells comes from the multiplication of survivors which have

reached that stage of differentiation, and not from the cells lining the conducting tubules. If all the cells of a convoluted tubule are destroyed, that tubule collapses and compensation occurs through the enlargement of another tubule. It is by no means denied that differentiation of less specialized tissue occurs in the course of regeneration in adult life, but it seems that the repair of highly specialized tissue is more readily and more commonly assumed by the remnants of tissue which has already reached that stage of differentiation.

Connective Tissues.—These tissues are preëminently capable of regenerating themselves rapidly and in profusion, so that they form the bulk of the new material used for local repair. In nearly all their modifications they are resistant to injuries, and will survive and grow readily after treatment which would kill more delicate tissues in a short time.

The character of their specificity has been discussed already, and it has been shown that, although in places undifferentiated cells persist and furnish the specific differentiated cells of the blood throughout life, most of the connective tissues of the body are differentiated, and in their multiplication reproduce the same type of cell. Nevertheless, the assumption of osteoblastic functions by connective-tissue cells quite away from the original osteoblasts is sometimes seen, and certain other lapses from strict specificity may be observed.

Ordinarily, white fibrous or areolar tissue produces, by the division of its cells, other cells of exactly the same character. The elongated cell, poor in protoplasm but with prolongations in all directions among the dense fibres in which it lies embedded, swells before division and retracts some of its processes. It becomes somewhat rounded and denser than the adjacent cells, and by division gives rise to two young cells which are temporarily rounded, but quickly put forth pseudopods and acquire an elongated form. A great variety of forms may be found, but the vascular nucleus and the elongated form generally suffice to distinguish these cells from the more rounded mononuclear wandering cells.

Occasionally, when newly formed connective tissue arises to constitute the lining of a cavity in the body or to form a bursa, the superficial cells which form the actual lining become flattened and assume the appearance of endothelium. This is exemplified in Fig. 85, which is from the granulation tissue lining an infected space left after an operation, among the muscles of a dog's neck. The cavity was filled with turbid fluid full of leucocytes. The new tissue is of the ordinary type, with distinct projecting granulations, but everywhere covering this nodular surface, and extending down into the crevices between them, there is a layer of cells resembling endothelium, although much stouter. These cells are often in two layers for a small space, and pass over by insensible gradations into the fibroblasts underneath. Evidently this is a mild kind of metaplasia analogous to that which occurs in the first formation of endothelium, but it is not to be believed that these cells ever play the part of real endothelial cells or are to be identified with them.

While at first these new cells lie loosely about so that the spaces between them accommodate fluid and wandering cells, they later produce in the marginal parts of their cytoplasm the fibrils which stain differently from the general protoplasm, and which, increasing in number and in thickness, become arranged in roughly parallel form, so as to produce a dense fabric in which the cells themselves finally become rather inconspicuous. This process, so carefully studied by Minervini, Maximow, and many others, constitutes the formation of scar tissue. The early stages are seen, however, to especial advantage in cultures of connective tissue in which the fibroblasts are seen to grow out separately from the margin, showing in the most beautiful way their long, streaming processes, and dividing actively by mitosis beneath the observing eye (Fig. 78).

Elastic Tissue.—The regeneration of elastic fibres is to be observed after the lapse of time in newly formed connective tissue, but perhaps especially in those places, as in the lung or in the vessel-wall, where those fibres play a particularly important part. There has been much discussion of the possibility that they may arise in the intercellular substance, but the work of Jores, Nakai, and others seems to show clearly that they are formed by differentiation of the protoplasmic processes of the cells. Though chemically and physically different, they are produced in much the same way as the collagenous fibres, and there is no way of distinguishing the mother-cells from each other. Nevertheless, although Jores thinks the collagenous and elastic-forming cells the same, it seems probable that, with finer methods, we may be able to show that they are differentiated from each other before they proceed to form their different fibres. Apparently the new fibres do not grow in connection with the old ones, but increase in size by accretion. Sometimes, however, as in the walls of blood-vessels, we may see very plainly that a new distribution of the lamellæ or fibres is brought about by the splitting and separation of the old ones.

Fat Tissue.—There is much evidence that the adipose tissue of the body is specialized at an early stage, and remains distinct from other forms of connective tissue. In the infant it is segregated in lobular masses in which, in the beginning, the large, round, isolated cells which are to become fat-cells have a deeply stained granular protoplasm, which later becomes filled with globules of fat until it is stretched out into a thin film and its nucleus pressed to one side. In wasting disease the fat may disappear from the cell and be replaced by fluid. In a sense regeneration occurs through the refilling of these cells with fat, but if the tissue is destroyed, it must probably be regenerated by the methods used in its first formation. In the neighborhood of old inflamed areas one may often distinguish, within the outline of an empty fat-cell, many polygonal or rounded cells with finely vacuolated protoplasm. These Marchand regards as evidences of regeneration or new formation of several fat-cells in place of one. Others (Maximow) have, however, thought of these cells as invading phagocytes which have taken up some remaining globules of fat.

Cartilage and Bone.—Defects in cartilage are in part healed by the

formation of fibrous tissue scars, but regeneration of actual cartilage also takes place. According to Marchand, this is brought about chiefly by the activity of the perichondrium, which produces a callus-like growth of new tissue which gradually assumes the characters of cartilage. Borst and certain Italian writers maintain, however, that the cartilage itself takes part in this new formation, a method which certainly prevails in such animals as the salamander; and that the defect is filled largely by the active division of its cells.

Bone is regenerated by methods identical with those concerned in its first formation. On account of its easily recognizable arrangement, it can be seen that rebuilding is in progress throughout life. By means of osteoclasts the well-preserved Haversian systems are irregularly eroded, and new Haversian systems fitted into the gaps thus left through the activity of the osteoblasts. The cells concerned in the regeneration

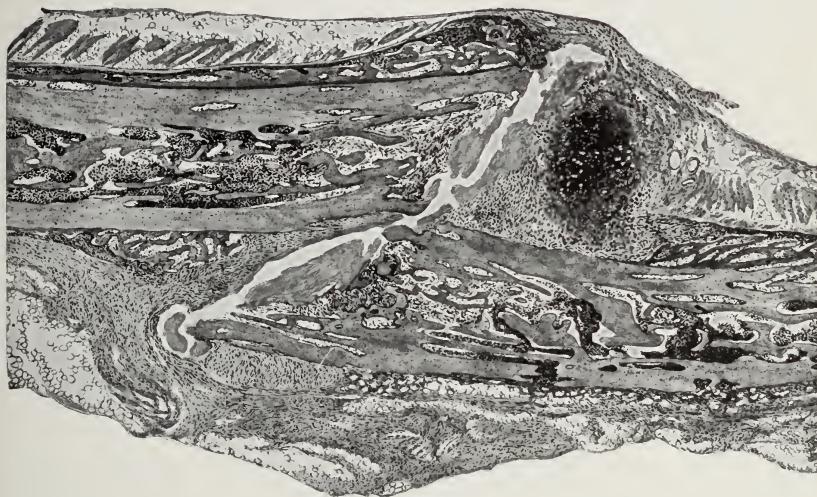


Fig. 86.—Early stage in the healing of fractured bone, showing periosteal new-bone formation, together with fibrous and cartilaginous growth.

and new formation of bone are always the osteoblasts, or at least cells which have assumed the function of osteoblasts. Therefore bone can be formed by the osteogenetic layer of the periosteum and by the endosteum, but probably not by the bone-corpuscles, which are buried in the rigid bone. If all the cortex of a bone be removed and the periosteum left intact, a new bone may be formed by the activities of that membrane—it can even be transplanted into some distant region of the body, where it will begin once more to produce bone, provided always that the nutrition be maintained and that the actual osteogenetic layer be not destroyed. Membranous bone is formed anew in the same way by the production of a mass or sheet of spindle-cells, some of which assume the characters of bone-corpuscles and give up part of their cell-body to the fibrillar substance, which first becomes hyaline and then calcified.

In fractures the broken ends of the bone are at first surrounded by a haemorrhage, but after the escape of blood from the bone-marrow is stopped by clotting, regeneration and healing begin through the proliferation of new tissue from the periosteum and endosteum. These produce a callus which flows in between the separated ends of the bone as the intermediary callus. It consists at first of cartilage and osteoid tissue, that is, tissue with homogeneous ground substance, inclosing the newly formed cells, and having the form of bone without being calcified. The osteoid tissue may be laid down as a solid layer on the surface of the old bone, or, through the guiding action of blood-vessels, assume a spongy form. Solid new formed tissue of this kind may be transformed later into spongy bone by the invasion of blood-vessels, and that in turn become compact by later growth. The cartilage which is formed by the activity of the periosteum is similarly invaded by osteoblast-carrying blood-vessels and converted into osteoid tissue, and finally into bone, exactly as in the intracartilaginous bone formation of the embryo. Great defects in the bone produced artificially or by disease may thus be made good, although for a time the new bone thus formed is very abnormal in its arrangement. Later modifications tend to reduce it with wonderful accuracy to the form best adapted to meet the strain put upon it.

Smooth Muscle.—Experimental and other study of the healing of defects in smooth muscle seems to show little activity in this regard—sometimes mitotic division has been described, sometimes a new formation by amitotic division, but more recent studies tend to the idea that there is in higher vertebrates very little regeneration of the muscle itself, but that healing brought about by scar tissue brings together the muscle edges at the site of the defect.

Striated Muscle.—Regeneration of striated muscle is complicated and difficult to follow. For a study, both anatomical and experimental, and a review of the literature, the student is referred to Forbus' paper. After destruction of the fibres, or their conversion into hyaline material (Fig. 46), phagocytic mononuclear cells invade and remove the débris, while new mononuclear muscle-cells, hardly to be distinguished from the clasmacytes, appear within the sarcolemma, if that is preserved, or form a bulbous mass at the end of the remnant of living muscle fiber. These new muscle-cells elongate, acquire sarcoplasm, and form new muscle fibres.

Heart muscle has been thought to regenerate itself little, if at all, any loss of substance being made good by a patch of scar tissue. Indeed, this seems to be generally the case, although Heller has recently described clear evidences of regenerative activity in the heart-muscle fibres, and we have seen one case in which a condition resembling closely the formation of the bulbous ends in the skeletal muscles appeared. The fibres could be traced in the scarred areas into deeply stained swollen masses of protoplasm, with numerous nuclei which seem to represent growing ends.

Blood- and Lymph-vessels.—In the early stages of embryonic growth blood-channels seem to be formed anywhere in the mesenchyme by the

mere separation of the cells, with later alteration of the innermost cells adjoining the cavity thus formed into definite flattened lining or endothelial cells, which, in turn, are supposed to produce any of the elements of the blood. Channels formed in this way are capable of obliteration by collapse and the adhesion of their walls, while other new channels are being formed. Thus it happens that in a network of such spaces there is finally emphasized one passage which, after the collapse of the rest, survives because it is best adapted to carry the blood according to the existing needs and pressure relations. Thus in early life the whole process is very labile, and the relation to the connective tissue extremely intimate. It is maintained by some that lymphatic channels are formed in the same way, becoming secondarily connected with the blood-vessels, but Sabin has shown that their genesis may be traced to an actual sprouting from certain points in the well-formed vessel-wall, of blind-ending canals which finally ramify in all directions in the tissue and constitute the lymphatic system. At any rate, there comes a period, somewhat later in embryonic life, at which the promiscuous formation of blood-vessels or lymphatics from spaces in the mesenchyme seems to be restricted, and thenceforth the endothelial cells become permanently specialized to carry out that function only and to give rise, by their division, to all subsequent endothelial cells. After this epoch new vessels are formed only by the formation of an endothelial bud from the wall of a vessel, which may grow out as a mobile strand of endothelial cells moving through the tissue until it meets another such strand. Exactly the same process is carried through in the case of the lymphatic channels, which are quite as completely walled off from the connective tissue by endothelial cells as are the blood-vessels.* When such strands of endothelial cells, which at first may be no more than whiplash-like protoplasmic filaments, become united with others so as to form a bridge and become thickened into a double row of cells by mitotic division, there gradually appears a cleft in the middle through which blood-corpuscles are forced. There has been much discussion as to the part played by connective-tissue cells in this process, but the evidence seems to be overwhelming in favor of the idea that when connective-tissue cells take any part they act merely as supporting cells, applying themselves to the outside of the new tube, of which the essential lining layer is composed of endothelial cells alone (Marchand). Coffin has traced carefully the formation of lymphatic vessels in newly forming granulation tissue, and has found that they appear in precisely the same way as the new blood-vessels.

Bone-marrow, Lymph-nodes, and Blood.—Bone-marrow regenerates itself rapidly after destruction through injury, disease, or poisoning, by the formation of a new connective tissue rich in vessels, in which there appear later fat-cells and the specific blood-forming cells. As to the source of these, some authors (Haasler, Enderlen, Marchand) have held to the idea that they are derived from the division of those which remained behind or are brought to the marrow cavity by the blood-stream

* MacCallum: "Relations Between Lymphatics and Connective Tissue," Johns Hopkins Hosp. Bull., 1903, xiv, 142.

or by wandering through the tissues. Others (Maximow, Weidenreich) regard them as derivatives of the young, undifferentiated connective tissue formed upon the invasion of blood-vessels with their periosteal cells into the cartilage. This seems well enough established in the case of embryonic marrow formation, but is more difficult to accept in the regeneration of marrow in the adult, although it is perhaps supported by the observation of the new formation of marrow in bone produced in such organs as the lung or aorta. Lymph-nodes and nodules of lymphoid tissue reappear, without doubt, in areas where they have been destroyed, but the mode of their regeneration is not very clearly understood. In the case of an autopsy assistant who had suffered repeated infections of the hands, after which infected lymph-nodes had been dissected from the axilla, new nodes appeared under the skin about the shoulder as well as in the axilla. Similarly, in the intestine, after destruction of Peyer's patches and solitary nodules, through ulceration in the course of typhoid fever, repair and new formation of these structures are in time very complete. Undoubtedly, as Ribbert points out, there are many scattered lymph-follicles in the tissues which become evident only when they are caused to swell by some inflammatory reaction, and it is possible that these, through their enlargement, compensate for the loss of the original lymph-nodes in places where the latter have been destroyed or removed. In the spleen, when the amyloid has occupied the whole of each Malpighian body, one may sometimes see, as in Fig. 49, the counterpart of this in the new formation of lymphoid nodules all through the splenic pulp. Bayer and others state that complete lymph-nodes may be newly developed in fat tissue, but it seems probable that this occurs rather in connection with preëxistent lymph-channels than with relation to the fat tissue itself.

The Blood.—Already much has been said about the regeneration of the cells of the blood. It is commonly held that the red corpuscles are formed, at least in the embryo, from modification of the endothelial cells lining blood-sinuses. In the adult the process is thought to be chiefly active in the bone-marrow where, in spaces spoken of as intersinusoidal capillaries, the nucleated forerunners of the red corpuscles appear and are finally set free into the venous channels. All the authors without further question accept their derivation from endothelial cells. Leucocytes of all characters are supposed to be formed in the same way by way of non-granular intermediary stages, the myeloblasts and the granular myelocytes (Doan, Peabody).

Leucocytosis.—Infections of all sorts cause regeneration of the greatest intensity in the blood-forming tissues, so as to furnish to the blood the necessary phagocytes. Polymorphonuclear leucocytes may be produced there with rapidity in a quantity far exceeding that ever called for in ordinary regeneration to make good a loss. It is not uncommon, then, to find the leucocytes chiefly of this type, numbering 50,000 or 60,000 per cubic millimetre, and cases are described in which this outrush, bringing with it the myelocytes, has so flooded the blood as to produce the picture of an acute myeloid leucæmia. Other infections, such as typhoid fever, through exerting another kind of chemiotactic action,

attract to the blood chiefly the mononuclear cells. It is even difficult to produce a polymorphonuclear leucocytosis in those cases. Similarly in tuberculosis, syphilis, and many other infectious processes, most of which progress slowly, and in malaria and other protozoan infections, the stimulus produced by the infective agent calls forth the production not of polymorphonuclear leucocytes, but of mononuclear forms.

Thus there is a certain independence among the cell types in their regeneration. Red corpuscles are produced in great numbers when those normally present have been destroyed, and generally there is a considerable coincident outpouring of leucocytes, but this too is dependent upon the nature of the destructive agent and not merely upon the fact that regenerative activity is going on in the bone-marrow.

When blood is suddenly removed, as by an extensive haemorrhage, regeneration begins in the bone-marrow (often very slowly after an extreme haemorrhage), and the red-corpuscle content of the circulating blood is gradually restored to normal. Naturally, immediately after the haemorrhage the number of red corpuscles in the circulating blood per cubic millimetre is unchanged; then there comes quickly an absorption of fluid from the tissues and from the digestive tract to make up the necessary volume of blood, and with this dilution the red-corpuscle content per cubic millimetre rapidly sinks. It is not until after the third or fourth day that the regenerative process begins to overtake this diluting process, so that from that time on the red-corpuscle content steadily rises. It may be observed that this new formation proceeds rather spasmodically, as indicated by the periodic "crises" of normoblasts which are swept out in the circulation. In the bone-marrow during this process evidences of most active growth of these cells can be found, and although they are present in such great numbers, it can often be seen that they are arranged roughly in groups or islands among the granular and other cells.

Chronic anaemias which follow long-continued infection or intoxication, or repeated small losses of blood, as from bleeding haemorrhoids, cause the same regenerative processes. The marrow of the long bones, normally yellow and composed chiefly of fat, becomes dark red, solid, and granular, and is found to be made up of compactly crowded formative cells and their products. In many cases, of course, the benefit from this regeneration is as promptly frustrated by the continued destruction or loss of the cells as they appear in the circulation. There are a few cases in which, in spite of extreme anaemia, no sign of regenerative processes begins in the bone-marrow ("aplastic anaemia"), and others in which it is prevented by the extensive destruction of that tissue by tumor growths or otherwise. The extreme anaemia produced by benzol poisoning seems to depend largely upon its coincident destructive effect upon the bone-marrow and blood.

Nervous Tissue.—If a peripheral nerve be cut, the proximal portion remains alive, except for the last two or three Ranvier's segments, but the whole peripheral portion degenerates. The myeline sheath loses its homogeneous character and breaks up into globules which now stain with fat stains. The axis-cylinder becomes granular and disintegrated.

The cells of the sheath of Schwann or neurilemma increase greatly in size and number, and become actively phagocytic, engulfing and removing the débris of the myeline sheath and axis-cylinder.

Up to this time the degenerating fibres show the presence of black-stained globules in the position of the myeline sheath by the method of Marchi, but after the phagocytic activity of the cells of the neurilemma is completed, nothing is left of the medullary sheath, and such degenerated and emptied fibres can now be made out best by their lack of staining, in contrast to the neighboring well-preserved medullary sheaths, which become blue black with Weigert's medullary sheath stain. The proliferated cells of the sheath of Schwann now become arranged closely together in long tubular strands—the so-called "band fibres." At this point arises the difference of opinion upon which there has been strife for many years. v. Büngner, Bethe, and others maintain that, inside these band fibres, there are formed new axis-cylinder fibres without any connection with the ganglion-cell, and quite independent of the proximal portion of the fibre from which they were originally separated. The weight of evidence, however, is overwhelmingly on the side of those (Waller, Ranzier, Howell, His, Ramón y Cajal, Perroncito, Stroebe, Harrison, and others) who have shown that new fibres appear growing along in these tubular band fibres, but only as sprouts from the axis-cylinders, which are still in the proximal part of the healing nerve and still in connection with the ganglion-cell. It is shown that the ends of these axones in the tip of the proximal stump become bulbous or branched, or peculiarly altered into a basket-like arrangement, and that when the peripheral portion is brought into apposition with this stump, filaments penetrate into the guiding canals furnished by the Schwann's sheath tube, and grow down them until they reach the end-organs and reëstablish connections there. If there is a large gap between the two ends of the nerve, the accomplishing of this process is delayed. It is hastened, on the other hand, by the accurate suture of the cut ends to one another. The band fibres thus form merely a guide for the newly sprouting axone, and in no case give rise to new axone material themselves. All this is particularly well shown by Harrison's experiments, in which he showed that axones could grow out to a great length if offered merely a suitable moist medium upon which to grow, and were not entirely dependent upon the facilitating and guiding influence of the band fibre. Functional capacity of such nerves is restored in a remarkably short time, and seems to depend largely upon the character of the nerve-endings and not upon the precise rediscovery by the axones of their proper band fibres. Indeed, a nerve accustomed to convey one set of impulses may be artificially united to a peripheral stump which had been used to act as the mechanism for a quite different sort of activities, but the old impulses will now produce the new function characteristic of the new nerve terminations. Such a person has to learn to interpret and control his impulses—in other words, learn again to do the right thing at will.

In the central nervous system a similar type of regenerative process is attempted, but seldom carried far, because no proper paths seem to be

prepared for the guidance of new fibres. At the scarred edges of wounds or defects, either in the brain or in the spinal cord, the same bulbous or branching ends of fibres are to be found, but there is little evidence of their crossing the scar and reestablishing the original connections. There is also little positive evidence of regeneration on the part of ganglion-cells—mitoses are sometimes seen, but at best it is only an attempt at new formation. Healing of a defect in the brain takes place partly by scar-tissue formation and partly later by the production of a rather broad zone of sclerotic neuroglia. The cleansing of the area is carried out by the so-called granule cells, large, rounded, mobile cells filled with globules of fat which accumulate in great numbers in areas where destruction of nervous tissue has occurred (Fig. 17). These cells, which are especially abundant in areas of softening, infarcts, etc., in the brain, resemble the mononuclear phagocytic wandering cells very closely, and are regarded as such by Borst and others. Although this view seems perfectly plausible, it is contended by others, including Fr. Marchand, Morzbacher, and Tanaka, that they are really wandering cells of neuroglial origin.

LITERATURE

- Coffin: Johns Hopkins Hosp. Bull., 1906, xvii, 277.
Doan, Cunningham, and Sabin: Carnegie Institution Publication 361, 1925, xvi, 163.
Forbus: Regeneration of Muscles, Arch. Pathol., 1926, ii, 318, 486.
Goldzieher and Makai: Ergebni. d. allg. Path., 1912, xvii, 344.
Jores: Ziegler's Beitr., 1900, xxvii, 381; 1907, xli, 167. (Elastic Tissue.)
Marchand: Process der Wundheilung, 1901.
Maximow: Ziegler's Beitr., xxxv; Suppl. v; xxxiv; xxxviii. (Suppuration.)
Minervini: Virchow's Arch., 1904, clxxv, 238. (Scars.)
Nakai: Virchow's Arch., 1905, clxxxii, 158. (Elastic Tissue.)
Peabody: Hyperplasia of Bone-marrow. Amer. Jour. Pathol., 1926, ii, 487.

CHAPTER XIII

DEFENCES OF THE BODY (Continued)

Transplantation of tissues and organs, its limitations. Healing of wounds—by direct union, under a crust, by granulation tissue, etc. The healing of an open ulcer, of inflamed wounds and abscesses. The healing of special tissues.

TRANSPLANTATION OF TISSUES AND ORGANS

THE result of attempts to transplant tissues or whole organs from one animal to another, or from one portion to another in the same animal, is a matter of great surgical interest, and also of importance in contributing to our knowledge of the growth of tissue and the function of the organs themselves thus transplanted. It is treated in detail by Marchand, Borst, Stich, Makai, and many others, to whose papers the reader is referred.

To graft tissue or a whole organ into a new situation is a matter of technical difficulty, but success depends not only upon the skill with which the operation is carried out, but also upon the nature and age of the animal, nature of the tissue, the intimacy of relationship of the new host, the efficiency of the blood-supply (often the restitution of the nerve-supply), and, finally, in many cases, the functional need for such tissue.

It seems possible to carry out successfully far more extensive transplantations in the lower animals, such as worms and coelenterates, than in higher forms. Probably this is because of their greater adaptability, and is quite like their great power of regenerating tissue and organs. At any rate, one may easily transplant half the body of one of these creatures by a sort of grafting on to half the body of another. But this can be done in embryos of much higher animals also, with the production of remarkable monsters. Complex organs, like the eye, may be implanted in unusual situations with a certain success which could not be attained in adults.

The success with which tissues can be transplanted is, to some extent, parallel with their degree of specialization and their need of constant and abundant blood-supply. Little difficulty is experienced in transplanting epidermis from one situation to another, or even from one individual to another. The so-called Thiersch grafts, which are thin films of epidermis, sometimes including the upper layer of the corium, are used daily in surgical operating-rooms to cover large denuded areas, and there is seldom any question about their success. So, too, bone with its periosteum may be made to fill a gap in another bone. With more highly specialized tissues transplantation is more difficult, probably because their cells will not survive long enough to allow capillary blood-vessels to grow in from the new site.

Nevertheless, pieces of thyroid, parathyroid, adrenal, etc., have been implanted in a cavity made in one tissue or another, and have grown

and functioned generally only after necrosis of the central part, with survival and increase of the marginal layers. It is important to observe that in some cases, as in the transplantation of bone or nerves, the graft may survive only as a sort of splint which supports and guides the new growth of tissue from the host, which finally absorbs and replaces it entirely. This is always true with nerves whose specialized structures invariably degenerate, but not always with bone, which may remain active and itself permanently occupy the new site.

Transplantation of whole organs by anastomosis of the blood-vessels has been carried out in a number of cases, notably by Carrel, and often with successful functioning of the transplanted organ. Thus in one animal the transplanted kidney was able, after the removal of the other, to maintain the life of the animal for a long time.

The reimplantation of an organ or tissue into the same animal is an *autoplastie* operation—its transfer to another animal of the same species is a *homoplastie* operation, while a *heteroplastie* transplantation involves its growth in an animal of another species. Transplantation of whole organs has succeeded so far only in autoplastie operations, although homoplastie transplantations of extremities or peripheral tissues have been successful. Heteroplastie transplantations have been uniformly failures. It is, therefore, necessary to have the most favorable possible conditions for the renewed growth of the more sensitive tissues, although those less dependent upon an uninterrupted blood supply may sometimes be transferred to other animals of the same species with success. Evidently the foreign biological character of the blood of another species makes life impossible for the graft and even in individuals of the same species the recognition of several blood types by various authors has explained the incompatibility of their blood and the serious results of the transfusion of blood which does not match that of the recipient. On this basis one could hardly expect a tissue graft to survive in a person whose blood and tissue fluids belonged to a different group. Stone and his coworkers, recognizing this, have cultivated tissue from the donor *in vitro*, gradually exposing it to the plasma of the person in whose body it is to be implanted so that when this operation is carried out, the tissue is already acclimated, as it were, to the new conditions and is found to grow successfully. Mechanical conditions, too, are important in the success of a transplant, and a piece of skin transplanted into the peritoneum or between the muscles is sure to act merely as a foreign body and be encapsulated.

In the case of some organs, such as the salivary glands, in which we know so well the important influence of the nerve-supply we must expect function to be greatly disturbed by transplantation, although others in which the function is governed rather by the chemical composition of the blood, as perhaps in the case of the kidney, may possibly be transplanted with more hope of the continuance of a function approaching the normal. The organs of internal secretion, in so far as they can be transplanted at all, seem to fall into this latter group.

Finally, it has seemed, especially from some experiments of Dr. Halsted, that successful implantation and growth of such organs as the

parathyroid depend upon a need for their functional activity. In animals with a normal amount of parathyroid substance he found it impossible to make an extra gland grow, while he succeeded in one already deprived of most of its parathyroid tissue. This seems a plausible suggestion, and has been supported by others, but as yet it is hardly possible to set it down as a general law.

LITERATURE

- Borst: Proceedings XVII Internat. Congress, London, 1913, Sec. 3, pt. 1, 171.
Halsted: Jour. Exp. Med., 1912, xv, 205.
Makai: Ergebni. d. allg. Path., 1912, xvi, 344.
Marchand: Process der Wundheilung, 1901.
Stich: Ergebn. Chir. u. Orthopädie, 1910, 1.
Stone, Owings and Gey: Ann. Surg., 1934, c, 613; Surg., Gynec., and Obstet., 1935, lx, 390.

HEALING OF WOUNDS

While the principles remain exactly the same, the details in the healing or making good of any destructive injury to the tissues vary with circumstances, and it forms a great part of the skill of the surgeon to be able to leave the tissues upon which he has operated in the most favorable possible condition for repair. Neglect of these precautions, which concern chiefly the mechanical adjustment of the tissues which should grow together, their proper nutrition, and the exclusion of infection, will readily defeat his object, no matter how ingeniously he has planned to cure his patient. As in the early days of surgery, the wound will in a short time break open and discharge a flow of pus and fragments of dead tissue, blood-vessels may burst their ligatures, and the secondary haemorrhage, dreaded of old, will follow. All this depends upon the malnutrition of tissue from crushing or cutting off the blood supply, and the infection which can thrive in such dying or dead tissue or in the material accumulating about it. But if the tissues be carefully brought together by light pressure, or by sutures so arranged as to leave them all very richly supplied with blood in rapid circulation, the few bacteria which may gain access to every wound, no matter how carefully made, are easily overcome by the living tissues, and healing proceeds apace.

Healing by Direct Union.—It is in wounds treated with this careful attention to the condition of the tissues, or in wounds so superficial and limited that apposition and good nutrition of the tissues are secure of themselves, that healing occurs with the slightest reaction and with the least requirement for new formation of cells.

If a clean incision be made through the abdominal wall and the tissues approximated edge to edge by sutures throughout, they become glued together almost at once, and in a short time heal together, with an almost imperceptible linear scar, with never any very evident inflammatory reaction and no sign of actual suppuration. In such an incision only the cells along the line of incision are killed,—some bleeding occurs, and between the approximated edges a little blood remains,—or if the escape from the blood-vessels has been stopped, at least a little coagu-

lable fluid oozes out between these edges. This clots about the severed cells, and cements the surfaces together. A few leucocytes appear from the slightly widened adjacent vessels. Mitoses arise in nearby epithelial cells of the epidermis, and in the connective-tissue cells close to the wound. Blood-vessels sprout from those on either side, and accompanied by fibroblasts grow across, absorbing and removing the fibrin and the dead cells which the leucocytes help to liquefy, and replacing this material by a more permanent bond. Later this new connective tissue

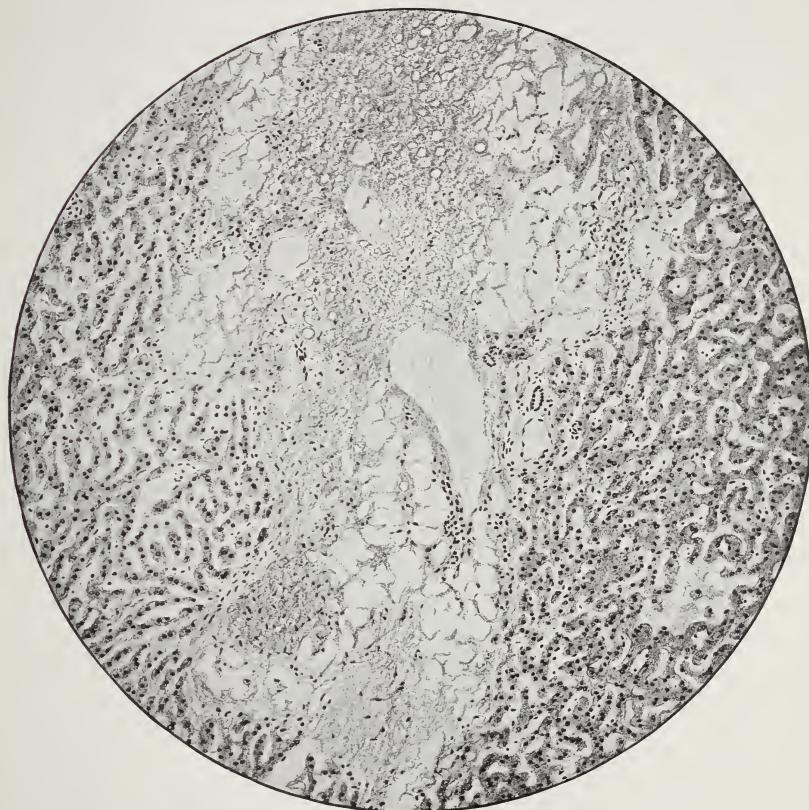


Fig. 87.—Fresh stab wound of the liver. A few cells have been killed and the edges glued together by the clot.

matures into a scar. Epithelium has by this time been pushed across to cover the outer surface and the peritoneal lining cells to close the interior, and the wound is healed. This is healing by first intention (Fig. 88).

Healing Under a Blood-clot or Crust.—In many cases, when apposition has not been so exact or when more tissue has been destroyed, a good deal of blood and serous fluid oozes out on the surface, clots, and dries, or the cavity of a wound whose edges are not brought together may fill up with blood which clots and remains. So good is such a clot

as protection against infection that, at times, surgeons have intentionally allowed large spaces to fill up in this way (Schede, Halsted), and have carefully preserved the clot as a covering. Not only is it a protective substance, which, on account of its bactericidal power, does not decompose or become further infected, but it forms a nutritive material, and at the same time a scaffolding for the up-growth of blood-vessels and fibrous tissue.



Fig. 88.—Scar of healed surgical incision through the abdominal wall.

When there is only a little blood or inflammatory or serous exudate which dries on the surface of the wound, healing proceeds under the protective crust thus formed, and is found complete when it drops off. Quite the same process goes in if the crust is formed by the necrosis and drying up of the superficial tissue. The epithelium works its way

beneath this dried mass and quickly grows over the surface of the underlying living tissue, even if it has not been covered by any thick,

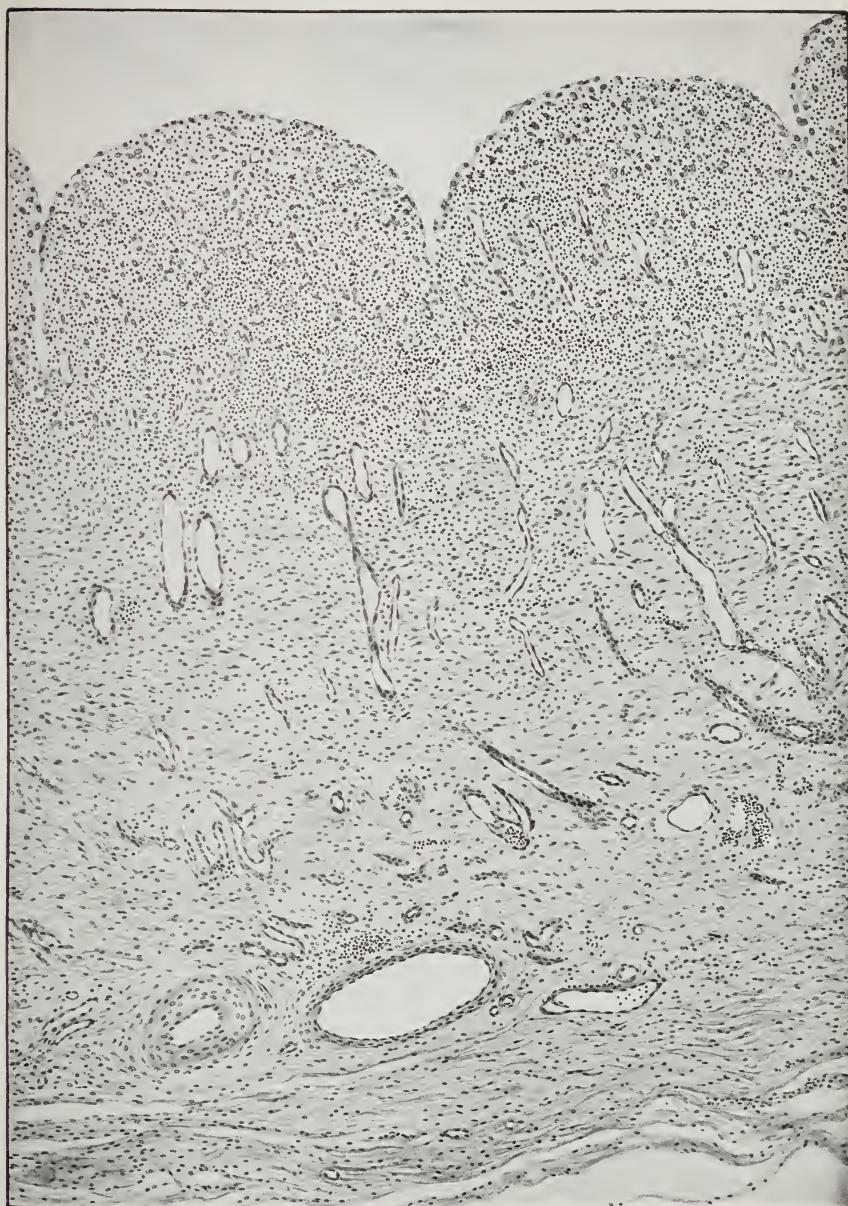


Fig. 89.—Granulation tissue lining a space left between the muscles in a dog's neck.

new-formed granulations. This is the peculiarly favorable feature of healing under a crust, with such perfect protection, the new epi-

dermal covering is completed without the previous slow and tedious formation of granulation tissue. It is true that later much new tissue of that sort is produced beneath, but at least it is closed in from the air and goes on unnoticed, the process being essentially finished and secured when the epidermal covering is complete.

Granulation Tissue—Secondary Healing.—When a wound is infected with bacteria, it is not apt to heal throughout any great part of its ex-



Fig. 90.—Granulation tissue with giant-cells developed around a foreign material (paraffin) injected into the tissues.

tent. Instead, it breaks open and discharges a purulent exudate, and heals finally by "secondary intention," in a way rather different from those just described. It builds up from the bottom a new connective-tissue layer which, beginning by covering and masking all the exposed structures with a thin gray film, heaps itself up in an ever thicker nodular, translucent, grayish-red substance, until the whole space may be filled or even until the granulation tissue projects in soft, fungus-like masses above the level of the skin. This sort of reparatory growth

is by no means limited to infected wounds—it is the regular method of filling up and repairing any and every gap in the tissue. It is inconspicuous and limited in the two sorts of healing already described, because in the one case very little of it is needed before healing is complete, and in the other because the epidermal covering is so soon finished that connective-tissue growth is held in check and covered from view.

If an open wound or ulcer be kept clean and moist and therefore unable to cover itself by a crust, it must heal slowly from the bottom. In the same way a space among the tissues kept open by the presence of bacteria and an accumulation of fluid will close itself gradually by the formation of a complete wall of new young connective tissue, which is gradually drawn together by the absorption of the fluid (Fig. 89). Any foreign body embedded in the tissues stirs up the same response. About it on every side, as though it were a space to be filled, there develops a wall of new tissue (Fig. 90). A portion of tissue itself, killed by any means, becomes a foreign body, and is treated in the same way—hence an abscess with its mass of bacteria and surrounding dead tissue is in time encapsulated. Any group of cells in an organ, such as the liver or kidney, on being killed and absorbed leaves a gap which is filled up by a new-formed connective tissue not limited exactly to their site, but extending a little into the neighborhood.

Other examples of this same tendency are seen when it is not dead tissue, but fibrin, that acts as the foreign body, and the replacement of a fibrinous exudate on a serous surface (Fig. 91), or of a thrombus in a blood-vessel by the growth of granulation tissue (Fig. 92), is perfectly well known.

In all cases the mechanism is the same. It is the standard method of healing adapted to deal with the most varied types of injury, but always proceeding on the same principles toward the patching of the injured area. The degree to which inflammation is mixed with it depends upon the sort of injury, and the nature of the wandering cells found in the new tissue depends upon the sort of injurious material and débris that must be treated and removed. The healing of an open ulcer may serve as one example.

Even if such a loss of substance is produced by actually cutting out a piece of tissue, bleeding soon stops, and the cut surface is found moistened by a thin layer of fibrinous exudate. Within an hour, although the surface becomes reddened by the widening of the capillaries, it is found, on injecting the blood-vessels, that none of the colored mass oozes out on the cut surface. The cut ends of the vessels are closed by the fibrinous exudate, and by contraction, many are definitely thrombosed. The exposed surface contracts somewhat, the skin edges tend to turn inward, and, as healing progresses, this contraction plays a considerable part in forwarding the closure of the wound.

The reparatory process begins first, in all probability, by the amœboid stretching out of the adjacent connective-tissue cells, and even of the epithelial cells at the skin edge. This is readily observed in tissues grown *in vitro*, and it seems probable that it occurs here too, since the mitotic figures which indicate the new formation of cells are found

some distance back from the actual margin of the wound. Connective-tissue cells reaching out their pseudopods from among the intercellular fibres find guidance in the filaments of fibrin. Through their multiplica-

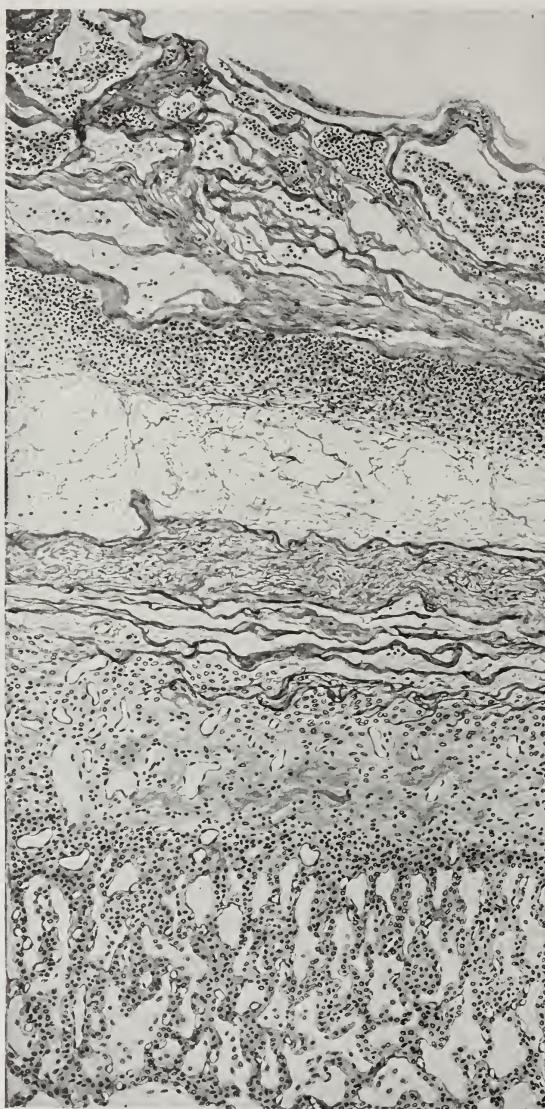


Fig. 91.—Organization of a fibrinopurulent exudate on the pleural surface by new blood-vessels and connective tissue from the pleura.

tion and that of the endothelial cells of the blood-vessels a recognizable amount of new tissue is formed in the course of a day or two. At the same time an acute inflammatory process arises, with all the features

described above: The vessels widen and pour out their fluid and cellular contents; the tissue becomes oedematous and infiltrated with leucocytes and scattered red corpuscles—on the surface, more exudate of leucocytes and fluid is poured out, and the network of fibrin becomes thicker; mononuclear wandering cells appear in numbers from the blood-vessels and from their resting places in adjacent tissues; sprouts of endothelial cells spring up from the intact capillaries and stretch forward into the

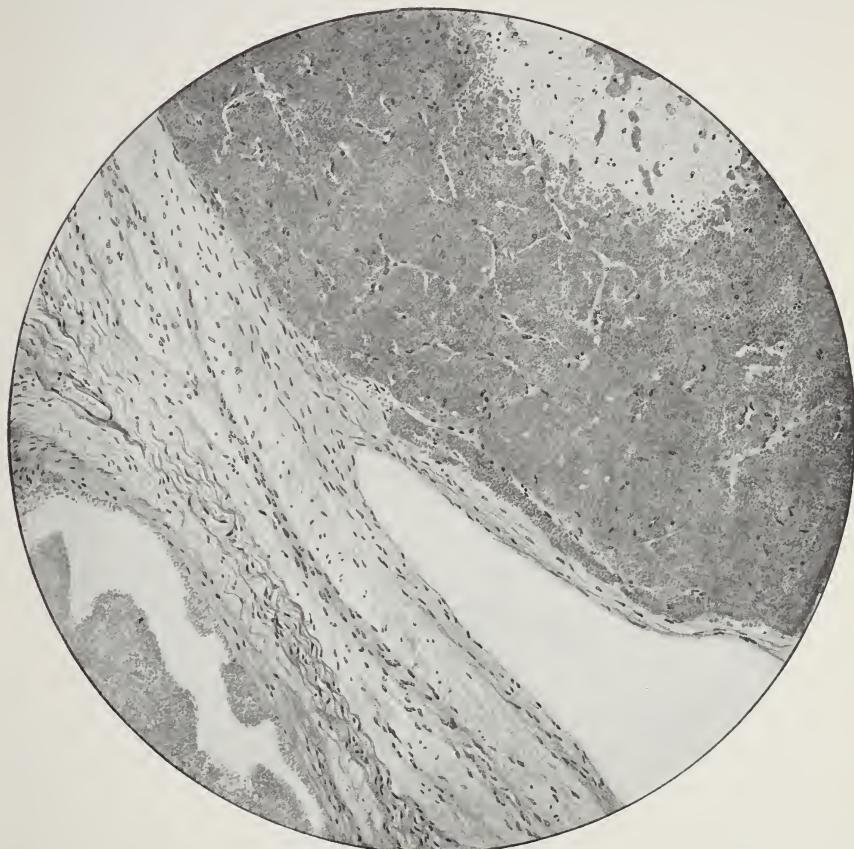


Fig. 92.—Thrombus formed behind a valve in a vein, being invaded by blood-vessels and fibroblasts.

fibrin, making way for themselves by their mobility and digestive power. These, as Lewis has shown, spread open into tubes quite independently of the pressure of the blood, and growing up in this way they anastomose and form arches supported and surrounded by the fibroblasts which accompany them. It seems probable that it is this arching forward of the vessels which produces the granular appearance of the surface of the new tissue (Fig. 93) (W. H. Lewis, J. H. Hospital Bulletin, 1931, xlvi, 242). Thus an actual new tissue is formed, and

continues to be formed with the greatest rapidity. It consists, as is evident, of abundant blood-vessels and young fresh connective-tissue cells, all spread apart by fluid, a large portion of which is an inflammatory exudate. Therefore it is easy to understand that this tissue should appear as it does. It is a soft gray or grayish-red, gelatinous, translucent layer of irregular nodular surface, bleeding at a touch, but quite insensitive to pain. When it is found, as it often is, in surroundings abundantly infected with bacteria, the inflammatory reaction becomes



Fig. 93.—Granulation tissue formed in the healing of an ulcer.

more intense, and the purulent secretion oozes out of the surface (Fig. 94).

Granulation tissue is subject to the same circulatory and other disturbances that affect other tissue—it may be congested with venous blood or become very edematous in patients whose circulation is embarrassed. Checked in its growth by some injury, that which remains becomes compact and forms the basis for the growth of a new layer. It may, therefore, present very different appearances in different cases, although in its essentials it is the same in all.

Having grown to such an extent that it fills or nearly fills the gap,

one becomes aware of the fact that a thin, grayish-blue film of epithelium is spreading out from the edges toward the centre of the wound, to cover the granulations, much as ice in its first formation spreads out from the edges of a pond. One can also plant a fragment of epithelium in the form of an island in the middle of the surface of the granulation tissue, and if successful, the spread of new epidermis will take place from there in just the same way, meeting that from the margin and completing the covering of the granulations (Fig. 83). Bluish at first, the new epidermis gradually becomes thicker, more opaque, and white.



Fig. 94.—Granulation tissue showing acute inflammation.

Naturally this process occurs most readily when the granulations are clean and oozing only a little serous fluid—it is often frustrated by infection and the consequent inflammatory process.

The influence of different diets upon the rate of healing has been studied by Clark and has already been mentioned. Other studies upon the rate of healing have shown that it may be expressed by a formula in which the original size of the wound and the age of the animal must be taken into account (*du Nouy*).

Finished in this way, the site of the original wound is occupied by a highly vascular, purplish looking tissue, hidden under a smooth, pearly

layer of epithelium, which has none of the lines and markings of the normal skin—no hairs, no sweat- or sebaceous glands, and no nerves. From this time on a process of maturing of this tissue begins, which as has been said, tends to mould it into the form of that which was lost. Much new connective tissue is formed. The new cells produce abundant new intercellular fibrillar substance. Many of the too abundant blood-vessels are pressed shut and disappear. Since the venous side is first compressed, the new scar retains for a time its congested appearance. The purplish healed area grows paler and firmer until, in the end, it becomes very white, hard, and tendon-like, and that dense connective tissue which is the final product of the growth of the granulation tissue

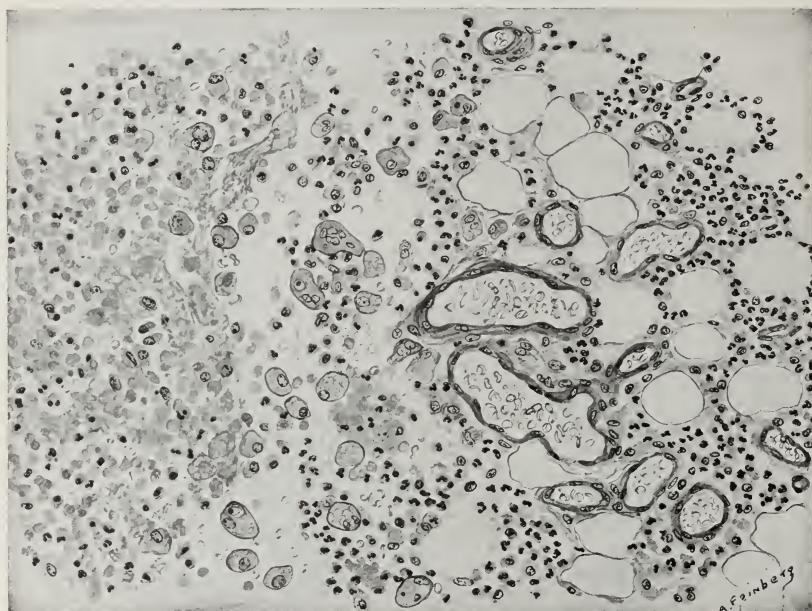


Fig. 95.—Margin of abscess in fat tissue with large phagocytic cells containing cell débris.

we know as a scar. In the first healing of the wound and in the course of formation of the granulation tissue a good deal of contraction occurs, and if it is an extensive superficial wound, such as might be caused by a burn of the skin, this contraction is apt to deform the person. After the scar is definitely formed, it tends rather to stretch out again (Minervini) or relax, and this extension is accompanied by a development in which nerves grow in, so that the place again becomes sensitive, and new cutaneous papillæ arise. The fine lines or wrinkles reappear when the scar becomes flexible, and on the palms or soles the characteristic fine corrugations develop in time and again cross the scar by which they were interrupted. Almost every one may test the truth of this in his own hands.

Abscesses.—In an abscess which has existed for some time we are accustomed to find the dead tissue separated from the living by a wall of this same granulation tissue. It forms all around in just the same way, but it is peculiar in the extraordinary number of wandering cells that haunt the meshes of its connective-tissue network. Inflammation still proceeding actively insures this, and such a wall, from this character, has often been called a pyogenic or pus-producing membrane. There is nothing peculiar about it though, and the point of greatest interest is the extraordinary array of very large, highly phagocytic, mononuclear wandering cells which crowd into this marginal tissue and aid in the cleaning-up process. They are probably free wandering cells, although some writers think them derivatives of the fibroblasts, and others, of the endothelium. As shown in Fig. 95, they are often loaded with fat and the débris of other cells. (See Chapter XIV concerning the formation of abscesses.)

Sinuses.—Sometimes such an abscess may break through the skin and discharge its contents, or if deep seated, it may burrow a long way and finally burst through the skin. A long channel or sinus results, and all along its course a lining or wall of granulation tissue is formed. As long as the infection persists in the original site this sinus may stay open and will discharge the products of inflammation. This is especially likely to be true if dead tissue, such as a fragment of necrotic bone or a foreign body, remains in the depths. Such a process is common with deep tuberculous lesions, with actinomycosis, and with various other chronic and tenacious infections, and sometimes the granulation tissue itself gives us a clue as to the nature of the infection.

Psoas Abscess.—A good example is seen in the tuberculous destruction of the centrum of one or more vertebrae, which reduces the bony substance to a soft, creamy, or mortar-like fluid. Inclosed as it is, this fluid seeks a way of escape and burrows into the psoas muscle and down along its course, to appear as a bulging sac at the femoral ring. Bursting out there, a sinus is established which leads from the inner side of the thigh far up to the mid-dorsal region. It is only its great extent which makes this example peculiar though, for with tuberculous disease of the hip-joint or tuberculous osteomyelitis at any point, the same thing may occur. The granulation tissue lining the sinus is quite like any other, except in that it is particularly rich in mononuclear wandering cells and contains tubercles and tubercle bacilli. It is, therefore, a precarious material for healing, since it itself is very prone to become completely necrotic, leaving only a basal part alive. On this remnant new granulation tissue forms. It is for this reason that there is built up about tuberculous lesions such a great amount of scar tissue, and this is true for actinomycosis and other infections of like character and for syphilis.

Fistulæ or channels leading into openings in hollow organs are lined in the same way by granulation tissue, which is often partly covered by epithelium, which grows inward from the skin or outward from the mucosa. Closure of these channels takes place partly by their gradual contraction, partly by their being choked with the ever-thickening lining of granulation tissue which finally fuses together to obliterate the lumen.

HEALING OF SPECIAL TISSUES

The healing of special tissues need not detain us beyond the description of one or two illustrative cases, since they are merely examples of the regenerative process already described.

Serosæ.—The flat lining cells of the serous cavities are peculiarly active in their growth, and cover with amazing rapidity any defect in their continuity. When, for example, a loop of intestine is brought through the abdominal wall and sutured there, its surface, where it passes, is glued to the parietal peritoneum by fibrin after the briefest interval, and in a very short time the serosa cells become continuous from the abdominal wall back over the intestine.

In peritoneal infections and inflammations these cells are much injured. When a fibrinous exudate is poured out upon their surfaces, burying them in its depths, they finally disappear, unless, as sometimes happens, the exudate arches up over a group of them—then they grow round to line this latter space and form a sort of cyst in which they preserve their characters. Many such little cysts may arise in this way, and are common enough in the pericardium; between them granulation tissue springs up into the exudate and, uniting with that from the opposite layer, finally composes itself into a fibrous adhesion or synechia (Fig. 96).

Exactly the same sort of thing is seen in *blood-vessels* in which thrombi have formed—if there is a point in the wall upon which the thrombus has not been laid down, the endothelium persists, and through multiplication of its cells, relines the little cavity thus left, while granulation tissue grows in and replaces the thrombus from the exposed tissues between these cavities (*cf.* Fig. 97). *Mucosæ* heal in exactly the way described for the skin, although the healing seems to take place more rapidly. Regeneration of the special features of the mucosa, including lymph-nodules, villi, etc., occurs in time, so that the scar may hardly be found.

Wounds and Injuries of Parenchymatous Organs.—Wounds in such organs as the liver heal with the formation of a scar, exactly like wounds in any other tissue. More interesting is the healing of the minute, but widely diffused foci of destruction of cells which are so common in the course of intoxications and infections. Different cells are picked out for destruction by different injurious agents, and it is very hard to tell why. Chromic salts kill one set of renal epithelial cells, uranium salts another; the poison of eclampsia destroys the cells of the liver lobule nearest the portal veins; that from the streptococcus peritonitis produces a midzonal necrosis (Opie), while the circulatory disturbance in chronic passive congestion destroys the cells about the efferent vein. The healing processes which follow each of these lesions are practically identical, but are modified by the differences of their situation.

They proceed by the gathering of phagocytic cells which dissolve or carry away the dead bodies of the specific cells of the organ, whereupon the connective-tissue framework in which they had been supported collapses. As in other places where tissue has been destroyed, a healing

or patching process ensues which consists in a new formation of connective tissue and blood-vessels—a granulation tissue bounded on all sides by the uninjured organ substance, so that it cannot show any free nodular surface, but otherwise is quite like that which fills up a healing ulcer. In the course of time such tissue settles into a scar. When organ



Fig. 96.—Chronic adhesive pericarditis showing small spaces in the connective tissue which represent the remains of the pericardial cavity.

cells are destroyed in small groups or singly, there may be a very fine diffusion of this scar tissue, and we have the condition known as cirrhosis in the case of the liver, and often loosely spoken of as chronic interstitial nephritis, pancreatitis, or hepatitis, as the case may be. That this latter term is practically always misleading may be shown,

however, by a study of the development of the lesion. The diffuse scarring and shrinkage of the organ is not due to an inflammation of the interstitial connective tissue, with the development of scars which contract and constrict the epithelial cells between them. On the contrary,



Fig. 97.—Organized thrombus in a blood-vessel canalized by clefts which are relined with endothelium.

the highly specialized epithelial cells are the first to suffer destruction by the poisonous substance which is the primary cause of the disease, and the scar formation is essentially a reparatory response to their disappearance. There is practically no evidence that the scar tissue

causes any further injury to the epithelial cells. Of course, it is true that the scar tissue may seem to be in great excess of what was necessary to repair or patch the gap produced by the loss of epithelial cells, but it must be remembered that in such cases the process of epithelial destruction and patching with connective tissue has been repeated frequently through years, each new scar heaping itself upon the old one near by. The constant regeneration of epithelium from remnants makes this possible, but there is also the possibility that the new connective tissue itself may be injured and later repaired in voluminous fashion.

LITERATURE

- Berry: Regeneration of Smooth Muscle, *Jour. Med. Res.*, 1920, xli, 365.
Clark, A. H.: Johns Hopkins Hosp. Bull., 1919, xxx, 117.
Davis, J. Staige: Plastic Surgery, Phila., 1919. See also the many papers of L. Loeb on Transplantation and Regeneration, *Jour. Med. Res.*, 1920, xli, 247, etc.
du Noüy: *Jour. Exp. Med.*, 1916, xxiv, 451, 461; 1917, xxv, 721; 1919, xxix, 329.
Schlaepfer: Skin Grafting, Johns Hopkins Hosp. Bull., 1923, xxxiv, 114.

CHAPTER XIV

ILLUSTRATIVE EXAMPLES OF INFLAMMATORY PROCESSES

Catarrhal inflammation. Serofibrinous and fibrinopurulent pericarditis, pleuritis, peritonitis, appendicitis, endocarditis, lobular pneumonia, puerperal infection, pyæmia, abscess formation, diphtheritic inflammation.

THE form assumed by the inflammatory reaction varies somewhat with the intensity and concentration of the irritant, and with the kind of tissue involved, but in principle it is the same throughout. Names are rather loosely applied to these different forms which indicate in some degree their anatomical characters. Thus a catarrhal inflammation is an affection of a mucous surface in which the irritant is not intense enough in its action to kill the epithelial cells. The same irritant applied to the peritoneal or pleural surfaces might produce an exudation of fluid with few leucocytes only. A somewhat more intense injury in these serous cavities or in the alveoli of the lungs may occasion the exudation of a layer of fibrin on the surface—a *croupous* inflammation. If the irritant is such as to cause the necrosis of the epithelium and the underlying tissue, with an extremely intense, often haemorrhagic, inflammatory reaction, in which the fibrinous exudate infiltrating into the dead tissue binds it together into a membrane-like layer, we speak of it as *diphtheritic* or pseudomembranous inflammation. Although the diphtheria bacillus gives rise to a good example of this type, it must be remembered that the term merely indicates the anatomical condition, so that not every diphtheritic inflammation is caused by the diphtheria bacillus. According to the distribution of the inflammatory irritant in the tissues the inflammatory reaction may be diffuse or concentrated. In the first instance, if it be very intense and accompanied by a fibrinous purulent exudate, it is often called *phlegmonous*; in the second, in which, on account of the concentration of irritant and exudate, necrosis of the tissue and intense digestive liquefaction ensue, an *abscess* is formed. Putrefaction may be associated with the more extreme necrotizing injuries if the tissue is exposed to invasion by putrefactive organisms, and this character, often spoken of as *gangrenous*, is added to the inflammatory reaction.

CATARHAL INFLAMMATION

Catarrhal inflammation is well represented by the familiar coryza, which is an acute inflammatory reaction following the invasion of some unknown infectious agent into the upper air-passages. It is probable that the infection is favored by exposure to cold, by drafts, and all the other widely credited causes of colds, but undoubtedly the main factor is the transmission of the organism from some infected person. Recurrences may well be due to the infection of pockets in which handkerchiefs are carried. The infection is quickly followed by dryness and reddening of the mucosæ, which then swell up and secrete a profuse

flow of clear, mucoid fluid with some desquamated epithelial cells. Later, from the advent of leucocytes, the mucus-containing fluid becomes thick and yellow. After a time it decreases in amount and dries on the mucous surfaces, producing crusts. The mucosa in section shows great hyperaemia and oedema, with an excessive production of mucus by the goblet-cells of the epithelium. Between these cells there wander leucocytes, but no fibrin is formed on the surface (Fig. 98). Catarrhal inflammations appear in every mucous surface, with characters similar

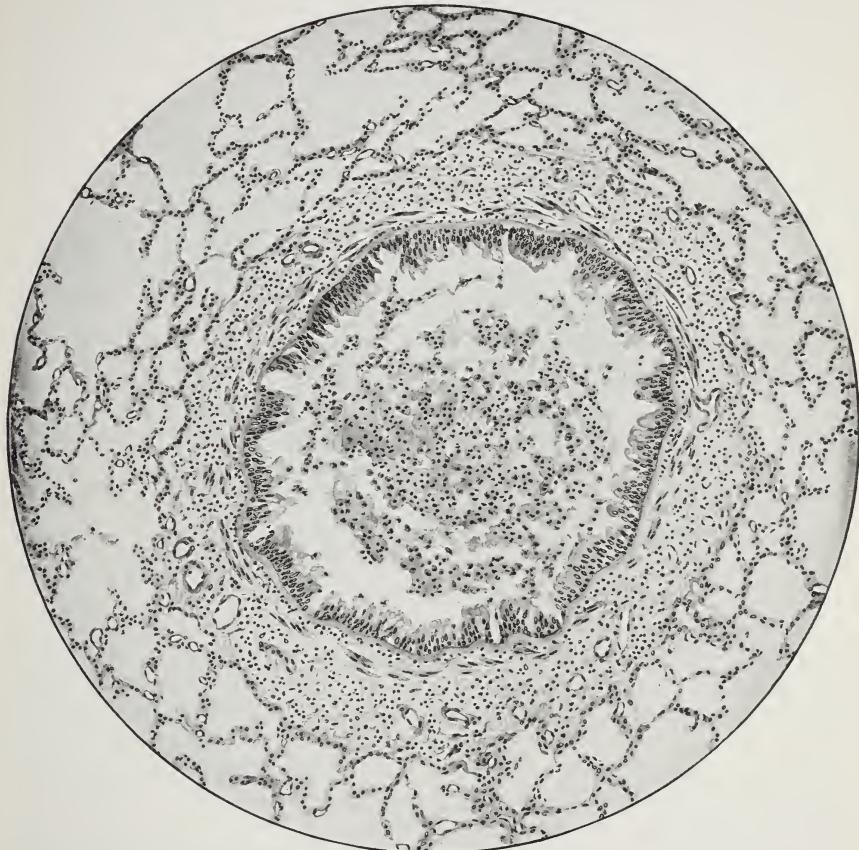


Fig. 98.—Catarrhal inflammation of a bronchus.

to those just described. When it is the affair of a narrow tube, such as the gall-duct or the Eustachian tube, the swelling of the tissue may produce obstruction.

SEROFIBRINOUS AND FIBRINOPURULENT INFLAMMATIONS

The more intense *serofibrinous* and *fibrinopurulent* inflammations are well illustrated by the various effects produced by bacteria in the serous cavities. The general characters of these processes are similar, and

they differ chiefly in their mode of origin or, rather, in the portals of entry of the organisms which cause them.

The walls of all these cavities are richly supplied with blood-vessels, and in the peritoneal cavity there hangs the peculiar omentum, which is largely composed of such vessels, although it may be also laden with fat. In each of the spaces there is normally a little clear fluid. Each is lined with flattened cells of mesoblastic origin, which are not identical with the endothelium of the blood and lymphatic vessels. These form a complete lining without any orifices or stomata, such as have been declared by so many authors to exist. The relation of the lymphatic channels to pleura and pericardium is very inadequately studied, but in the case of the peritoneum it is better known. In the abdominal surface of the diaphragm and in the floor of the pelvis are the two most conspicuous areas, where an absorbent mechanism is presented. There, there project between the connective-tissue fibers, which are spread apart in lozenge-shaped spaces, thin-walled, sac-like endothelium-lined structures which connect abundantly in the depths of the tissue with lymphatic trunks. These are completely lined by the endothelium, and separated from the peritoneal cavity practically only by this cell layer and the overlying layer of serosa cells. Occasional fibres stretch across them when they are distended like a rope across a full sail. There is no direct communication with the peritoneal cavity, but fluids enter by diffusion, and solid particles are carried through by leucocytes between the cells, or are pressed through free along the same lines. Bacteria injected into the peritoneum reach the retrosternal lymph-glands or the thoracic duct by this route very quickly indeed.*

Many leucocytes and mononuclear wandering cells lie in the omentum and elsewhere in subserous tissues, and the serosa cells themselves are somewhat phagocytic.

Absorption from the pleura seems to occur, in part at least, through the lung, since, when carcinoma cells are scattered in that cavity, they lodge and grow on the surface and later invade and actually inject the lymphatic channels running toward the hilum.

Pericarditis may be caused by a great many organisms, among which the most common are the pyogenic micrococci, the unknown cause of rheumatism, and the tubercle bacillus. They are thought to be brought directly to the pericardium by the blood-stream, since it is difficult to trace a direct extension from a pleural infection, and such pleurisies occur so often without pericarditis. It seems, however, that they must sometimes enter in this way or from adjacent lymph-glands. Endocardial and myocardial infection may also extend to the pericardium. That bacteria may be introduced in stab wounds or other forms of traumatism is obvious. Rather curious is the frequent occurrence of pericarditis in the terminal stages of chronic nephritis, and in those cases it is generally difficult to find any bacteria.

Sometimes only a thin film of fibrin is exuded on the pericardial surfaces without effusion of fluid (dry pericarditis). In that case a loud creaking or rubbing sound is made by each movement of the heart. If, then, fluid appears in excess, the surfaces are held apart, and the sound is lost or cut short. So, too, when a thick soft layer of fibrin is formed on the surface the sounds may be greatly muffled. In this condition (serofibrinous pericarditis), or even when the fluid is pus-like (fibrinopurulent pericarditis), one may observe that, through the motion of the heart, the fibrin is beaten into compact ridges which run, roughly speak-

* MacCallum: "Absorption of Granular Materials from Peritoneum," Johns Hopkins Hosp. Bull., 1903, xiv, 105.

ing, in certain transverse and oblique lines which are fairly constant. The heart is given a very shaggy appearance by this process (Fig. 99).

If a very great deal of fluid be exuded into the pericardial cavity, the sac is gradually dilated and will accommodate a large amount—far



Fig. 99.—Acute fibrinous pericarditis.

more than could be forced into it suddenly. There comes a time, however, when the heart is greatly embarrassed by this fluid because it can no longer expand properly to receive the blood.

This condition is especially well seen when a sudden haemorrhage occurs into the pericardial sac, and may be imitated experimentally by distending the sac with oil or salt solution under pressure. The arterial pressure falls, the venous pressure rises, and the heart collapses and stops beating. If the pressure is removed quickly enough, it will recover, with restoration of normal pressure relations.

In other cases, as so often happens, when a little or no fluid is exuded, or if, later, the fluid is absorbed, the pericardial layers covered with exudate come together and adhere; granulation tissue springs up from each surface and, replacing the fibrin, binds the pericardial sac to the surface of the heart. Blood capillaries arising from opposite layers anastomose with one another and complete the organic union of the two surfaces, by forming a vascular fibrous tissue. The motion of the heart stretches and keeps loose these adhesions, so that practically always the heart can move about a little within the sac. Nevertheless, if dense

adhesions exist also between the outer surface of the pericardium and the lung, the heart in contracting will be forced to pull directly upon the lungs and upon the diaphragm. This shows itself in each contraction by a drawing in of the diaphragmatic insertion, which visibly retracts the chest-wall along that line in children, and is followed by a very great hypertrophy of the whole heart. In other cases in which the external adhesions are absent there is no such hypertrophy.



Fig. 100.—Acute pericarditis, parietal pericardium. Cross-sections of compact ridges of older fibrin are separated by a network of fresher fibrin. The serosa cells are still visible.

The fresh exudate is composed, of course, of outwandered leucocytes, red corpuscles, and fibrin, beside the fluid. Most of the serosa cells persist for a time in an indistinct row in their old site (Fig. 100), while, as stated above, they remain able to proliferate actively in any place where they are not covered by exudate, and quickly reline any part of the pericardial cavity which has not been obliterated. In the midst of the fibrous adhesions one may find spaces lined with such cells which

have proliferated in this way (Fig. 96). The adhesions may be localized in certain areas, where they are usually drawn out into bands. If these break through, the stumps flatten themselves into opposed plaques which remain for a long time on the surface of the heart and the opposite area of the sac-wall as the so-called tendinous flecks or milky patches. Other explanations are offered for these thickenings of the epicardium, and will be referred to later.

If very thick, dense layers of fibrous tissue are formed—if the adhesions are firm or tunneled with channels filled with yellowish, opaque fluid, or if, with the thickening of the sac and epicardium, a haemorrhagic, fibrinous, and fluid exudate accumulates, the tuberculous nature of the affection may be suspected, and close inspection will usually show little nodular tubercles in the granulation tissue (*cf.* under Tuberculosis).

Pleuritis or **pleurisy** arises in a similar way, although there are more opportunities for the advent of infection into the pleural cavity. Every pneumonic process which approaches the surface of the lung causes at least a localized pleurisy. The occurrence of a sterile, haemorrhagic infarction in the lung is equally productive of a localized pleural exudation or coagulation of fibrin. The types of exudate and the method and results of its organization, with the formation of adhesions, are exactly as in the case of the pericardium (Fig. 101). It is generally thought that the severe pain in pleurisy is caused by the rubbing together of inflamed surfaces and relieved by their separation by an effusion of fluid, but Bray* has shown that it is essentially inspiratory and continues if the breath is held at the height of inspiration, and that it is intense if the pleura is artificially distended with air. He therefore thinks that it depends chiefly upon the stretching of the inflamed pleura.

Great accumulation of fluid in the pleural cavity tends to cause the collapse of the lung with the expulsion of contained air.

Slight inflammatory processes in the pleura may heal completely, leaving no trace behind. More severe alterations with fibrinous exudate usually cause the formation of granulation tissue to replace the exudate, which finally binds together the pleural surfaces, with adhesions. Repetition of the infection may call out a new exudate in the meshes and crevices of these fibrous adhesions. In other cases an abundant purulent exudate persists for a time and becomes walled off (empyema) and surrounded by a dense fibrous capsule which must be cut into and evacuated if recovery is to be expected in a reasonable time (Fig. 102). Otherwise a long time is required for the inspissation and gradual removal of the exudate, and in the meanwhile the pleural tissues about it become enormously thickened and form a dense, tendon-like wall as hard as cartilage and sometimes nearly an inch thick. Great deformity of the chest follows such protracted empyemas, for if the accumulation of exudate is large, the lung is generally found compressed into a small mass retracted against the vertebral column, and fixed in this compressed state by the growth of fibrous tissue throughout it.

Peritonitis.—Little is known of peritoneal inflammation produced

* H. A. Bray: Amer. Rev. of Tuberculosis, 1926, xiii, 14.

without the agency of bacteria, although in some instances in which bacteria have not been actually demonstrated the exudate has been ascribed to chemical irritants. Bacteria may enter by way of the blood-stream, by growth and spreading from an adjacent or contained tissue which is diseased, or by being directly introduced through a wound in the abdominal wall or a perforation of one of the bacteria-laden organs

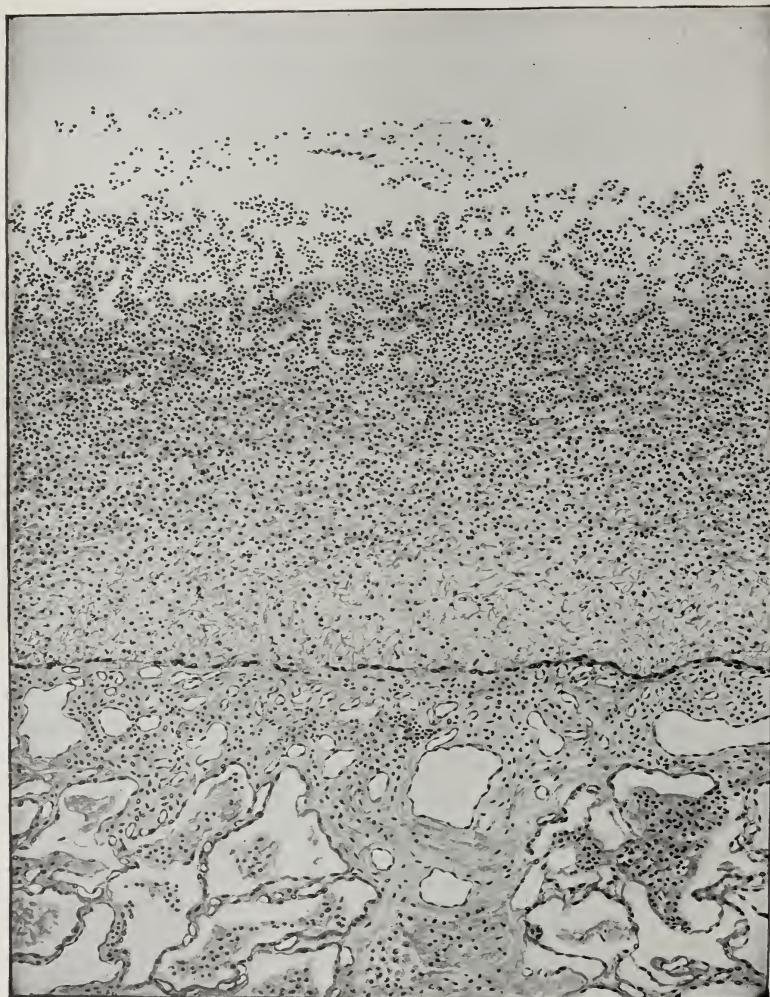


Fig. 101.—Acute fibrinopurulent pleurisy. The serosa cells are still to be seen covering the lung.

which lie in the peritoneal cavity. Naturally, the variety of organisms which may be concerned is almost unlimited, but in the ordinary course of events the pyogenic micrococci and bacilli of the colon group are most commonly found. The tubercle bacillus occupies a special place as a common excitant of peritoneal inflammation, and the gonococcus is

occasionally responsible. Of other organisms, something will be said elsewhere.

From an anatomical point of view peritoneal inflammation resembles closely that of the pleura and pericardium, except that it is more frequently seropurulent in character. Nevertheless, there are many instances, especially when the inflammation is not diffuse but confined to a limited region, in which it appears as fibrinous or fibropurulent



Fig. 102.—Empyema with thick fibrinopurulent exudate lining the pleural cavity. Compression and atelectasis of the lung caused by the large amount of fluid which was in the pleural cavity.

exudate, which glues together opposing surfaces and is soon replaced by a growth of blood-vessels and connective-tissue cells which form fibrous adhesions. This is, of course, the most favorable type, for the adhesions prevent the further spread of infection and may themselves be mechanically harmless, or later, when healing is complete, even become attenuated and finally disappear. On the other hand, a general

diffusion of bacteria, especially if there be injured tissue, foreign material, or a considerable accumulation of fluid to favor their growth, leads to hyperæmia of the whole enormous surface of the peritoneum, with the pouring-out of quantities of fluid, leucocytes, and fibrin, and the absorption of much poisonous material and many bacteria into the blood-stream. Naturally, the outcome of such an infection depends upon the balance between the power of resistance of the individual and the virulence of the bacteria, and this balance is greatly affected by the presence of injured tissue in the peritoneum. The normal peritoneum can annihilate many bacteria without the appearance of any peritonitis.

Primary or haematoogenous peritonitis is often produced by the pneumococcus, which gains entrance to the body by way of the tonsils or some similar portal of entry. In a case recently observed at autopsy no distinct lesion which could have played this part was discoverable on most careful search, and yet the whole peritoneal surface was covered with a thick, greenish-yellow, fibrinopurulent exudate which slipped off easily into the turbid fluid which filled the cavity. The Pneumococcus Type III was there in pure culture. Secondary forms of peritonitis include those which follow gunshot or other wounds of the abdomen, among which surgical operation wounds unfortunately hold a high place, because they are so frequently concerned with infected tissues and organs in the cavity. The seriousness of such injuries as gunshot or stab wounds lies chiefly in their penetrating into the stomach or intestine and allowing the escape of food or faecal material loaded with bacteria. The peritonitis which follows surgical intervention is usually the result of unskilful attempts to anastomose intestinal loops or other infected organs in which tissues are left stretched and badly supplied with blood, or sutures passed through an infected area with constriction of too much tissue.

Secondary peritonitis resulting directly from disease of the organs lying in the cavity may begin in several ways. Ulceration of stomach or duodenum proceeds often to perforation and discharge of their contents. Were it not for the food, the juices of these parts of the digestive tract are almost sterile, and prompt surgical operation with closure of the perforation usually cures the patient. Typhoid ulcerations in the lower ileum, tuberculous ulcers, amœbic and other dysenteric ulcers and the phlegmonous and gangrenous forms of appendicitis rupture and perforate in the same way, with discharge of bacteria of the intestinal contents, as well as those which have directly caused the lesion. Of these, the typhoid ulcers are perhaps least likely to be guarded by adhesions. Even without actual perforation, peritonitis arises when the wall of the intestine becomes necrotic, so that bacteria can wander through, as happens in strangulated hernia, intussusception, volvulus, infarction of the intestine through embolism or thrombosis of the mesenteric vessels, etc. In intestinal obstruction from whatever cause the part of the intestine above the obstruction becomes greatly dilated and stretched, and its mucosa ulcerated, so that the passage of bacteria through the wall is easy, even if not precipitated by actual rupture of one of these ulcers.

Extension of the infective process from inflammatory lesions of the gall-bladder and duets, from renal and perirenal abscesses, from the Fallopian tubes, or even through the walls of the uterus in puerperal infections, occurs but requires no special explanation here.

Gonococcal infection by way of the Fallopian tubes may produce diffuse peritonitis, with rather dry, tenacious exudate of fibrin. It is not common.

APPENDICITIS

The extraordinary frequency of appendicitis, and its extreme seriousness in many cases, make its study important. It will serve well as an example of bacterial infection, followed by inflammation and generally by healing.

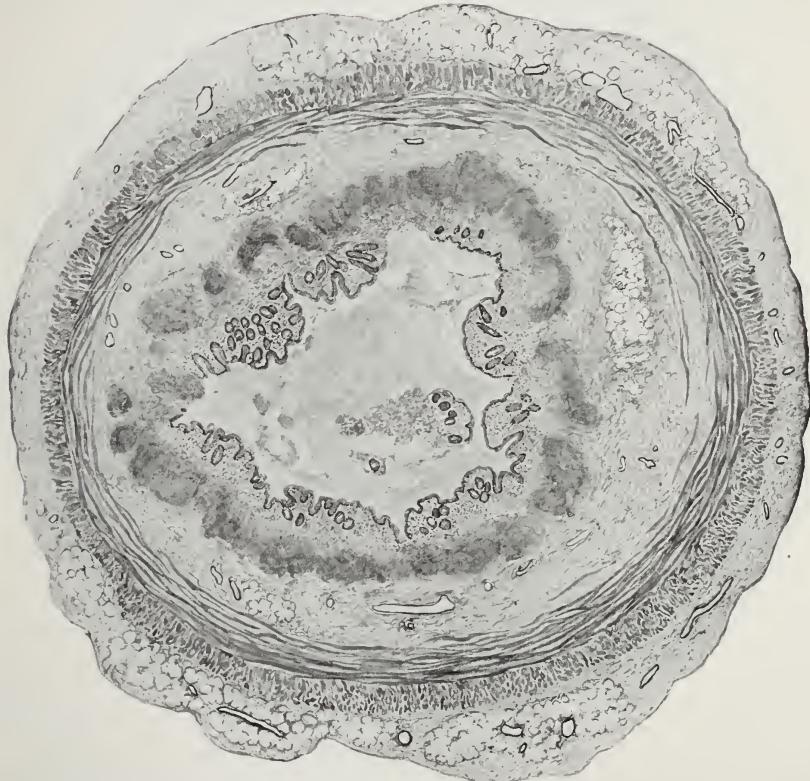


Fig. 103.—Acute appendicitis with beginning necrosis of the mucosa.

The wall of the appendix is composed of various tissues which correspond with those making up the rest of the intestine. The lumen may be stretched into cylindrical form, but in general collapses into a narrow space, which is Y-shaped on cross-section, one limb of the Y reaching toward the mesenteric attachment. The mucosa sinks into crypts, as in the colon, but has no villi. It is peculiarly rich in agminated nodules of lymphoid tissue. The appendix most commonly extends inward to the brim of the pelvis from the cæcum, but great variations are found in its position,

as well as in its size, its mesenteric attachment, and in its relation to the folds of the peritoneum. These matters of surgical interest may be read of in Kelly's monograph.

Appendicitis is an acute infectious disease produced by the invasion of bacteria from the lumen into the mucosa and other walls. The haematogenous infection of the appendix wall by bacteria transported from infected tonsils, which Kretz regards as a common origin of appendicitis, has not been clearly shown to take place. If it does so, it must be considered an exceptional occurrence, and does not explain the



Fig. 104.—Acute appendicitis. A portion of Fig. 103 enlarged to show the earliest changes.

majority of cases in which infection from the lumen can be conclusively demonstrated. Appendicitis may heal, leaving characteristic scars which predispose to a renewed attack, and it is usually in this way, that is, in the occurrence of repeated attacks, that one is justified in speaking of a chronic appendicitis.

Strangely enough, there is still much question as to the bacteria

which cause it, and probably several sorts are concerned. Aschoff and his students find a Gram-positive diplococcus and Gram-positive bacilli as the most characteristic organisms. Apparently, streptococci, perhaps accompanied by the colon bacillus, have been found most often, but a great many other forms are also described, even including certain anaërobic bacilli. Mechanical factors favor the lodgment of the organisms in the mucosa, especially the kinking or sharp bending of the terminal portion or the presence of obstruction caused by previous inflammation and scarring. Infected foreign bodies of a sharp angular form may have the same effect, but the prevalent idea that foreign bodies are commonly present and the ordinary cause of the disease is quite erroneous. Nearly all the "cherry-stones" and "date-seeds" or "grape-seeds" which are found in the appendix are really not seeds at all, but concentrically laminated masses of faecal material. They are



Fig. 105.—Acute appendicitis with perforating ulcer.

injurious inasmuch as they may cause obstruction and allow bacteria to accumulate behind them, but Aschoff insists that they do not themselves injure and infect the mucosa, but that they rather protect it.

As may be determined from the study of the very early stages, infection begins in the mucosa in the bottom of one of the grooves which form the Y- or X-shaped lumen in cross-section. Starting as a tiny break in the epithelium, with an underlying accumulation of polymorphonuclear leucocytes, the inflammatory reaction spreads outward in a widening area toward the outer surface. This diffuse inflammation may be practically bacteria free in its outer part, but nevertheless reaches the serosa and extends along the walls of the appendix. It is the phlegmonous type of Aschoff, and may sooner or later show the formation of small abscesses anywhere in the affected region. Such abscesses,

causing liquefaction of the wall, bring about perforation either into the lumen of the organ or into the peritoneum. Such rupture to the outside



Fig. 106.—Acute phlegmonous appendicitis.

is, of course, the origin of an acute spreading peritonitis, unless it is limited by adhesions from a previous attack. Even without actual

perforation, however, the extension of the phlegmonous inflammation sets up an acute fibrinous exudative peritonitis over the wall of the appendix itself. The organ is swollen and reddened, and roughened by the presence of the fibrin. When an abscess approaches the surface, it is recognizable as an opaque yellow spot in the congested wall (Fig. 105).

It is even more common to find that, instead of remaining as a minute lesion of the mucosa, the infection spreads so as to cause rather



Fig. 107.—Sequel of old healed appendicitis. Obliteration of lumen.

extensive patches of necrosis, in which the outlines of the crypts can still be made out, although a dense fibrinous exudate welds the dead tissue of the mucosa into a sort of false membrane. Numerous haemorrhages accompany this, and with the loosening and discharge of the false membrane deep ulcers are left (Fig. 106). Extension into the depth is rapid, and may proceed to destruction of the whole thickness

of the wall and perforation, especially since the cavity is often distended to bursting with the exudate. Such extreme lesions are not likely to heal, and unless saved by operation, the patient succumbs to a general peritonitis. If, however, there have been previous attacks of milder character, the appendix may have become adherent to the surrounding tissues by the organization of fibrinous exudate between its surface and that of adjacent coils of intestine. In that case the material discharged through the perforation may not pass into the general peritoneal cavity, but only into contact with these adhesions, where an abscess is then formed. Such periappendiceal abscesses are sometimes quite large, and may contain the necrotic débris of the appendix, floating in pus. They are perhaps not so common now as formerly, nor so common as they would be in an age of less prompt and aggressive surgeons.

Slighter lesions which stop short of destruction of the whole wall may heal without intervention, and such a person is then liable to a renewed acute attack unless his appendix is removed by operation in the interval. The mucosa may not have been very widely destroyed, especially in the suppurative form, but even when it is ulcerated away over one side of the lumen, it is regenerated from that which remains and the lumen is kept open. If it be destroyed all the way round, the cavity usually collapses and becomes obliterated by a continuous growth of granulation tissue (Fig. 107). Even when the destruction has been very slight and the inflammatory reaction in the walls moderate, scars are left which indurate the submucosa and which persist in the interstices of the musculature. The elastic tissue, which has a characteristic arrangement for each layer, is partly destroyed, and though regenerated, is left greatly distorted.

Various complications and sequelæ occur, among which is the general or localized peritonitis already mentioned. This, if survived, often leaves adhesions, which may later cause mechanical obstruction to the intestine, either by kinking and constricting loops, or by facilitating the occurrence of internal hernial entanglements. Extension or burrowing of the periappendiceal abscess may lead to the accumulation of pus in extraordinary places, among which the subdiaphragmatic region about the liver, in front or behind, and on either side, is conspicuous. These are the so-called subphrenic abscesses, which may, of course, have other points of origin.

Thrombosis of the nearby iliac and femoral veins may follow appendicitis, but more serious, and even more characteristic, is the formation of an infected thrombus in the branches of the portal vein which lead away from the appendix itself. A case was recently observed in which the branches of the vein leading from an abscess around the appendix were found filled not with blood, but with a purulent, greenish-white material. The main trunk of the vein, greatly dilated and thickened, was full of the same material. The splenic vein was plugged at its entrance by a firm thrombus, so that the inferior mesenteric vein which joins it before that point was reached evidently discharged its blood by way of the splenic vein and anastomosing channels to the

stomach and oesophagus. In the liver every branch of the portal was full of soft, purulent thrombus material, and there were numerous large

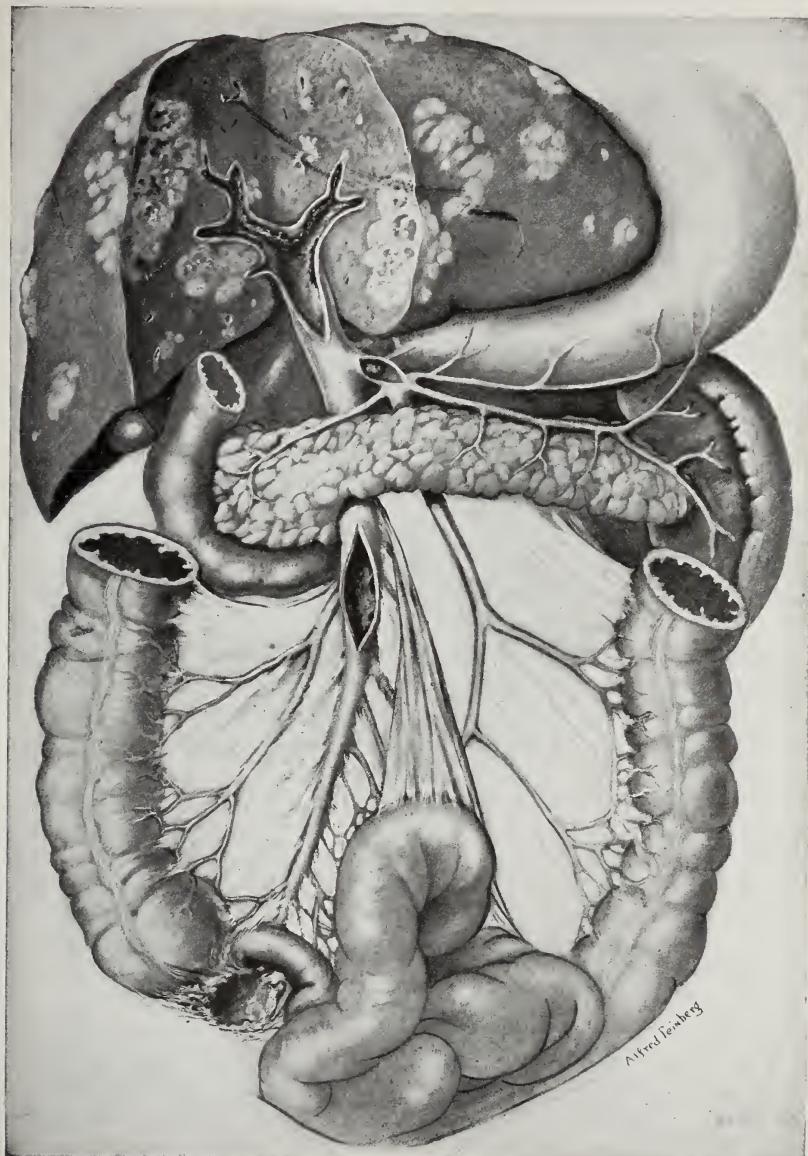


Fig. 108.—Suppurative pylephlebitis arising from appendix abscess. Numerous abscesses in the liver.

abscesses and groups of smaller ones. This is the so-called *suppurative pylephlebitis*. In this case the infection extended even further, and there were abscesses in lungs and spleen (Fig. 108).

LITERATURE

- Aschoff: *Wurmfortsatzentzündung*, Jena, 1908.
Aschoff: *Ergeb. d. inn. Med. u. Kinderh.*, 1912, ix, 1.
Kelly and Hurdon: *Diseases of Vermiform Appendix*, 1905.
Kretz: *Mitth. a. d. Grenz. d. Med. u. Chir.*, 1907, xvii, 1.
Kretz: *Verh. Dtsch. Path. Gesellsch.*, 1907, x, 229; 1910, xiv, 157.
Noll: *Mitth. a. d. Grenz. d. Med. u. Chir.*, 1907, xvii, 249.
Obendorfer: *Ergeb. d. allg. Path.*, 1909, xiii, 527.
Wätzold: *Ziegler's Beitr.*, 1907, xlvi, 260.

ENDOCARDITIS

By endocarditis is meant an inflammation of the endocardium which is most commonly found to affect the valves, but may also occur upon the lining of auricle or ventricle, or upon the chordæ tendineæ, and may extend into the underlying tissue. Various bacteria may cause such an inflammation, although certain well-recognized ones, such as streptococci and pneumococci, are by far the most frequently found.

But it must be especially emphasized here and at once that two other diseases, rheumatism and syphilis, are responsible for a very great number of cases of disease of the heart-valves commonly classed as endocarditis, although very different in character from that caused by bacteria. Indeed, it seems probable that many of the cases of bacterial endocarditis arise because the valves have been injured and distorted by rheumatic infection. This is not true of the syphilitic distortion of the valves, upon which bacteria seem rarely to settle. There are many cases in which the valves, especially the mitral and aortic, are found thickened and shrunken so as to become incompetent to close the orifice or so as to narrow the orifice to a rigid space, and we have been accustomed to speak of such insufficiencies, or stenoses, as the result of chronic endocarditis. Care must be observed, however, in making any such assumption, for the known cases of bacterial endocarditis nearly always end fatally, and there are hardly any reported cases in which one can feel sure that the injuries produced by bacteria have healed so as to leave thickened and distorted valves. On the other hand, the contraction and thickening of the aortic valves with insufficiency produced by syphilis is perfectly characteristic and easily recognized. Rheumatism is a recurrent disease, each attack throughout years injuring the valves in a peculiar way and leaving them to heal in scarred and thickened form. It is probable that a very large proportion of such deformities of the valves depend on rheumatism. There still remain cases in which great thickening and scarring and even calcification of the valves are found, especially in elderly and old people, and the cause of this, particularly in the cases of aortic valve stenosis, is not known. It has been loosely ascribed to the extension of arteriosclerosis from the aorta, but this is not based on any good evidence. Or else it has been equally carelessly spoken of as chronic endocarditis, suggesting that these are scars left by the healing of bacterial endocarditis, but this is almost certainly untrue.

The peculiar changes produced by rheumatism, those due to syphilis, and the mechanical effects of injury and scarring of the valves will be

described later in the appropriate places. Here it is planned only to discuss, as an example of an inflammatory process, the general character of bacterial endocarditis, although that too will be mentioned again under the heading of each organism concerned in producing these important diseases, and then it will be seen that endocarditis is no disease

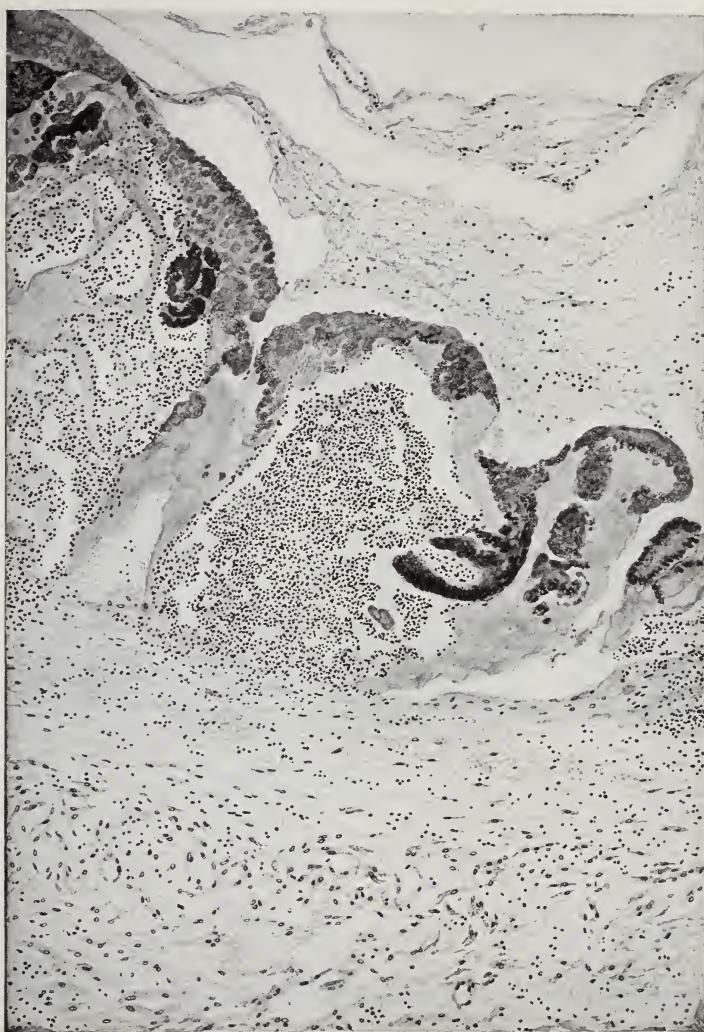


Fig. 109.—Acute endocarditis. Vegetations upon the wall of the auricle showing great numbers of bacteria and an intense inflammatory reaction.

by itself, but only an incident in the course of many different types of infection.

The student is at once referred to the remarkable monograph of Dr. Thayer, and to the analyses of Clawson, Horder, and others for a sur-

vey of what actually happens. It appears with surprising constancy in all these studies that certain bacteria are found always, no matter in what part of the world, in about the same proportion of the cases—streptococci in about 60 per cent., pneumococci in about 18 per cent., staphylococci in about 13 per cent.—the only others that figure at all prominently are the influenza bacillus and the gonococcus, about 2 or 3 per cent. each, while there are rare single cases of infection with other organisms.

The bacteria enter the blood-stream by various portals of entry, teeth, tonsils, wounds, infected thoracic, abdominal and pelvic organs, etc., and they lodge on the valves along the line of closure on the surfaces that come together, and there produce the first injury.

The structure of valves should be minutely reviewed in this connection, better by looking at the valves than by reference to any book. It will be seen that each has a thin, filmy margin which completes the water-tight closure, although the brunt of the occlusion of the orifice is borne by the stronger part of the valve up to a certain line which is slightly fortified, along which the valves come tightly together when closed. This is spoken of as the line of closure. In the mitral and tricuspid, chordæ tendineæ are implanted in rows almost down to the base of each valve, strengthening like guy-ropes every part of the valve—they are particularly strong along the back of the line of closure, but some delicate ones go even to the edge of the filmy margin which completes the closure. Blood-vessels from the coronary circulation run far toward the margin of the auriculo-ventricular valves, but enter only a short way into the bases of the semilunar valves.

It seems, since bacteria are found first lodged on the face of the valve along the line of closure, that they are somehow caught there from the blood-stream as the valves beat together. The mechanism of this is not particularly clear, and, indeed, there are those so dissatisfied with this explanation as to insist that the bacteria are brought into the substance of the valves by way of the coronary circulation. But this seems much harder to understand or believe, because the coronary circulation could bring them to that spot in the mitral or tricuspid only rarely and to the line of closure in the aortic and pulmonary not at all, while in that case all the rest of the endocardium lining the auricles and ventricles should be just as readily the site of localization of the bacteria. Grant has shown, as one can easily see in many cases of endocarditis (Fig. 110), that when bacteria have lodged on a valve and have eroded it so that it flaps about, new implantations occur on whatever part of the heart lining it strikes against and nowhere else. He mentions the fact that implantations of bacteria from aortic valve infections, which may produce excavations in the adjacent lining of the aorta, are never found in the pulmonary artery, although the coronary supplies both pulmonary and aorta—they must be from contact, as it obvious from their distribution.

The mitral and aortic valves are most commonly the site of localization of bacteria, pulmonary and tricuspid far less often. Other sites, as already mentioned, may occasionally appear as the primary point

of localization, but are generally affected by extension or by contact. Thus, bacteria, spread down on the chordæ tendineæ or upward on the auricular wall, or they burrow into the tissue at the base of the valve and may extend through the muscle to appear in another chamber of the heart.

However they arrive, the bacteria are found on or near the surface of the valve, although those who maintain that they come by way of the coronary arterioles have once or twice been able to show them rather in the depths. They produce necrosis of the endothelium and adjacent cells and quickly bring about a deposition of platelets and fibrin, and leucocytes and red corpuscles from the passing blood. In other words, the injury exposed to the circulating blood causes the formation of a thrombus which grows as a soft, red mass which, in the



Fig. 110.—Endocarditis caused by the *Streptococcus viridans*. Implantations from a torn valve on the septum membranaceum, the aorta, and the mitral, with mycotic aneurysms in aorta and mitral.

agitated position in which it arises, has not much of the orderly arrangement of a thrombus formed in a vein, or even in an auricular appendage. Great masses of bacteria grow in such a position and spread into the underlying tissue, causing its further destruction and an acute inflammatory reaction. With the lapse of time, reparatory changes occur and blood-vessels grow into the valve, bringing fresh inflammatory exudate. Such a "vegetation" is, therefore, partly a thrombus, partly an inflammatory exudate with débris of necrotic tissue and ineffectual efforts at healing.

When it is large enough and easily crumbled, portions break off and are thrown as emboli, carrying bacteria into those arteries to which the blood goes from that part of the heart. If the crumbling vegetations are upon the mitral or aortic valves, any arterioles except those of the lungs may receive the emboli, and this includes the coronary

vessels of the heart itself. Indeed, the gross plugging of a coronary artery is occasionally the cause of death in such a case, but infected infarcts in the spleen and kidneys are especially frequent.

The destruction of the valve itself, which justifies the term "ulcerative endocarditis" (a term which should not be applied to the mere crumbling of thrombi on its surface), leads to various curious changes. An aortic valve may be perforated so that blood streams back through the hole in diastole, or it may be reduced to a loose flap attached only at one angle. In either case aortic insufficiency arises, and when such a flap beats against the near-by endocardium or lining of the sinus of Valsalva, it may implant bacteria there and so start new vegetations, or the vegetation on the end of such a loose flap may be forced into the mouth of a coronary artery, causing death. When the valve is weakened by the injury caused by the bacteria, it may be distended into a little sac—a "mycotic aneurysm"—and this in the case of the aortic



Fig. 111.—The same heart seen from the auricular surface of the mitral valve. Vegetations along the edge of the valve and on broken chordæ tendineæ. The sacculations of the multiple mycotic aneurysms are seen as smooth projections.

valve projects into the ventricle, while in the mitral one sometimes sees several such sacs with their orifices on the ventricular side of the valve and their convex surfaces projecting on the auricular side (Fig. 111). Mycotic aneurysms, or infected excavations, occur often, too, in the sinuses of Valsalva or even higher in the wall of the aorta, and are sometimes quite large cavities filled with disintegrating heavily infected thrombus material in the tissue about the root of the aorta, and connected with the aorta by only a small opening. They may, of course, burrow into the wall of the auricle or deep into the interventricular septum, and bulge into the auricle or into the right ventricle. I saw one which re-entered the left ventricle from the sinus of Valsalva, and by rupturing there produced a roundabout aortic insufficiency.

Vegetations on the mitral valve, especially in infection with the *Streptococcus viridans*, tend to spread down on the chordæ tendineæ and up on the wall of the left auricle. Perhaps their spread into this

auricular extension is favored by rheumatic lesions which often exist there. The chordæ tendineæ are covered with a thick, beaded, thrombus mass, and many of them break and flap about loose in the ventricle. Such broken chordæ are quickly clothed about their loose ends with club-shaped masses of granular clot. This loss of the supporting chordæ must in itself contribute to the insufficiency of the valve, but it is rather rare to find the mitral valves so perforated and torn as to approach the degree of insufficiency so often seen in the aortic valves.

The vegetations in both situations may reach a very great size so as to obstruct by their bulk the passage of blood through the mitral or



Fig. 112.—Large vegetations on mitral valve (*Streptococcus viridans*). Infected infarctions in spleen.

aortic orifices. In this way they not only prevent the accurate closure of the valves, but produce an effect resembling that of stenosis.

Aside from the gross invasion of bacteria into the muscular wall of the heart already mentioned, a few bacteria may be distributed by the coronary stream and give rise to an acute myocarditis, which shows itself in the necrosis of muscle-fibres and the out-pouring of an inflammatory exudate.

LITERATURE

- Clawson: Arch. Int. Med., 1924, xxxiii, 157.
Grant: Heart, 1924, xi, 9.
Libman: Jour. Amer. Med. Assoc., 1923, lxxx, 813.
Thayer: Johns Hopkins Hosp. Reports, 1923, xxii, 1.
Wright: Jour. Pathology and Bacteriology, 1925, xxviii, 541.

LOBULAR PNEUMONIA OR BRONCHOPNEUMONIA

As a terminal event in all sorts of illnesses, both in children and adults, it is an extremely common thing to find patches of inflammation in the lungs produced by bacteria. These are not strictly lobular, and as all inflammations of the lung involve the bronchi, neither name is especially appropriate. In such cases as are due to the invasion of only one kind of bacterium, the changes in the lung have corresponding specific characters, and we can recognize fairly accurately some of these, but very often there is a mixture of bacteria, and it may be said that, as a rule, it is impossible to tell from inspection of the lungs at autopsy what bacteria are present, and even after they have been isolated in culture it is not easy to say which played the principal part. Pneumococci, streptococci, staphylococci, and influenza bacilli are perhaps most commonly found, but every sort of bacterium may be there. There is one type of lesion in which the influenza bacillus is usually found, but it would not be safe to say that it alone is capable of producing this appearance. So, too, the staphylococcus tends to produce abscesses, but there are other organisms that can do this and, in many cases, a staphylococcus is present without any evidence of abscess formation. The tubercle bacillus can produce an easily recognizable form of patchy pneumonia quite unlike the common forms, and this will be described elsewhere, but even this may be simulated by other organisms. In short, it is quite necessary for the comprehension of lobular pneumonia to make careful smears and cultures of the bacteria in each case.

It is possible for bacteria to reach the lung by way of the bronchi or by way of the blood-stream, and the effects produced may be nearly the same. Still it seems that in most instances the infection occurs by way of the bronchi, and in many this is grossly apparent. The upper respiratory tract is always more or less loaded with bacteria, and the wonder is only that they do not more commonly extend into the bronchioles. There is much evidence, however, that a tolerance for these organisms is reached, and signs of infection appear when a new and virulent organism is drawn in from outside. Of course, such massive introduction of bacteria into the bronchi as comes when a person vomits while under an anaesthetic, or otherwise unconscious, and aspirates stomach contents and saliva into the lungs is easily recognized at autopsy. Gastric juice can be smelt in the lungs and there are greenish-black patches in which the lung tissue is softened and disintegrated, without much evidence of inflammation. The tissue fails to stain and is partly digested and food particles are found in the bronchioles. Death probably follows such an event pretty quickly, and digestion goes on after death. So, too, in the untoward accident when a child or an unconscious adult is being fed milk through a tube, and some of the milk goes into the trachea, the kind of pneumonia can be recognized by finding the alveoli full of phagocytic cells containing fat droplets.

But a very important factor in all lobular pneumonias is a predisposing disease. In beginning it was said that lobular pneumonia is the common terminal affection in all sorts of diseases. Sometimes this is

because the patient is weakened by a long illness, such as a cancer or nephritis or some disease of the heart. Then when resistance is low, perhaps intensified by a long stay in bed, during which the circulatory conditions in the lungs are supposed to be unfavorable, bacteria creep into the bronchioles from the upper tract. When the chronic disease involves bacterial infection—as in a case of typhoid fever of long standing—it might seem that the same organisms would be found in the lungs, but generally it is a secondary infection with other bacteria that produces the pneumonia. Even in general septicæmias of streptococcal or pneumococcal origin, although bacteria borne by the blood-stream may lodge in the lungs and produce patches of pneumonia, this is not an invariable consequence, and often when pneumonia is associated with such a septicæmia one has the impression that it arises from aspiration of infected material or extension from the larynx and trachea. In such affections as diphtheria or streptococcal laryngitis and tracheitis, the growth and extension of the bacteria down the trachea into the finest bronchioles may often be directly traced.

But even more remarkable as predisposing factors in lobular pneumonia are those diseases which commonly affect children and may run in epidemics, such as measles, whooping-cough, scarlet fever, and others. We know little of their own direct effect upon the tissues, and if the patients are protected from secondary infection they may proceed uneventfully to recovery, but if streptococci or influenza bacilli or other virulent organisms gain a foothold in the pharynx and larynx, they grow apace and quickly penetrate to the lungs. This was tragically apparent among enlisted troops during the mobilization for the Great War where epidemics of measles were serious because of the secondary infection with haemolytic streptococci, and the great epidemic of influenza produced different types of lobular pneumonia in each camp according to the prevalent bacteria capable of producing secondary infections there. The accidental introduction of one man with streptococci in his throat into a ward full of cases of measles, up to that time progressing smoothly, would precipitate an outburst of streptococcal pneumonia throughout the ward. In children after these common diseases, infection of the throat with advance of the bacteria up the Eustachian tubes and otitis media, is very often terminated by some form of lobular pneumonia.

Apart from tuberculous pneumonia and other rarer forms produced by uncommon infective agents, we ordinarily recognize two forms of patchy pneumonia with frequent admixtures. Of these, the most common is that in which there are areas of consolidation scattered through the lung, usually more abundant in the lower lobes and posteriorly, and surrounded by broad zones of oedema and haemorrhage. The areas may be very small, or much larger and confluent. The lung is commonly glossy on its pleural surface unless foci of consolidation lie near, when that region of the pleura at least is covered with a thin fibrinous exudate. On the cut surface the consolidated parts can be felt and can usually be seen as slightly elevated patches varying in color from a dark red, or blackish-red, through the precise color of the remainder

of the tissue, to pale grayish-rose or yellowish-gray (Fig. 113). It is hard to see them when their color is quite the same as that of the surroundings, but they can generally be made evident by gently pulling the lung this way and that. The alveoli stretch out into long rhombs as though one stretched diagonally a fine silk gauze, but those which contain exudate resist this slightly and stand out by contrast. From the bronchioles there may usually be expressed a drop of purulent fluid. When the process is rather advanced the plugging of the bronchi with exudate extends past the next branches and seems to exclude air from



Fig. 113.—Lobular pneumonia in adult lung, showing patchy areas of consolidation.

the surrounding lung tissue, so that it sinks collapsed into a pasty, bluish mass. The anterior and upper parts of the lung are distended with air to compensate for this.

Microscopically, one finds the bronchioles and alveoli filled with leucocytes (Fig. 115), some red corpuscles, fluid, and fibrin. Many bacteria are present in the bronchioles and in the more central or bronchiolar part of the area of consolidation, while as we pass toward the periphery the leucocytes become fewer and the fibrin more con-

spicuous. This applies to just those alveoli which are supplied by a terminal bronchiole—those belonging to the next terminal bronchiole repeat the arrangement. But often the leucocytic exudate and hæmorrhage are so compact that it is hard to make out any such differences from bronchiole to periphery, or to outline one such area from the next. At the margin of the area of consolidation the alveoli at first contain fluid—an inflammatory oedema—and then air, or, as described above, are collapsed so that their walls lie flattened together, all the air having been absorbed.

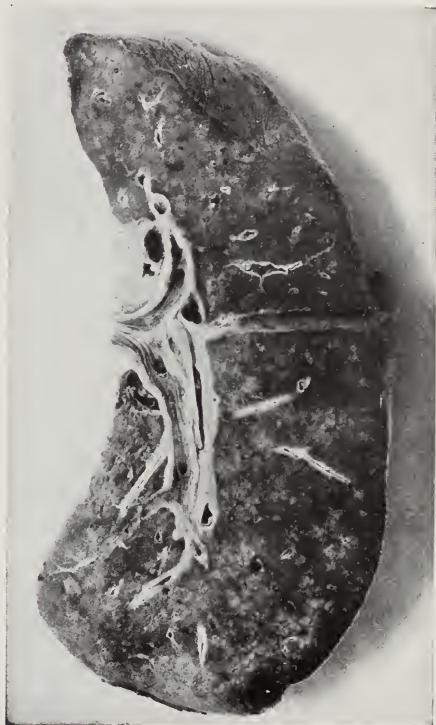


Fig. 114.—Terminal lobular pneumonia showing somewhat indistinct patches of consolidation.

The other type is that frequently found in children after measles or whooping-cough (Fig. 449) and found, too, among the susceptible enlisted men in the great epidemics of measles (Fig. 263). This we have called interstitial bronchopneumonia because so much of it is due to accumulation of cells in the interstices of the bronchial walls and of the alveolar walls. In the children the influenza bacillus is very commonly present, and in some cases, during the war, this organism was found in the lungs of adults, although in the cases following measles a hæmolytic streptococcus was always the infecting organism, producing also a tremendous pleurisy and other lesions. Other organisms, too, are often found in the lungs of children in this condition.

On the cut surface of the lung one can trace clusters of yellowish nodules following the branching of the thickened bronchioles, which themselves are filled with a yellow exudate. Sometimes these nodules are very small, but they may grow into larger masses and even coalesce. In many cases they look very much like small caseous tuberculous areas. The surrounding lung tissue is generally collapsed, and there is not much haemorrhage or oedema. Microscopically, one finds



Fig. 115.—Bronchopneumonic patch showing infiltration of bronchial and alveolar walls with the inflammatory exudate.

the bronchioles filled with leucocytes among which are bacteria. Their walls are greatly thickened, chiefly by the accumulation of small mononuclear cells in their meshes, and this infiltration extends out into the neighboring alveolar walls which are thus greatly thickened. The alveoli contain a few red corpuscles, some fibrin, some mononuclear cells and desquamated epithelium, but relatively few leucocytes.

Combinations of these two forms are not uncommon, and in both the lymphatics of the bronchial walls and the interlobular septa may be

distended with leucocytes, or actually plugged with clots of fibrin loaded with leucocytes and bacteria.

The healing of these types of pneumonia is brought about by the destruction of the bacteria and the liquefaction and absorption of the exudate. Sometimes when this is interfered with, possibly by some neutralization of the digestive ferments of the leucocytes, the exudate remains long enough to be replaced by an ingrowth of connective tissue with blood-vessels. Occasionally in children there are found large multinucleated giant-cells in the alveoli which may enclose fibrin and leucocytes.

Special organisms, such as the fusiform bacilli and spirilla found by Buday, and characteristic, too, of Vincent's angina, may produce gangrene of the lung, a condition in which a progressive softening and excavation of the necrotic tissue forms cavities lined by shreds of unbelievably foul-smelling material.

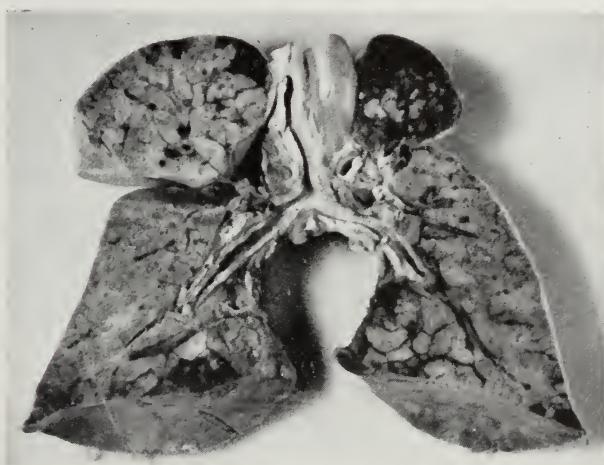


Fig. 116.—Lipoid cell pneumonia in a child.

Lipoid Cell Pneumonia.—The peculiar form of pulmonary lesion which we have become accustomed to speak of as lipoid cell pneumonia is the result of the aspiration of some oily material into the lungs. It is discussed at length by Pinkerton who studied it at autopsy, and experimentally. Such introduction of oil or milk may readily result in infants or in persons whose reflexes are dulled, especially during gavage or feeding with a tube. The fat in droplets is taken up by mononuclear phagocytes, some is absorbed into the tissue or into lymphatic channels and there is in many cases a great thickening of the alveolar walls (Figs. 116, 117), or at times the appearance of giant-cells, especially when with decomposition of the fat, the free fatty acids cause widespread necrosis. In such cases the necrotic patches look like caseous areas of tuberculosis with marginal giant-cells. As a rule there is a secondary bacterial infection which adds the elements of an ordinary pneumonia.

Pinkerton finds that neutral vegetable oils produce no reaction and are expectorated. Animal oils cause fibrosis and giant-cell formation in a few days while mineral oil is emulsified and the alveoli are filled with mononuclear phagocytes. Scarring and giant-cell formation then come very late.

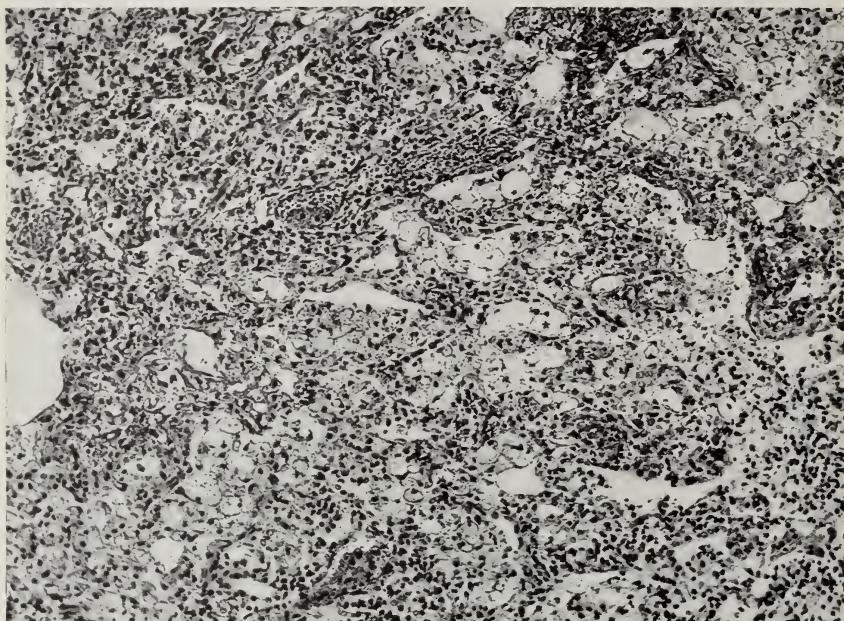


Fig. 117.—Lipoid cell pneumonia in a child. Section from lung shown in Fig. 116.
The large phagocytes are loaded with fat globules.

LITERATURE

MacCallum: Pneumonia Following Measles, *Rockefeller Institute Reports*, 1919, x;
Johns Hopkins Hosp. Reports, 1921, xx, 2.

Pinkerton: *Amer. Jour. Dis. of Children*, 1927, xxxiii, 259; *Arch. Pathology*, 1928,
v, 380.

PUERPERAL INFECTION

Particularly favorable opportunity for the development of a serious infectious process is offered in the puerperal uterus, not, as is so often stated, because in the detachment of the placenta many blood-channels are torn open, but because tissue which is no longer permeated by the circulating blood is often left adhering to the uterine wall, and because fluid stagnates in the cavity. It is the same danger which threatens the patient after an unskillful operation upon some internal organ in which a portion of tissue is left constricted so as to be deprived of its blood-supply. It is practically the same danger of infection that exists in a strangulated hernia.

An example will make this clear: A man whose leg was crushed and torn below the knee was treated by a surgeon who washed out the dirt from among the exposed muscles, stopped the bleeding, and sewed up all the tears in the skin. Within a

few hours the sutured skin became tense almost to bursting, and when the stitches were removed, a bloody, turbid fluid poured out. Next day the muscles and shreds of tissue were bathed in this pus, the man's temperature was high, and there were evidences of a rather profound poisoning. In spite of every proper surgical intervention he finally died, and many abscesses were found in lungs and elsewhere. Undoubtedly the accumulation of fluid within the sutured skin gave a medium for the growth of bacteria from the dirt left behind, and at the same time rendered the tissues anæmic through pressure.

Differences of opinion still exist as to the source and nature of the bacteria which are responsible for puerperal infection, and doubt prevails still as to whether they may be the bacteria already present in the genital tract, or only those introduced by the hand or instrument of the operator. Krönig adheres strongly to the latter view. The Streptococcus pyogenes in one or other of its modifications (*q. v.*) is almost always found, although the pneumococcus or staphylococcus may be the organism concerned, and various bacilli, including the *Bacillus aërogenes capsulatus*, may play a part. Harris and Brown* found that puerperal infection due to aërobic beta haemolytic streptococci is almost invariably of exogenous origin while infection due to gamma non-haemolytic streptococci, commoner in negro women, is probably derived from organisms harbored in the vagina and cervix during pregnancy.

In cases of criminal abortion at any stage in the course of pregnancy infection is likely to take place on account of the haste and secrecy with which instruments are forced into the uterus at the hands of persons ignorant of the conditions of bacterial growth. Fortunately, with the advance in the knowledge of bacteriology puerperal infection is no longer the dreaded scourge of obstetrical practice that it once was before the time of Semmelweis. Even yet, however, the cases in which, after a complicated delivery, infection occurs are not all too rare. It may result only in a temporary fever, or, on the other hand, it may advance to general septicaemia and death. The uterus is found at autopsy relaxed and soft, with the widened blood-vessels characteristic of the late stages of pregnancy. In some cases the lining seems fairly clean, with no discoloration and only slight fragments of placenta adherent. But often it is greenish-black and necrotic looking and the muscular wall oedematous. Occasionally, as shown in Fig. 118, there is a thick, ragged, necrotic layer lining the whole cavity of the uterus and the wall shows widened veins, some of which are plugged by thrombi while others are now filled with greenish-yellow pus, their walls converted into opaque yellow, necrotic material or destroyed entirely so that the uterine musculature itself edged with yellow, necrotic tissue, forms the wall of the canal. For a long way nothing remains of the more solid thrombus and one may trace such channels far out into the broad ligament and to the walls of the pelvis.

Dr. Williams found upon analyzing a large number of cases, that the infection is carried to the rest of the body in three main ways. Lymphatic channels, infected and partly obstructed, transport the bacteria to the peritoneum and the patient dies with general peritonitis.

* Harris and Brown: Johns Hopkins Hosp. Bull., 1929, xliv, 1.

The Fallopian tubes play no part in this. Next in frequency is the thrombosis of veins above described, with gradual extension of the softening and entry of the organisms into the general circulation.



Fig. 118.—Puerperal endometritis. Great necrosis of endometrium. Purulent thrombophlebitis.

Lastly, there is the sudden invasion of the circulating blood by streptococci and rapid death from an overwhelming septicæmia.

ABSCESS FORMATION, PYÆMIA, ETC.

Certain bacteria, notably the staphylococci, show a marked tendency to grow in the tissues in closely packed colonies about which the cells are rendered necrotic for varying distances. A violent inflammatory

reaction ensues, and the immediate neighborhood becomes tumefied, red, and painful. Coagulable fluid exuded from the vessels into the necrotic tissue clots there, and converts it into a firm mass, rather larger than it originally was. Leucocytes in great numbers accumulate outside these neighboring vessels, and wander into the necrotic mass, dying and becoming disintegrated as they pass beyond the zone of safety into the poisoned area. Such quantities of them appear, however, that the proteolytic ferments which they produce become suffi-

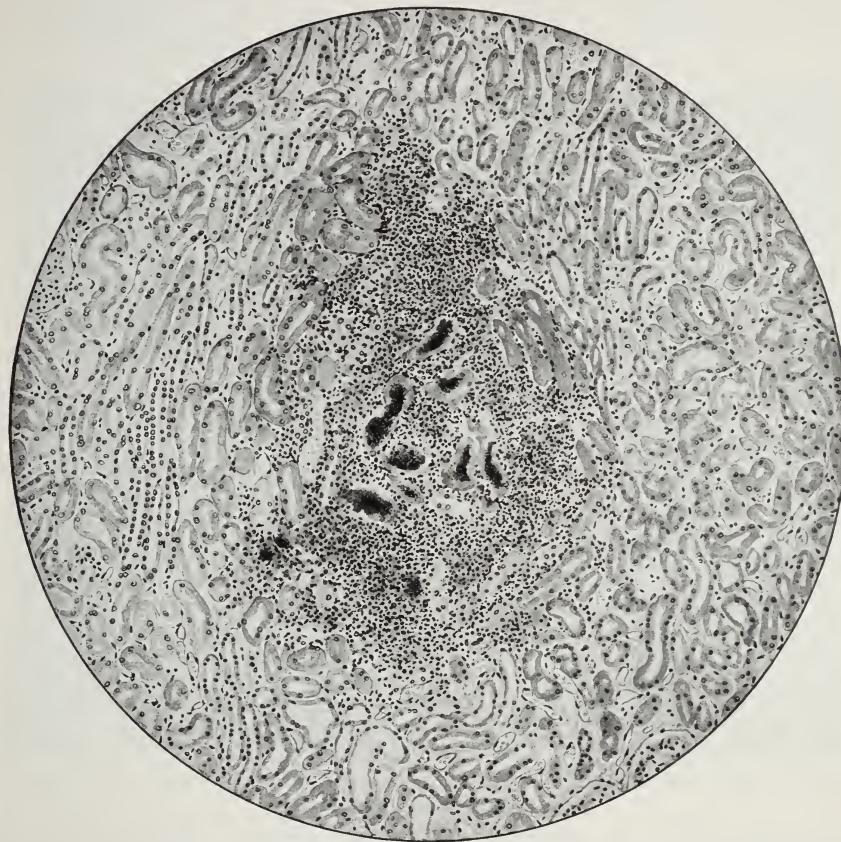


Fig. 119.—Abscess of kidney showing necrosis of tubules, some of which are filled with bacteria.

ciently concentrated to digest the outer portions of the coagulum, so that it comes to lie loose in a cavity surrounded by a thick yellowish fluid filled with intact and partly disintegrated leucocytes (pus). At this stage the remainder of the coagulum, loaded as it is with bacteria, constitutes the core or central plug (Fig. 119), often recognizable when an abscess is incised or when it bursts through the skin. Later the ferment process may succeed in dissolving the whole of it, and the abscess is then merely a cavity filled with pus and surrounded by an

intensely inflamed wall. Further necrosis of this wall may occur, and the abscess increases in size, often in the direction of least resistance, so that the pus seems to burrow its way along natural lines of division of the tissue. It is reabsorbed only with difficulty, and unless it is evacuated by the surgeon or bursts its way to a free surface or into the lumen of some hollow organ, it remains *in situ* for a long time and is gradually inspissated and thickened. In this case, and indeed in all abscesses which persist for a long time, even when they have been opened, a thick layer of granulation tissue springs up to line the cavity and to encapsulate the remainder of the pus, or more frequently to obliterate the cavity. This granulation tissue is exceptionally thickly

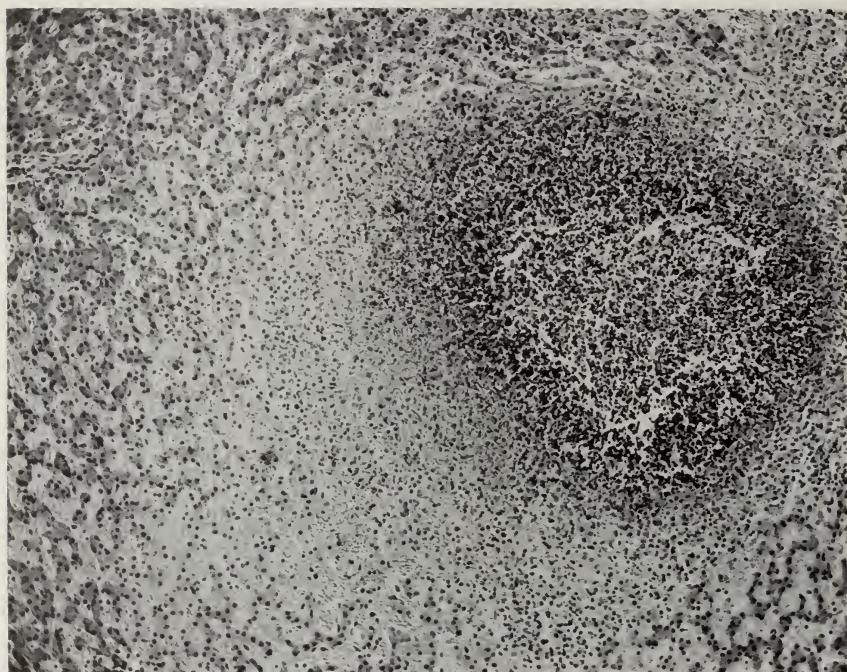


Fig. 120.—Abscess in the liver. There are many small clumps of bacteria closely approached by the leucocytes.

infiltrated with leucocytes, and shows the presence of many large, mononuclear wandering cells, which become larger as they approach the surface of the granulations. Here they exhibit their voracious phagocytic characters, loading themselves with the débris of injured and dead cells, and usually containing many large fat-droplets (Fig. 95).

When bacteria and dead tissue are quite removed, as when an abscess is opened and thoroughly cleansed, healing proceeds rapidly and the granulation tissue later forms a dense scar.

Abscesses arise at the point where direct introduction of the bacteria from without takes place, or else they appear, often in numbers, through the transportation of infected emboli from some focus of in-

fection in another part of the body. These emboli may consist practically of masses of bacteria, and while the flooding of the circulating blood with organisms of this sort is known as septicaemia, the condition which we are discussing is often called pyæmia.

Abscesses from direct introduction of bacteria are often seen in the skin, where they are called boils or furuncles, or, when very large, with several communicating centres of infection, carbuncles. Most often the organisms are rubbed into a hair-follicle by a chafing collar, or in some similar way, hence their great frequency on the back of the neck or on the buttocks. Frequently, too, they are seen about the nose or lips. The course of such abscesses is modified by the thickness of the skin and the obstruction to their breaking through. Thus an abscess within the red line of the lip readily ruptures and is cured, while one which

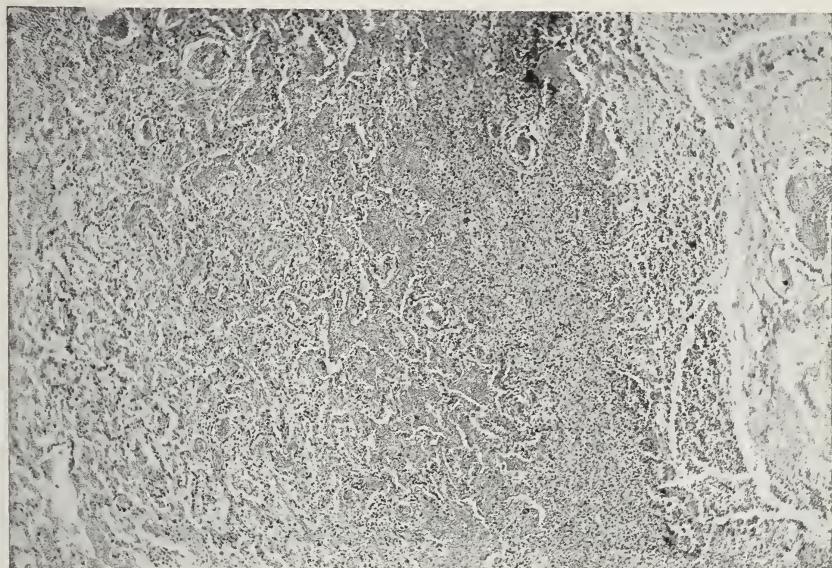


Fig. 121.—Abscess of lung.

arises a few millimetres away, in the thick skin, may be much more extensive and last much longer.

In some persons whose resistance is lowered by any one of the many things which seem to have that effect, such as overwork, unsanitary surroundings, or wasting diseases (among which are other infections, such as typhoid fever), a whole series of boils may make their appearance—one is no sooner healed than another appears. In these cases it seems that the skin becomes smeared with the bacteria, which readily find the opportunity to lodge in hair-follicles or sebaceous glands and to form abscesses. From the fact that bacteria of a pyogenic character are normally present in the superficial layers of the skin it appears that the matter of resistance is of the greatest importance. When a number of hair-follicles become infected side by side with the staphylococcus,

a most extensive necrosis of the skin and underlying tissue may occur (carbuncle), and with the liquefaction of each focus of dead material a perfect honeycomb of communicating passages filled with pus may be formed.

Such, in brief, are the circumscribed abscesses. As the result of pyæmic distribution of emboli or cocci they appear in the lungs, heart, kidneys, or any other organ (Figs. 120, 121). In the lung such a focus, at first very haemorrhagic, is soon found to have a gray, solid, or rapidly liquefying centre, surrounded on all sides by a barrier zone of haemorrhagic pneumonic consolidation, outside of which the lung is oedematous. Such abscesses seem to reach a considerable size before coming into communication with a bronchus. Frequently confluent with one another, their origin may generally be traced by finding a whole colony of cocci lodged like an injection mass in the lumen of a central blood-vessel. So, too, the embolus may be found in the blood-vessel in the centre of those deeply haemorrhagic abscesses sometimes found in the submucosa of the small intestine. Rupture of such abscesses through the mucosa leaves a ragged ulcer which heals by granulation.

While there is thus a great similarity in the mode of formation of abscesses wherever they occur, it must be recognized that the feature which they have in common is the concentration of the whole effect, which not only allows the bacteria to kill tissue which might resist a less concerted attack, but also allows the inflammatory exudate (perhaps aided slightly by the ferments of the bacteria themselves) to digest and liquefy that necrotic tissue.

Phlegmons.—When the bacteria are spread quickly throughout a considerable area of tissue, as often happens in the loose tissues of the neck after invasion from suppurative processes in teeth, salivary glands, or mouth cavity, there is nowhere sufficient concentration to produce the effects seen in an abscess. The tissue is not all dead, and the exudate is so spread out that no liquefaction takes place. Such an intense diffuse inflammation may be called a phlegmon, and so dense and hard may the affected tissue become that the phlegmons of the neck are often called ligneous or woody inflammations.

DIPHTHERITIC INFLAMMATION

On any mucosa the invasion of bacteria or the destruction produced by a chemical irritant may cause a peculiarly intense inflammatory reaction, usually haemorrhagic, and different from the milder forms in that the necrotic surface layer is welded together with the fibrinous exudate into a membrane-like film. This is well seen in the mucosa of the intestine when bacteria of the dysentery group invade it, or when, at the end of a long illness, streptococci or other organisms from the intestinal lumen attack it. Perhaps the most striking changes of this sort are produced in cases of poisoning with bichloride of mercury, possibly because the corrosive salt is excreted again into the colon.

In the early stage of any of these cases it is found, on stretching out the wall of the intestine, that certain parts of the mucosa are covered

with a grayish or bile-stained, opaque, rough substance which may be scraped off, showing beneath it a raw surface (Fig. 122). Such patches are bordered or separated by mucosa, which is soft and velvety, but swollen and deeply haemorrhagic. The distribution of the chaff-like exudate in the small intestine is primarily along the crests of the transverse folds or valvulae—in the colon, where it is far more commonly found, it is in patches, inasmuch as the intestine, in its contracted state, exposes only a part of its mucosa to the lumen. The rest is hidden in the depths of the folds, and less constantly exposed to the intestinal contents. Perhaps this is inconsistent with accepted ideas of the normal relation between the intestinal mucosa and intestinal contents, but the appearance of the inflamed intestine imposes such an explanation upon one, and it is easily conceivable that the presence of a sharply ir-



Fig. 122.—Diphtheritic enteritis. The inflamed and partly necrotic mucosa is covered with a tenacious layer of exudate.

ritating substance might keep the walls at their maximum contraction. Thus, in addition to transverse or circular bands of exudate, there are three longitudinal streaks which correspond with the part of the mucosa thrown into relief by the longitudinal muscle-bands.

Microscopically, it is found that the superficial part of the affected mucosa is completely necrotic and sharply marked off from the underlying tissue, which is intensely inflamed (Fig. 123). Continuous with it, and overlying it, is a layer of matted fibrin filaments which can be traced through the dead tissue. Through both parts of this dead layer, which constitutes the false membrane, remnants of leucocytes are to be found, with many signs of haemorrhage, and in the tissue beneath and about the site of the pseudomembrane there is an exudate extremely rich in red corpuscles, leucocytes, and fibrin. All this is often par-

ticularly well seen in the stomach after intense corrosive poisons have been swallowed.

Later the oedematous and hyperaemic parts of the mucosa between the lines and patches of intensest injury become involved in the same process if the condition progresses and does not heal. The older sites of injury may then discharge the dead tissue into the intestine, and present themselves as ulcerations which may go deep into the intestinal

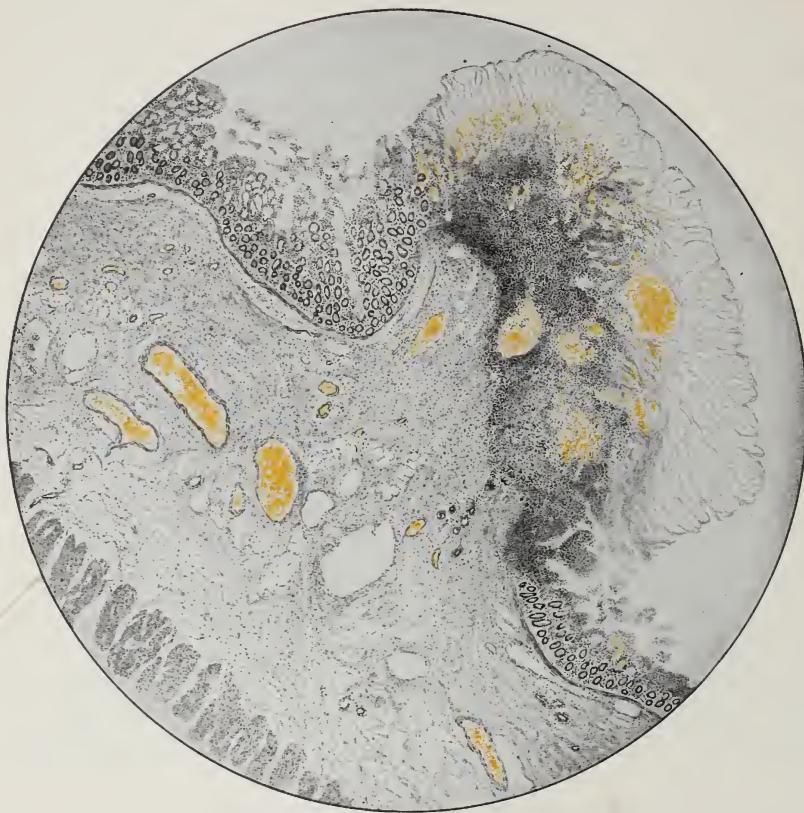


Fig. 123.—Diphtheritic enteritis. The crest of the fold of mucosa is necrotic, haemorrhagic, and intensely inflamed.

wall. Such ulcers are found especially in the colon, and are characteristic of the more chronic forms of dysentery. They may arise, too, when there is an obstruction of the intestine, so that its contents accumulate above and remain a long time in the dilated upper part of the loop. Probably this dilatation, with its stretching of the wall and narrowing of the blood-supply, may be a contributory cause of the ulceration.

CHAPTER XV

INJURY WITH INFLAMMATORY REACTION AND ATTEMPTED REPAIR.—NEPHRITIS

Nephritis: General nature. Relation of anatomical changes to functional disturbances. Nephrosis. Acute and subacute nephritis. Acute interstitial nephritis. Tubular nephritis. Chronic glomerulo-nephritis. Chronic arteriolosclerotic nephritis. Functional derangements resulting from these.

NEPHRITIS

THE kidney, as one of the chief paths of excretion, is called upon to deal with the waste products of the body and, in some cases, with poisons or with bacteria. In this sense it would seem it be rather exceptionally exposed to injury, even if we disregard such special injuries as are caused by obstruction in the urinary tract, with or without infection ascending into the pelvis through the ureter, or by the formation of calculi in the pelvis, or such as are caused by the cutting off of the blood-supply by occlusion of the blood-vessels. Indeed, in the ordinary course of autopsies the kidneys of most elderly and old people show some scars from old injuries, although these have been completely healed, and the remaining kidney substance has been able, perhaps with some compensatory hypertrophy, to carry on quite well the normal function. Even the loss of one kidney is easily compensated for by the hypertrophy of the other. It is for this reason that in the records of autopsies it is common to find the diagnosis "chronic nephritis" carelessly given when there is no real progressive disease of the kidney. But progressive and severe disease of the kidney, such as to cause great disturbances of its function, is common enough and fatal enough to demand the most intense study. We are, indeed, very ill-informed as to the nature of such affections, for, although we may learn with precision what anatomical changes are brought about in the kidney and other organs, we rarely know the cause. In fact, it is only in the case of a few infections and one or two mineral poisons that we are familiar with the exact effects, and can say with certainty that this was the actual cause of the disease. But in most cases, more especially in the chronic and insidious forms, we have no idea of the cause, nor are we even sure that the symptoms are caused by the disease of the kidney—they may well be the effect of a general disturbance of which the disease of the kidney is also a manifestation. This rather extreme statement is by no means so improbable as it seems, especially with regard to some of the metabolic disturbances, although it is still conservatively believed by most people that the symptoms are the result of the inability of the kidney to rid the body of those substances which accumulate in excess.

Above all it must be realized at this point, that, however precise our ideas as to the anatomical changes found in the kidney at autopsy,

we are quite unable to correlate them with particular derangements of function. Probably such work as that of Aschoff and Suzuki, Baer, and others upon the localization of special function in the different parts of the tubule and in the glomerulus, may one day teach us how to do this, but at present no one can say what part of the kidney is at fault when salt is not excreted, nor even whether the fault is in the kidney or in the muscles and other tissues, nor can anyone say what lesion in the tubule is responsible for the retention of urea or creatinine, nor even why albumen escapes into the urine. And especially it should

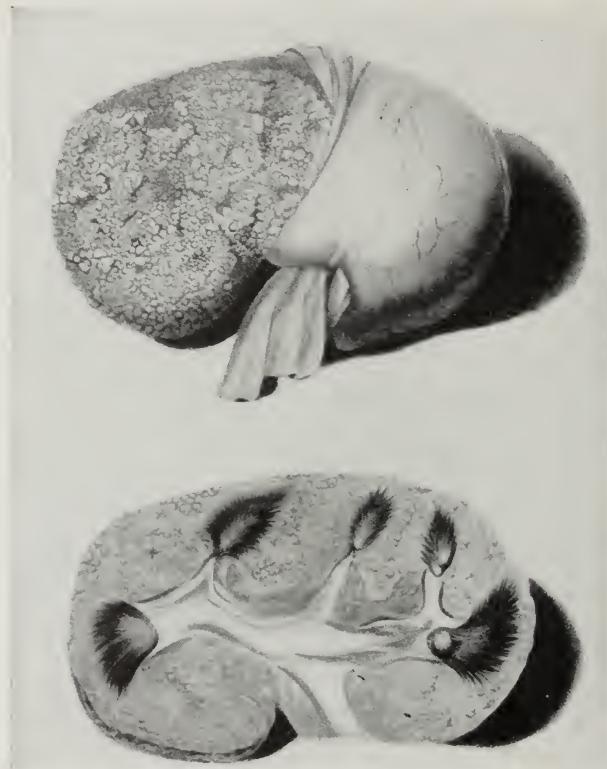


Fig. 124.—Hard, contracted, granular state of kidney connected with secretion of albuminous urine, obstinate anasarca and effusion into cavities. (From "Reports of Medical Cases selected with a view of illustrating the symptoms and cure of diseases by reference to Morbid Anatomy." By Richard Bright, F. R. S., Physician to Guy's Hospital, London, 1827.)

be said that such functional defects are not to be assumed from the appearance of the glomeruli or of the tubules, except in so far as we have grown accustomed to expect a certain set of clinical phenomena when we find a certain collocation of anatomical changes in the kidney. But the diagnosis of clinicians on the basis of the symptoms and even on the chemical study of blood and urine still meet with extraordinary reverses at autopsy—and will, until a most extended study by clinicians in coöperation with pathological anatomists is completed.

In the face of this discouraging outlook we must consider here what is ordinarily found at autopsy in cases in which there is disease of the kidneys. In general we can recognize, on the one hand, acute renal disease occurring usually in the course of some infectious process or as the result of some poisoning, with sudden severe symptoms with which the patient may either die or recover completely without any remaining trace of renal defect, although sometimes, perhaps, with persistence of the exciting cause these pass on into a chronic form. On the other hand, there are cases of chronic nephritis (and these are far more common) in which slight symptoms, gradually increasing in severity over months and years, or repeated attacks with intense symptoms but with remissions, end in profound disturbances which bring about death in the so-called uræmia, or are interrupted by some fatal complication. It is especially in these insidious cases that the question may well arise as to whether this is essentially a disease of the kidney, or primarily a general metabolic disturbance often associated with arterial disease.

The classification of the affections of the kidney is notoriously difficult as might be expected from our state of knowledge, and it seems best to make as few divisions as possible. Such terms as "chronic parenchymatous" and "chronic interstitial nephritis," in the sense in which they were formerly so commonly used to express a predominant visible change in the secreting elements or in the framework of the kidney, we cannot accept because it is clear that in all cases it is the highly specialized vascular and secretory tissue of the kidney which suffers the injury and may be destroyed, after which its place may be taken by scar tissue. It is never primarily the connective-tissue framework that is irritated into growth and contraction so as to destroy the enclosed glomeruli and tubules, as the term "chronic interstitial nephritis" would suggest. Weigert made the point that in acute and chronic forms of nephritis, apart from such local affections as abscesses or infarcts or tubercles in the kidney, the process is a diffuse one and affects both kidneys alike and, in some degree, all the elements of both kidneys. This is in the main quite true, but it will be seen that there may be a predominant injury to certain parts of the tubular epithelium or to the glomerulus, and even that these may occur in a patchy way, affecting seriously some areas or perhaps some tubules while others escape. Possibly this may be due to the fact, pointed out by Richards, that some glomeruli are collapsed and quiescent, while others are expanded to receive the full current of blood, and similarly it might be expected that the tubules from quiescent glomeruli would be inactive since they would receive little blood at that time. Of course, this period of quiescence is presumably short, but it is perhaps conceivable that it might tide over the period in which an injurious agent was thrown into the kidney.

Nor shall we use such terms as "secondarily contracted kidney," meaning the change which persists after an acute or subacute process of infectious or toxic origin, or "primary or genuine contracted kidney," meaning the arteriosclerotic type, although these terms are in constant use in the literature and especially in the writings of German authors.

Such terms as "large white kidney," "small red kidney" have long been abandoned, although they give a rough idea of the gross appearance of the organ. Indeed it is very difficult to exchange the generally accepted names for anything more rational since our knowledge is so fragmentary, but it must be kept in mind that if we speak of acute or chronic glomerulo-nephritis which would suggest the exclusive or even the primary involvement of the glomeruli, it is in the full recognition of the fact that this is only because the lesions of the glomeruli are conspicuous and the first to attract one's attention. It is quite well known that the tubular epithelium and other parts of the kidney are also affected. So, too, if we speak of arteriolosclerotic nephritis, it is again because such changes in the arterioles are a striking feature but not that we know with any certainty that the arterial changes are the cause of the lesions in every other constituent of the kidney. With this in mind we shall discuss acute and subacute nephritis, including the so-called lipoid nephrosis, and later the more chronic forms of glomerulonephritis, after which come those slowly developed types in which the arteries and arterioles are so much affected.

The kidney normally serves by a complex mechanism to remove from the circulation water, inorganic substances such as salt, calcium, phosphorus, etc., and various non-protein nitrogenous products of metabolism. The mechanism in spite of all the careful and ingenious studies since the pioneer work of Ludwig, seems even yet to be incompletely understood but the student is referred to the papers of Marshall, Richards and others for a discussion of this. At any rate, the activities of the kidney are under control so that its excretory function as far as these substances are concerned is regulated to correspond with the needs of the body. Therefore, in studying the contents of the urine there should always be a precise comparison with the contents of the circulating blood plasma. Gross abnormalities, such as the excretion of protein, are due to injury of the specific filtering apparatus which makes it incompetent to prevent, as it normally does, the passage of such materials from the blood while the retention of an excess of non-protein nitrogenous materials which should be excreted, seems to result from such intense injury as limits the power of the kidney. But such vague statements hardly explain the specialized disabilities of the organ, nor the retention of some substances while others are allowed free passage.

The injuries which we can recognize are most often in our experience caused by poisonous substances, even when these, acting slowly, appear to affect especially the blood-vessels, narrowing them and limiting the nutrition of the renal tissue. The acuter injuries are apparently most often caused by the toxins produced by certain bacteria as emphasized recently by Blackman. Of these the streptococci, pneumococci and staphylococci are most prominent and it is only through the work of the last few years that the formation and destructive effect of toxins from these organisms has been recognized. Naturally, these bacteria can also be carried about in the circulation and pass through the glomeruli of the kidney, and Löhlein has supported the idea that in the nephritis associated with streptococcal endocarditis the lesions are em-

bolic. This may well be true in certain cases in which extreme lesions are found in a few glomeruli but when all the glomeruli are moderately affected, it appears more reasonable to ascribe the changes to the toxins, which were demonstrated by Rich and Bumstead, rather than to the bacteria which are hurried through their capillaries. Even when bacteria are found in numbers in the capillaries, care must be taken to exclude the possibility of their having multiplied there after the death of the patient when the autopsy is delayed.

Much more convincing, however, is the fact that all the characteristic lesions have been produced experimentally by the injection of the toxin alone with complete exclusion of bacteria. This has been done with the toxin of the pneumococcus by Blackman, and with the toxin extracted from the *Staphylococcus aureus* by Rigdon and his co-workers, and Von Glahn and Weld. It is remarkable that the instances of acute nephritis associated with infection are very often the consequence not of an extensive lesion such as lobar pneumonia, erysipelas, etc., with intense inflammatory reaction, but of some localized or limited infection where it seems that the toxin is produced and absorbed into the circulation. It is surprising to find in contrast with our long-held impression that in the cases of infection with the *Streptococcus viridans* which last for months and produce endocarditis and general septicæmia, the involvement of the kidneys is not always conspicuous although the most extreme changes are found in many cases. In 58 cases with endocarditis of this origin which we have studied recently, there was a record of nephritis in 27. Other organisms are responsible for renal changes and no doubt a toxin from haemolytic streptococci will shortly be demonstrated in the cases in which it is active. Virus diseases have so far played relatively little part.

Poisons of inorganic nature can, of course, injure the kidney and bichloride of mercury is most familiar in its destructive action on the epithelium of the tubules. Various poisonous substances such as uranium nitrate, chromium salts, cantharidin, diphtheria toxin, etc., have been used in experimental studies of nephritis but they are not likely to be taken into the human body in poisonous doses.

Clinically, severe injury to the kidney is recognized by changes in the urine and in the blood. The urine is decreased in amount, darker in color, and of high specific gravity and contains albumen and globulin, and sometimes blood and casts or moulds of the tubules formed by hyaline, albuminous material. The urea clearance, or power of removing urea from the blood, and similarly the excretion of creatinine, uric acid, etc., from the blood is changed and the proportion of these substances in the blood becomes abnormal—so, too, with chlorides and other inorganic materials although the exchange in these is very variable. Evidences of intoxication of an indefinite character come on later. It has long been known as uremia but its exact nature is not even yet understood. Oedema of the tissues is frequent and for this, too, various explanations have been offered. It may be that the retention of salt is important in this since withdrawal of salt from the diet sometimes reduces the oedema in a striking way, but the loss of albumen

from the blood doubtless changes the osmotic index of the blood as compared with that of the tissues. The damage to tissues in general and to the capillary walls which then allow the escape of fluids and proteins, must also be considered. The student is once more referred to the work of those specially interested, Peters, Van Slyke and others, for a discussion of this difficult subject.

The kidneys in any of these types of poisoning are found at autopsy to be swollen and tense, the surface under the capsule is smooth and usually rather moist and translucent, although with many flecks of yellowish opacity and sprinkled with little haemorrhages (Fig. 131). Such a kidney is pale yellowish-gray with a tinge of rose color, sometimes dark red. On section the cortex is thick, swollen with broad bulging striations which are only much later distorted in their arrangement. Opacities and flecks of hemorrhage occur throughout and sometimes the glomeruli are greatly enlarged and so prominent as to be readily visible to the naked eye, as projecting granules, but this is only



Fig. 125.—Nephrosis in a child of five years. See section, Fig. 126.

after the condition has lasted a considerable time. In still older cases, the kidney tissue becomes distinctly translucent and firmer and the yellow opacities are in sharper contrast. This description applies to the more intense forms and especially to their later stages. There are other cases in which the toxic effect is less marked, in which the kidneys are swollen and opaque yellow, without any obvious haemorrhages. These are generally spoken of as lipoid nephrosis.

Lipoid Nephrosis.—We may begin with the so-called lipoid nephrosis which has been shown by Blackman to be associated with pneumococcus toxin, and in the animal experiments is the result of the slightest or least intense injury by this bacterial toxin. The name is unsuitable and has been used for a great variety of things but it must perhaps still be used so that the literature may be followed.

It is usually found in children and young adults in whom extreme edema or anasarca and albuminuria are associated with no other disturbances of renal function than temporary oliguria, albuminuria, and retention of chlorides. There is slight or no rise in blood pressure.

Albumen is excreted until the albumen-globulin ratio in the blood is reversed. There is microscopical haematuria and some secondary anaemia of haemolytic origin but no marked change in the non-protein nitrogen of the blood.

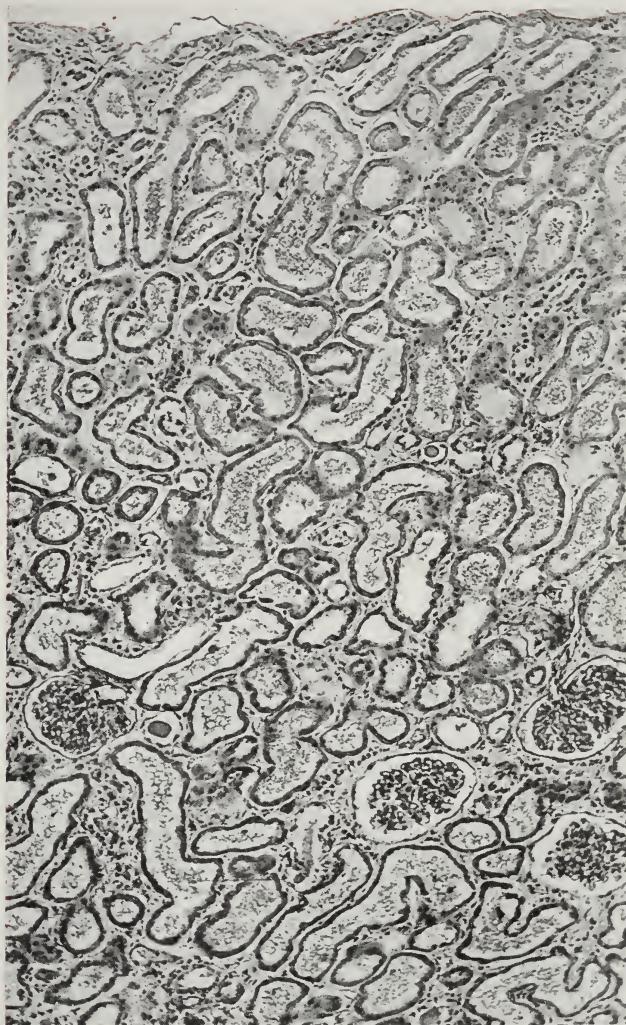


Fig. 126.—Nephrosis showing dilatation of tubules, albuminous content, etc., from same kidney as shown in Fig. 125.

At autopsy one finds the kidney greatly enlarged and pale yellow with swollen pasty or putty-like cortex (Fig. 125). Microscopically the blood-vessels and glomeruli appear normal, but the cortical tubules are widened, the epithelium rather low and full of fat globules, some of which are doubly refractive globules of cholesterol esters (Fig. 126). Fat-globules are also found in the liver and other tissues but this is not



Fig. 127.—Intercapillary glomerulo-nephritis. From a boy age eighteen, showing patent capillaries with intact endothelium.

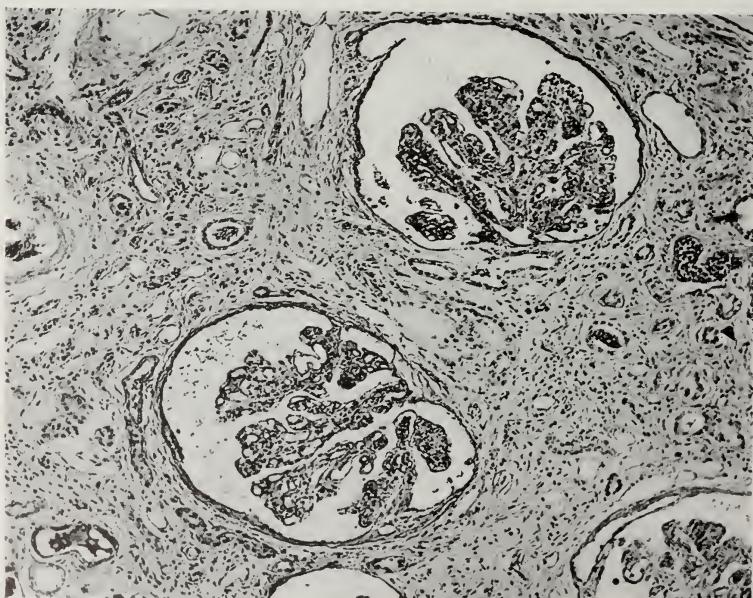


Fig. 128.—Intercapillary glomerulo-nephritis from same case, showing extensive scarring and loss of tubules.

distinctive of this affection. Blackman feels that while this condition can be experimentally produced with small doses of a pneumococcus toxin which in large doses produces a definite acute nephritis, the essential distinction between nephrosis and nephritis depends upon the absence of fibrin coagula and scars within the glomerular capsules in the milder affection, nephrosis. Such clots with organization and scarring destroy the glomeruli and produce renal insufficiency in nephritis but are absent in nephrosis probably because globulin which gives rise to fibrinogen is relatively held back while albumen is excreted.

The pneumococcal infection which is usually localized at first, spreads later and commonly appears in fatal cases as a septicaemia and generalized pneumococcal peritonitis. Such peritonitis may be transient, and one child in the series had five attacks of acute peritonitis. Persistent chronic pneumococcal infection of the tonsils or of the middle ear is common. If recovery is incomplete and long postponed, increased globulin excretion occurs and the symptoms pass over into those of a more characteristic nephritis and at autopsy glomeruli are found scarred, with areas of tubular collapse and scarring of interstitial tissue.

Acute and Subacute Nephritis.—With what appears to be a bacterial intoxication of maximum intensity, acute forms of nephritis occur which may end fatally in a very short time, because of heart failure or generalized infection, and of these we have had a series of cases. Most of these get well without progressive nephritis. This is usually thought to be associated with streptococcal infection but in our cases there has been found a mixture of bacteria, including beta haemolytic streptococci, staphylococci and pneumococci, generally starting from a focal infection in the nasopharynx. Since toxins have been definitely demonstrated so far only from pneumococci and staphylococci, the origin of the toxin from the mixed infection is not established.

The kidneys at autopsy are swollen, reddened and flecked with haemorrhage but microscopically, despite the profound disturbance of function, there is little to be seen except upon careful study of the glomeruli. There, in some glomeruli but not in all, the capillary tufts stand out rather stiffly, the overlying epithelium is a little swollen, but between the basement membrane and the wall of the capillary there is a collection of leucocytes and formless coagulum. The endothelial lining of the capillary is unchanged but the lumen is compressed. In some cases there are beginning adhesions with the capsule or new formation of epithelial cells, and the tubular epithelium shows moderate changes with haemorrhages and fibrin in the lumen.

More slowly developed renal changes in cases of bacterial infection show the more familiar picture of acute, or rather subacute glomerulonephritis. In the glomeruli the simplest change is the formation of fibrin clots filling and obstructing the capillaries. Closely related is the obstruction of the capillaries by coalescent masses of red corpuscles, probably together with fibrin, which form hyaline pink-staining plugs and distend the capillary loop into a rigid projection from the rest of the tuft (Fig. 130). Bacteria are hardly to be found even in septicaemia, unless the autopsy has been so delayed that colonies have grown

there after death. There follows upon the obstruction of the capillary loop a further inflammatory process, usually with haemorrhage into the capsule and thus into the tubule, and with exudation of leucocytes with the coagulable fluid (Fig. 130). The clot formed from this sometimes acts at once as a plug in the entrance to the tubule, thus completing its isolation from the glomerulus. The epithelial cells covering the capillary loops are injured and some may be desquamated. Adhesions are formed between the rigid obstructed capillary loop and the capsule and, as in similar adhesions in the peritoneum, the epithelial cells grow and become

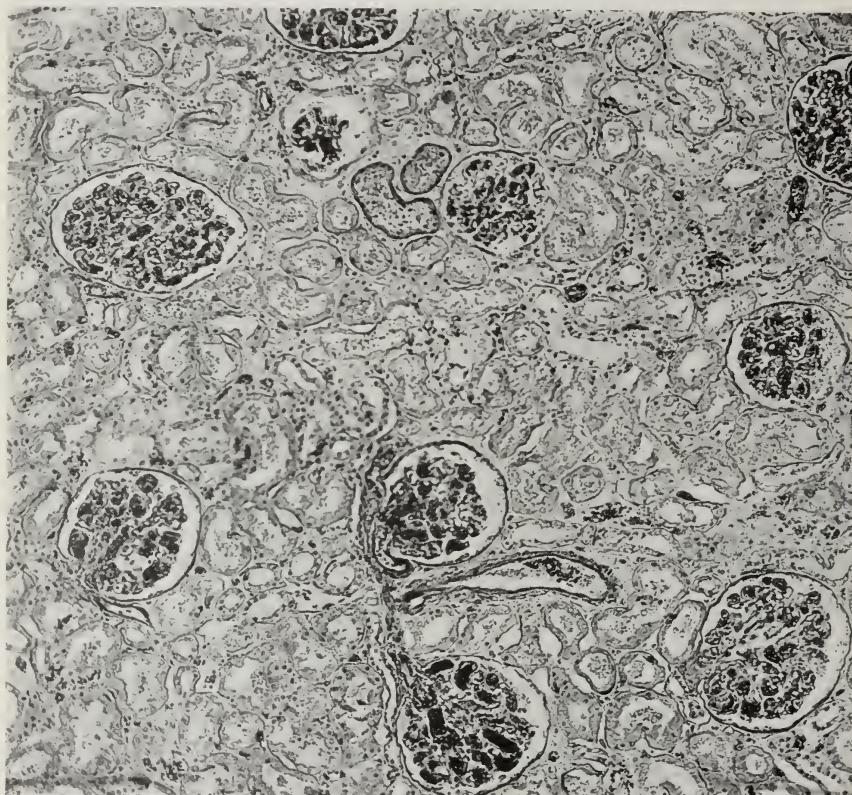


Fig. 129.—Acute nephritis. Hyaline fibrinous thrombi in glomerular capillaries.

continuous from capsule to tuft. So, also, a clot formed in the capsular space may be enveloped by epithelial cells (Fig. 132). Indeed, it seems that the epithelium is commonly stimulated to growth so that adhesions are quickly clothed by it and it even throws up folds with supporting central connective tissue, the coalescence of these folds forming a labyrinth of spaces which constitutes the so-called crescent (Fig. 133). This is by no means a mass of desquamated epithelial cells, as was formerly thought, but a new-formed network of tissue through which the lumen of the capsule is still continuous with that of the tubule, although this tissue occupies so much space (Fig. 134).

In some cases of subacute nephritis, and in many more of longer duration, or chronic forms, there arise changes in the capillary loops of the glomerular tufts which convert them into solid looking club-shaped masses in which the capillaries as seen in the section are pressed out to the periphery beneath the epithelium by the new formation of material in the central part of the loop and greatly narrowed thereby, although they are still patent and show no changes in their endothelium. This is the type long known as intracapillary glomerulo-nephritis and ordinarily explained as the result of proliferation of the endothelial cells. But, with stains which mark out sharply the basement membrane of the epithelium which covers the tuft—a membrane which is continuous with that of the capsule and of the tubule—and which stain equally sharply

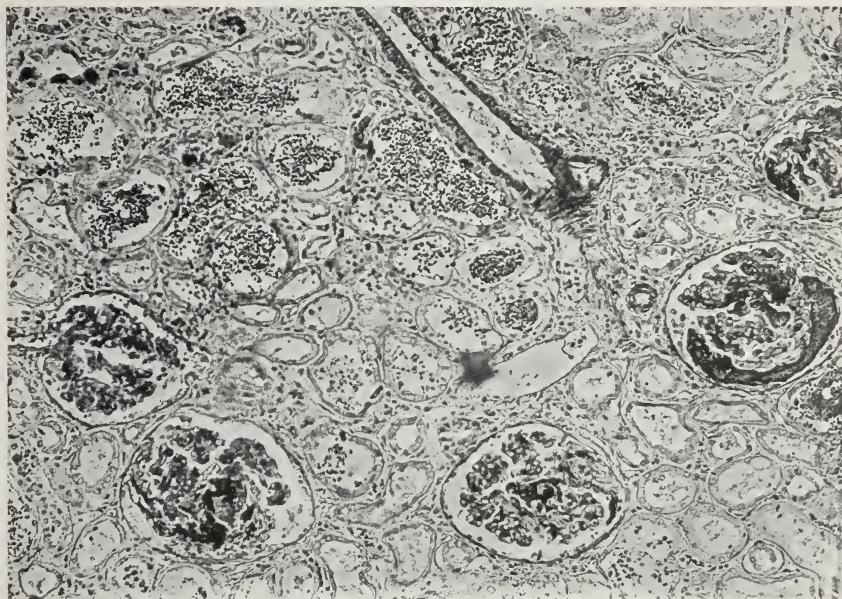


Fig. 130.—Acute nephritis with fibrinous clots in glomeruli and haemorrhage in tubules. Colloid droplets in epithelial cells.

the capillary wall, it is easily seen that the new material surrounds the capillary and separates it from the basement membrane although it is in much greater bulk in the centre of the loop, pressing the capillary outward. In the very acute forms described above, this material appeared as a network with fluid and some leucocytes. Later this appears to become hyaline and stains brightly with eosin, and still later the few connective-tissue cells which are normally present in the glomerular tuft nearer the stalk, proliferate to extend into this formless material between the capillaries so that finally the club-shaped mass which was the delicate capillary loop, is mainly composed of dense connective tissue in which the still patent capillaries occupy a marginal position (Figs. 127, 128). In the chronic cases where this has existed for

a long time, a network of reticulum is found there, branching between the capillaries and easily made evident by the special stains which bring it out in black threads (Fig. 148). This seems to prove finally the connective-tissue character of the intercapillary material and we prefer, therefore, to speak of this as intercapillary glomerulo-nephritis. But in some of the more chronic forms, as described later, it seems that the same end-result is produced by the extension of the peculiar hyaline material which occurs in the walls of the entering arterioles in arteriolosclerosis, with later

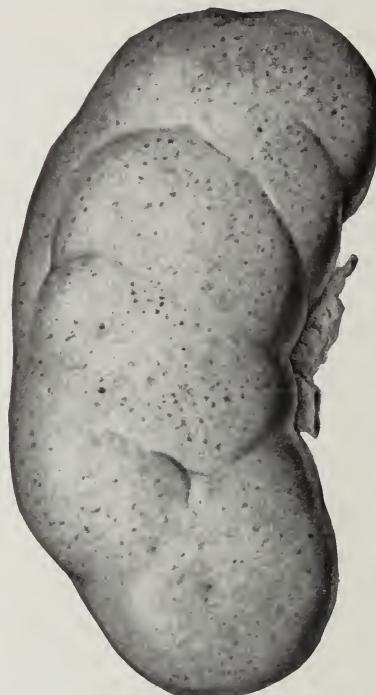


Fig. 131.—Acute and subacute nephritis, showing punctiform haemorrhages and opaque yellow flecks which are produced by the degenerated epithelium.

replacement by connective tissue. Here, however, in acute and chronic glomerulo-nephritis we have an early stage with outpouring of fluid with occasional leucocytes and coagulation which ends in a formless hyaline material later to be replaced by tissue growth. The essential point is that it is not as we have always thought a proliferation of the capillary endothelium, but a compression of the capillaries from outside—an intercapillary instead of intracapillary process.

LITERATURE

- Blackman: Bull. Johns Hopkins Hosp., 1934, lv, 1, 85; 1935, lvii, 70.
de Wesselow: Lancet, 1934, ii, 579.
Govaerts: Paris Medical, 1934, ii, 305.
Harvey: Proc. N. Y. Path. Soc., 1912, xii, 154.
Leiter: Medicine, 1931, x, 135.
MacCallum: Bull. Johns Hopkins Hosp., 1934, lv, 416.
Rigdon and others: Amer. Jour. Path., 1934, x, 424; Arch. of Path., 1935, xx, 201.
Von Glahn and Weld: Jour. Exp. Med., 1935, lxi, 1.

Such changes in the glomerulus may obstruct the course of the blood which forms part of the supply of the corresponding tubule, the rest coming directly from branches of the arteriolæ rectæ. The fluid which ordinarily pours into the lumen of the tubule is also modified, and



Fig. 132.—Glomerulus with blood-clot adherent to capsular wall.

either greatly decreased or completely stopped. Whatever reaches the tubule is changed in character and contains blood and leucocytes or is at least loaded with coagulable albuminous material. From these elements hyaline casts or moulds of the tubules, partly derived from débris of injured tubular epithelial cells, are readily formed and slip down the tubules, threatening their obstruction.

The tubules, like the glomerular capsule, may contain blood, leucocytes, coagulated albumen, and disintegrated epithelial cells (Fig. 130). Their own epithelial cells suffer every degree of injury, and are often completely destroyed and desquamated. The obstruction of the glomerular circulation must interfere greatly with their nutrition, but still one finds them in most cases alive, although swollen and loaded with fat or with colloid droplets which stain like fibrin (Fig. 45). At times one may even find them in mitosis. But in the end they are largely destroyed, for the tubule from a diseased glomerulus loses its normal appearance with most of its epithelial cells, contracts and atrophies, and disappears.



Fig. 133.—Proliferation of capsular epithelium in contiguous folds.

The interstitial framework of the kidney is usually oedematous and may be infiltrated with leucocytes and other wandering cells. As glomeruli and tubules are destroyed, connective tissue increases about the place they occupy and, at a late stage, remnants of such glomeruli and tubules are recognizable for a long time in a scarred area.

Still another type is found in those cases also chiefly seen in children and young adults, in which, without very characteristic symptoms or with symptoms confused by associated changes of other sorts, the kidney is found at autopsy not greatly changed in appearance, but clouded with grayish areas on section, especially in the lower levels of the cortex and in the pyramids. Microscopically these kidneys show

no glomerular or tubular alterations in general, but the clouded areas are those in which the tubules are widely separated by accumulations of mononuclear wandering cells, with a few leucocytes and eosinophiles. Generally some necrotic tubular débris or even a hyaline or necrotic glomerulus may be found in the centre of such a patch, and one has the impression that this *acute interstitial nephritis* (Fig. 135), which has been described as common in epidemics of diphtheria and in scarlatina, is really a reaction to local infection of the kidney.

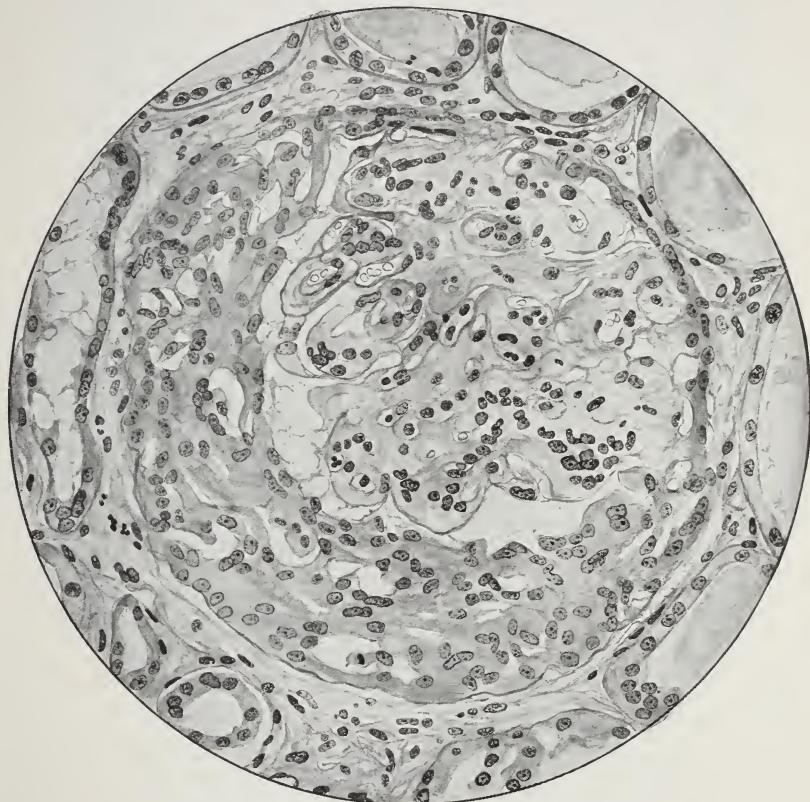


Fig. 134.—Glomerulus with epithelial crescent. The cavities among the epithelial cells communicate with one another.

Much has been written of *tubular nephritis* as distinct from glomerulonephritis and, indeed, certain specific poisons act in such a way as to justify this term, although, in general, Weigert's statement that nephritis is diffuse is usually true. The most familiar example, unless we regard the nephrosis mentioned above as a form of tubular nephritis, is that caused by mercuric bichloride. This poison destroys the epithelium of the convoluted tubules without producing any gross changes in the glomeruli (Fig. 136). If the patient survives long enough such dead cells are found still in the tubules, and calcified and often

encapsulated by newly formed epithelial cells which grow round them (Fig. 53). Death in such cases may come from the direct effects of the poison, or later with uræmic symptoms resulting from the great injury to the kidneys.

Chronic Glomerulo-nephritis.—It has been said that acute nephritis, such as we have described, may end in some cases in complete healing with the return of function to a normal state. Doubtless some glomeruli and tubules are irretrievably lost and shrink into inconspicuous

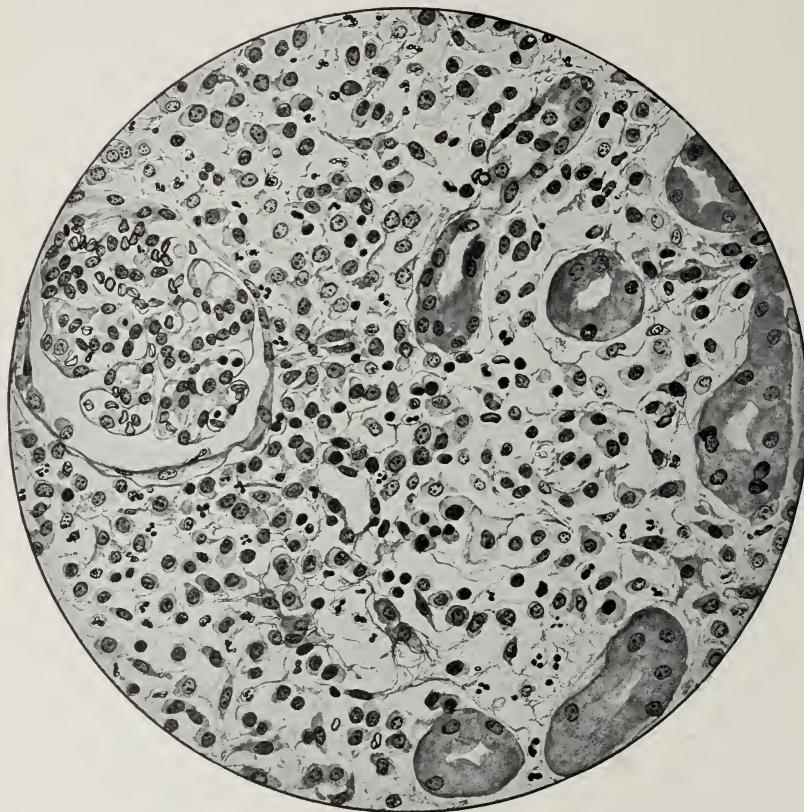


Fig. 135.—Acute interstitial nephritis from a child dying of diphtheria.

scars, while in other tubules there is regeneration of the epithelium and the glomerulus is either uninjured or heals in such a way as to resume its normal function. Unaffected glomeruli and tubules may compensate for those injured during the attack, and the patient is apparently well and suffers no recurrence. But in other cases symptoms persist and increase in severity, especially assuming forms more familiar in the chronic types of nephritis.

Indeed, without any history of an attack which could be regarded as acute nephritis, or more commonly after several severe attacks with

intervening periods of fairly good health, the persisting symptoms increase in severity with headache, nausea, vomiting, dimness of vision or transient blindness, until with increasing oedema and drowsiness there

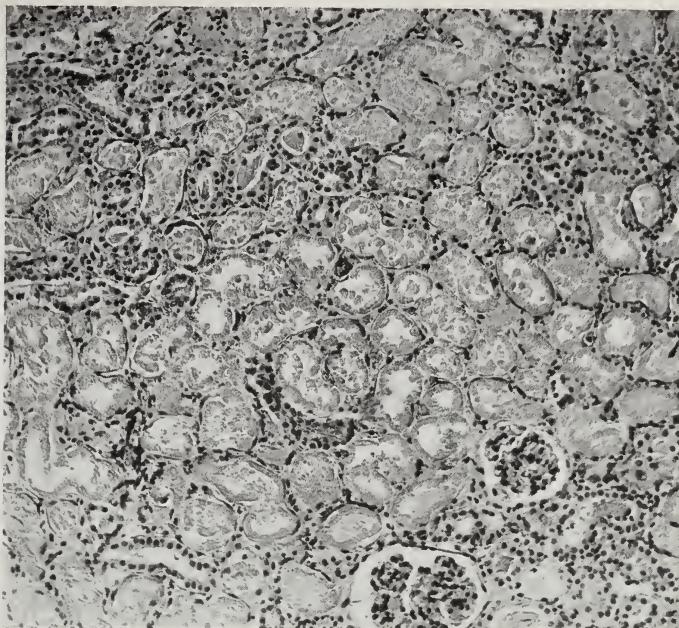


Fig. 136.—Destruction of tubular epithelium caused by poisoning with mercury bichloride.



Fig. 137.—Chronic glomerulo-nephritis. Very fine scarring obliterates the lobulation on the surface. There are a few minute ecchymoses.

appear profound nervous disturbances with convulsions and coma which are spoken of as uremia. Examination of the urine reveals albumen and casts, and a chemical study of the blood shows the retention of

those substances already mentioned. A disproportion between their concentration in the blood and in the urine shows the inability of the kidney to excrete them normally.



Fig. 138.—Section of same kidney. Cortical striations slightly distorted and opaque. Although the kidney appears but little altered from normal, this was a typical chronic glomerulo-nephritis causing uræmia and death.

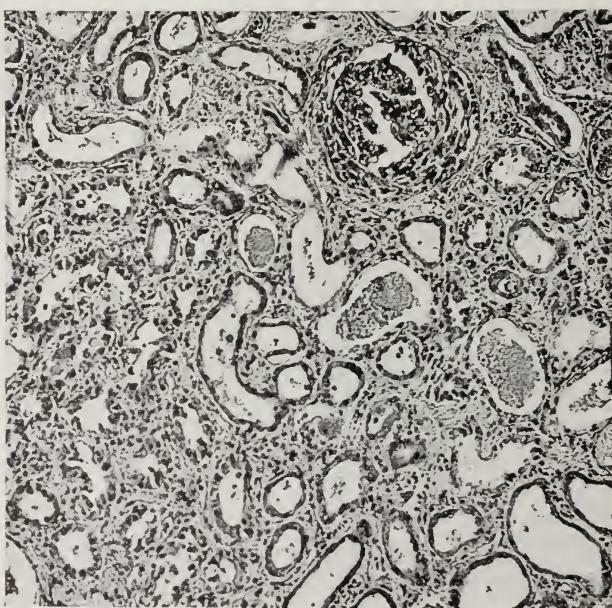


Fig. 139.—Chronic glomerulo-nephritis. A section from the kidney shown in Figs. 137, 138.

At autopsy the kidneys are found sometimes smooth and translucent (Figs. 137, 138), in other cases distorted with adherent capsule and rough nodular surface; often they are greatly decreased in size and

evidently scarred and indurated. The projecting nodules are grayish-red and rather opaque, while the intervening sunken parts tend to be rather translucent and show minute blood-vessels in their depths.

Microscopically one finds no recognizable changes in the blood-vessels; even the smallest branches and the arterioles entering the glomeruli are normal. But the glomeruli show in exaggerated form the changes already described in the acute and subacute types except that in most of them the alterations of capillaries and capsular epithelium have progressed much farther (Fig. 139). Capillary tufts are obliterated and hyaline, and the capsule has contracted about them or the whole glomer-

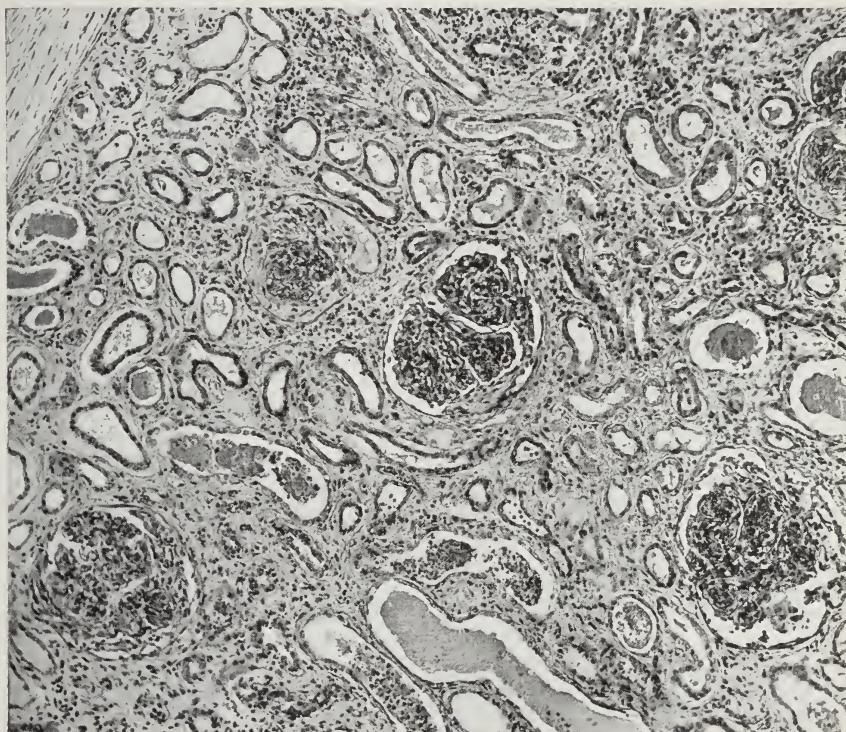


Fig. 140.—Chronic glomerulo-nephritis.

ulus is reduced to a scarred hyaline nodule. Throughout areas of greater or less extent the glomeruli and all the tubules are clearly too far diseased to function properly, if at all, the tubules corresponding with the obstructed glomeruli being greatly contracted and lined only with atrophic remains of epithelium. Between them there is a great deal of fairly dense connective tissue, usually infiltrated with wandering cells. Sometimes this condition is very widespread, but usually there are areas, and these are the nodules which project on the surface, in which some glomeruli and their tubules are relatively well preserved. These glomeruli are larger than normal and the tubules are obviously hypertrophied,

being by actual measurement much longer and at the same time much wider than normal tubules. It is because of their extremely active effort at carrying on in some way the function of the kidney that the patient has remained alive so long, but they in their turn suffer injuries, and the large epithelial cells are often found loaded with globules of fat which is largely composed of doubly refractive cholesterine esters and other lipoids, and with the colloid globules mentioned above which stain like fibrin. Some of these tubules, or perhaps those connected with more seriously injured glomeruli, are greatly dilated with flattened epithelium, and these are usually full of hyaline casts. Such casts are also found in most of the atrophic tubules, often associated with leucocytes and disintegrated epithelium.

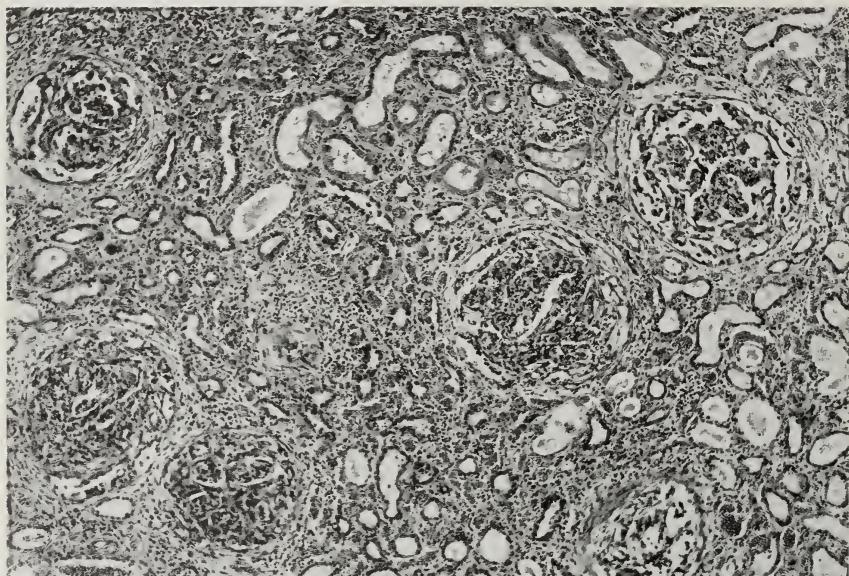


Fig. 141.—Chronic glomerulo-nephritis.

It will be seen that the striking features which distinguish this sort of change in the kidneys from that in the arteriolosclerotic form consist in the absence of arterial thickening and in the prominence of the glomerular alterations, but really, since extreme glomerular changes are also found in the arteriolosclerotic form and the functional disturbances are not very different, it is only fair to say that the distinction is made on the presence or absence of arteriolar sclerosis.

Chronic Arteriolosclerotic Nephritis.—In any long series of autopsies when one studies the cases recorded as nephritis, there are, as has been said above, many nondescript cases in which the symptoms attributable to disease of the kidney were negligible, the patient dying of carcinoma or prostatic hypertrophy or myocardial failure at an advanced age, so that the scarring found at autopsy in the kidney doubtless represents only the remainder of some old injury which has long been healed

and compensated. Even when there has been a history of great hypertension ending in cerebral hemorrhage or some other accident, the kidneys may show no marked alterations. This is only one instance



Fig. 142.—Arteriolosclerotic contracted kidney.

which proves that arterial hypertension is not by any means necessarily the consequence of renal disease. There are many other causes, and we need not look forward in each case to finding chronic nephritis. Indeed,



Fig. 143.—Section of same kidney showing great distortion and atrophy of cortex

when there is arterial hypertension, cardiac hypertrophy and every proof of the existence of chronic nephritis, we may perhaps still ask ourselves whether the arterial hypertension was the cause of the chronic neph-

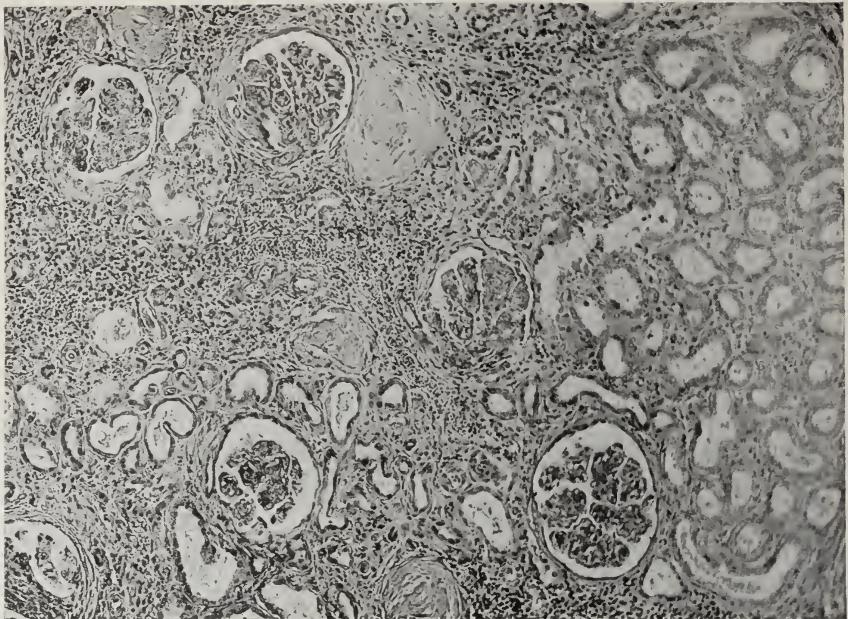


Fig. 144.—Arteriolosclerotic kidney. Section from kidney shown in Figs. 142 and 143.



Fig. 145.—Hyaline changes in arteriole and glomerulus. Arteriolosclerotic nephritis.

ritis or its result, or whether both resulted from some metabolic disturbance, perhaps affecting especially lipoid metabolism.

It is well known that, when a valvular insufficiency or myocardial failure produces a general chronic passive congestion, the function of the kidney is disturbed in such a way that abnormalities of secretion and retention are greatly accentuated.

If we dwell on arteriolosclerotic nephritis and make little or no mention of an arteriosclerotic type it is because the sclerotic changes in the larger branches of the renal artery seem to cause, at most, the destruction of some patches of the kidney cortex, and not the intimate, diffuse change that results from the thickening and narrowing of the minute arterioles. The clinical consequences are accordingly different, and

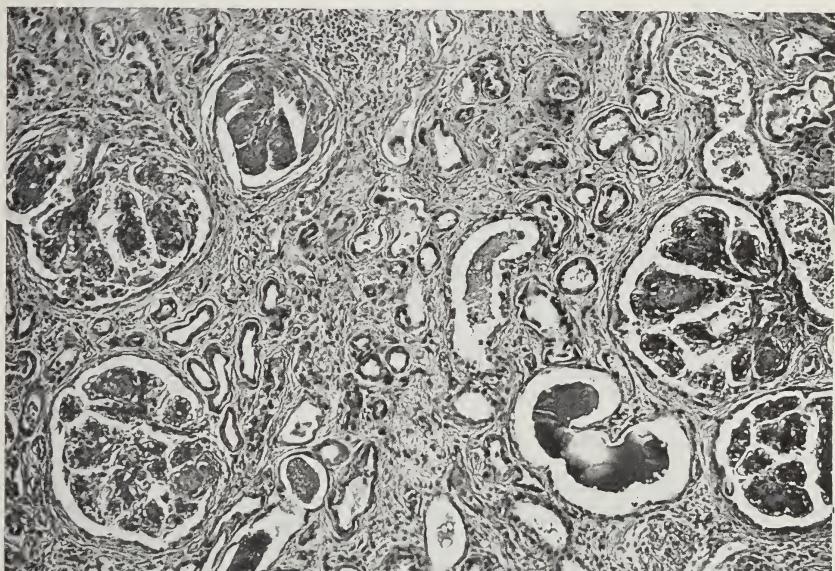


Fig. 146.—Arteriolosclerotic nephritis with intercapillary glomerular changes.

extreme arteriosclerosis, affecting aorta, renals, and their branches need not be accompanied by the disturbances which characterize chronic nephritis. But there are many cases which pursue a clinical course almost monotonously uniform, leading gradually with increasing and often extreme arterial hypertension to uræmic symptoms and death, in which at autopsy the kidneys are found contracted and scarred with or without advanced arteriosclerotic changes in the renal arteries but with hyaline thickening of the arterioles, which narrows their lumen to an extreme degree. The nature of these changes was long ago recognized by Gull and Sutton, who spoke of the condition as arterio-capillary fibrosis, and has been emphasized recently by Löhlein and others.

This is especially an affection of middle age—persons who reach the age of sixty-five or seventy are apparently past the danger—but it may



Fig. 147.—Extreme arteriolosclerotic nephritis with punctate haemorrhages in the cortex.

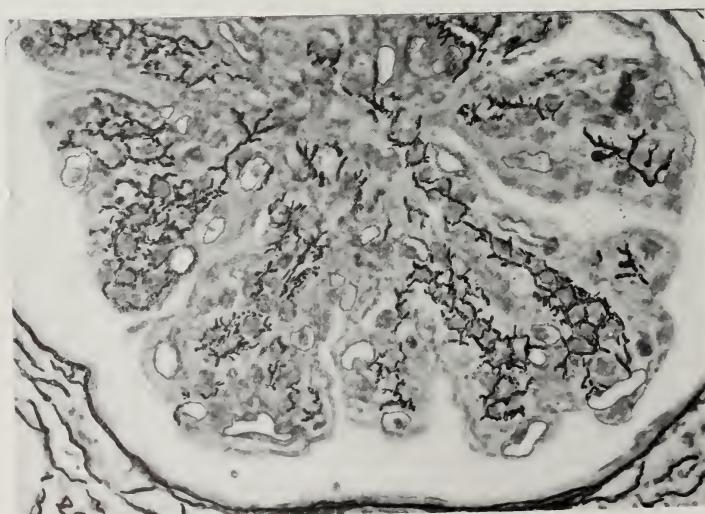


Fig. 148.—Arteriolosclerotic nephritis; glomerulus with intercapillary connective tissue growth with reticulum.

be found in much younger people and, exceptionally, in children. Its course is almost indistinguishable from that of chronic glomerulonephritis, beginning insidiously with slight headache and dyspnea with nocturia. Later there appear gradually anaemia, emaciation, oedema, often with blurring of vision or even blindness. Still later nausea and vomiting, stupor, delirium, convulsions, coma, and death. The blood-pressure is found high, increasing to great heights as the end is approached. Systolic pressures of 250 and diastolic pressure of 150 are common, and the figures may be much higher.

The kidney loses its power to concentrate the solids of the urine and continuously secretes a fluid of low specific gravity (about 1010), clear, without abundant cells or casts, and containing relatively little albumen. The normal variations in amount and specific gravity are lost in this uniform elimination at fixed concentration, and nocturia is evidence that the quantity secreted at night is as great as in the day time. The blood is found to contain increased amounts of non-protein nitrogen, 40 to 60 mg. per 100 c.c. at first, and 200 to 300 mg. or more when uremic symptoms indicate the fatal termination. Creatinine and uric acid are similarly retained. The retention of chlorides varies, and in the later stages inorganic phosphates fail to be excreted, so that a certain acidosis arises. This is made evident by the lowering of the CO₂ combining power of the blood. It is well recognized that these abnormalities, which may have maintained a moderate degree for months or even years, are disproportionately intensified in the last days and weeks of life.

At autopsy one may find the kidneys (Fig. 147) not much decreased in size and fairly smooth. Such kidneys are hard, rather translucent, with indistinct cortical striations showing minute opaque yellow flecks here and there, and with conspicuous thick-walled blood-vessels which stand open. But very often the kidneys are small, rough, nodular and scarred, and, when cut, show that the tissue has shrunken away from the pelvis also, so that the space is filled with adipose tissue—usually fat accumulates about the kidney, too, except in emaciated persons (Figs. 142 and 143).

The cortex is usually much decreased in thickness and the normal striations are so distorted that they cannot be made out. Instead, opaque granules of secreting tissue alternate with grayish-red scarred areas, and these granules, when near the surface, project to produce the roughening. The capsule is more or less adherent, but can often be pulled off easily in spite of the extensive scarring. The blood-vessels are thick-walled and stand open, and even very small ones project roughly on the cut surface.

Under the microscope attention is at once drawn to these vessels. The larger ones show a conspicuous thickening of the intimal layers, often with much reduplication of the elastic lamellæ, and this is even more striking in the smaller arteries entering the cortex and in the arterioles. In the terminal arterioles, however, especially where they enter the glomeruli, all this is obscured by the appearance of a thick intimal layer of hyaline, pink-staining material, which encroaches so much upon the lumen as to reduce it to the tiniest orifice. This hyaline

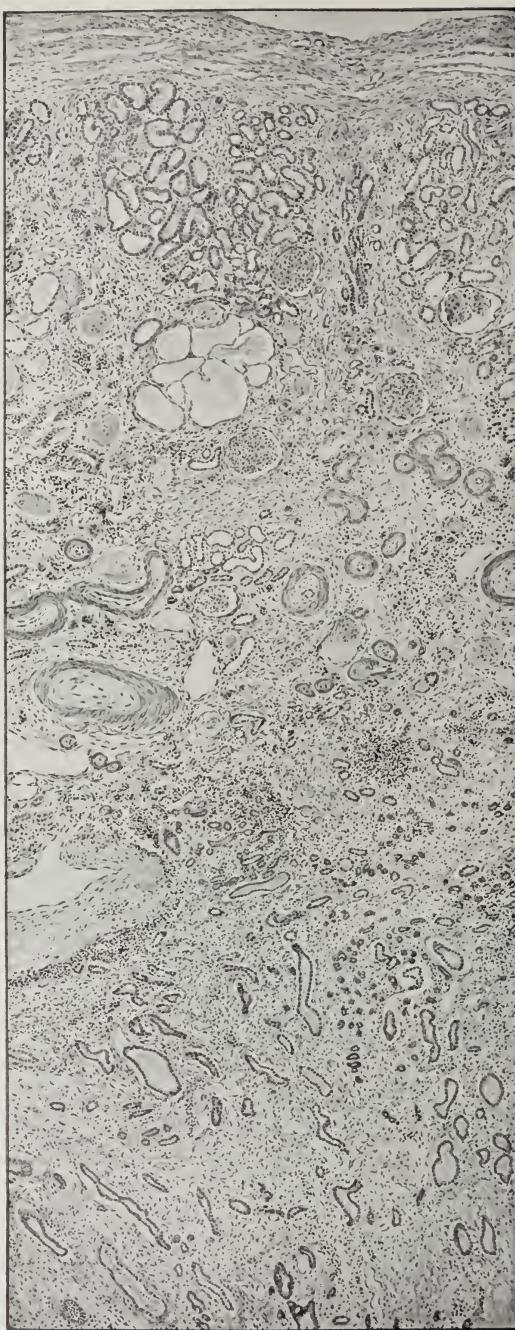


Fig. 149.—Cortex from arteriosclerotic contracted kidney. Narrowed blood-vessels and obliterated glomeruli and tubules are conspicuous. Hypertrophied and dilated tubules are present in groups.

may extend far into the glomerular tuft, and evidently obstructs almost completely the entrance of blood (Fig. 145). Stained with Sudan such

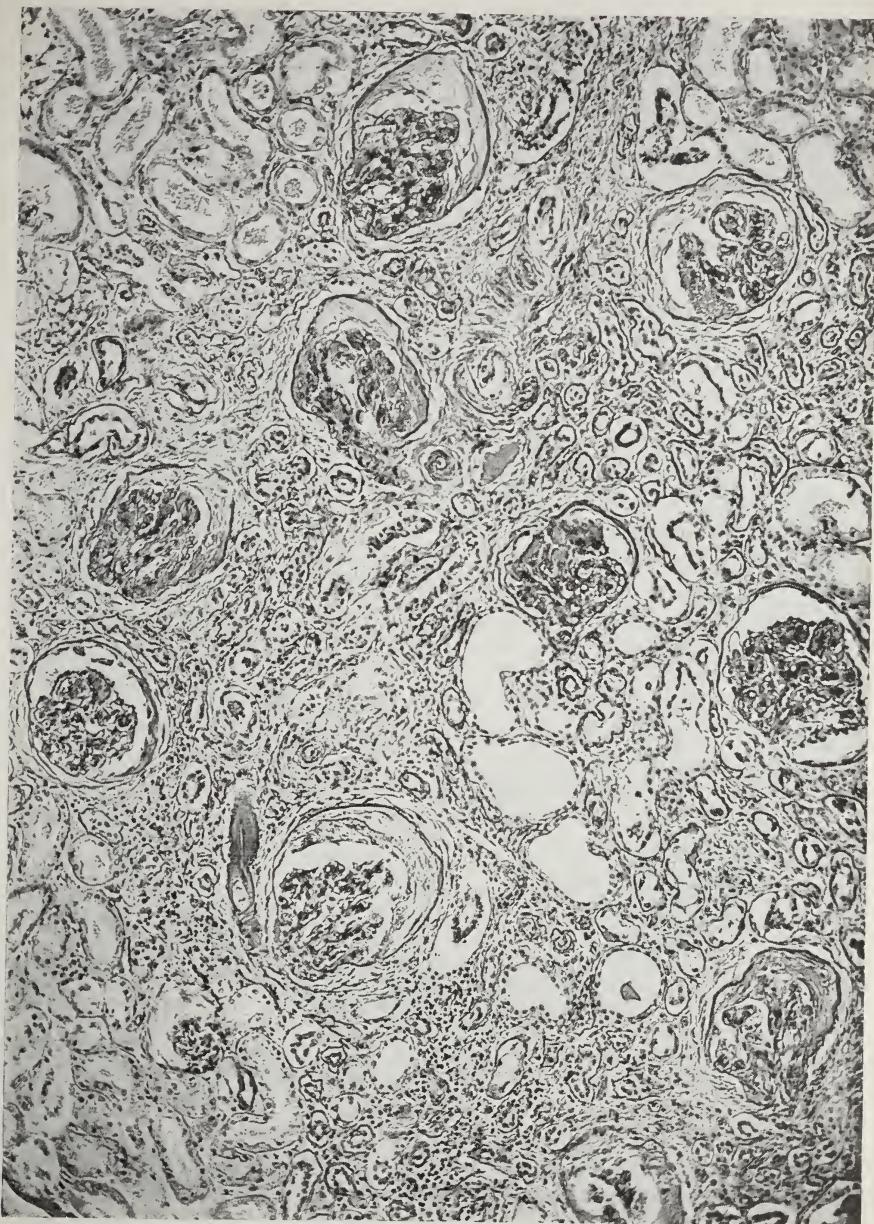


Fig. 150.—Arteriolosclerotic nephritis.

arterioles appear as bright red, thick-walled tubes, the fat being evident in very fine particles. It is in such glomeruli that the intercapil-

lary extension of hyaline material, as is well shown in Fig. 145, compresses the capillaries and forces them into a peripheral position. If there is time, connective tissue growth replaces in large part this hyaline material, as is well shown in these figures. Fusion of the capillary loops may occur so that the epithelium covers the whole mass in a smooth layer. Such glomeruli show various changes (Figs. 150, 151, 152). Usually the capillary tuft is more or less collapsed, and this seems partly due to the obstruction of the blood-flow, partly to changes in the epithelial cells covering the capillaries. These become swollen and filled



Fig. 151.—Glomerulus from arteriolosclerotic kidney. The capillary tuft is converted into a compact mass, smoothly covered with epithelium.

in some cases with colloid droplets and some fat droplets, so that in that state they tend to compress the capillaries, and do this even more when later they fuse into a hyaline material. The parietal epithelium shares this change to some extent, but most striking is the thickening of the glomerular capsule by the formation of a layer of tissue on its inner surface, which stains like connective tissue in contrast with the actual basement membrane of the capsule, and usually includes in its meshes cells laden with fat. Thrombosis of the capillaries of the tuft is often

seen, and most striking is the effect of thrombosis of the efferent vein or venous sinus, for then if the arteriole is not already occluded the capillary tuft becomes hugely distended with blood.

All of these things lead toward the obliteration of the glomerulus, and the end-result is further thickening and contraction of the capsule about the collapsed capillary tuft and the final subsidence of the whole into a hyaline nodule. Fahr has maintained for some years the existence of a particularly severe form of renal disease which he calls "maligne Nephrosklerose" and this has been described at great length and in



Fig. 152.—Late changes in the glomerulus in an arteriolosclerotic kidney. Collapse of tuft with great thickening of Bowman's capsule. Atrophy of adjacent tubules.

detail by Schürmann and MacMahon, but to us it appears to represent only an extreme development of what has been described as arteriolosclerotic nephritis. Corresponding degenerative changes are found in the epithelium of the tubule in which fat globules and colloid droplets appear for a time, after which the cells are desquamated and go to help form casts, while the thickened basement membrane of the tubule, conspicuous for a time, finally collapses and is merged in the scar which forms where tubules and glomeruli are lost (Fig. 149). That not all

the secreting elements are equally disturbed is shown by the small groups of hypertrophied tubules with intact and enlarged glomeruli with unaffected arterioles which are carrying on the whole function of the kidney.

It will be seen from this that the distinction between chronic forms of nephritis requires a microscopic study of the kidney, although the history of the clinical course of the case may enlighten us. Physical examination and chemical studies of blood and urine offer little, so far, with which to make this distinction.

When we consider what is found in all these kidneys it must be evident that many of the changes described in glomeruli and tubules

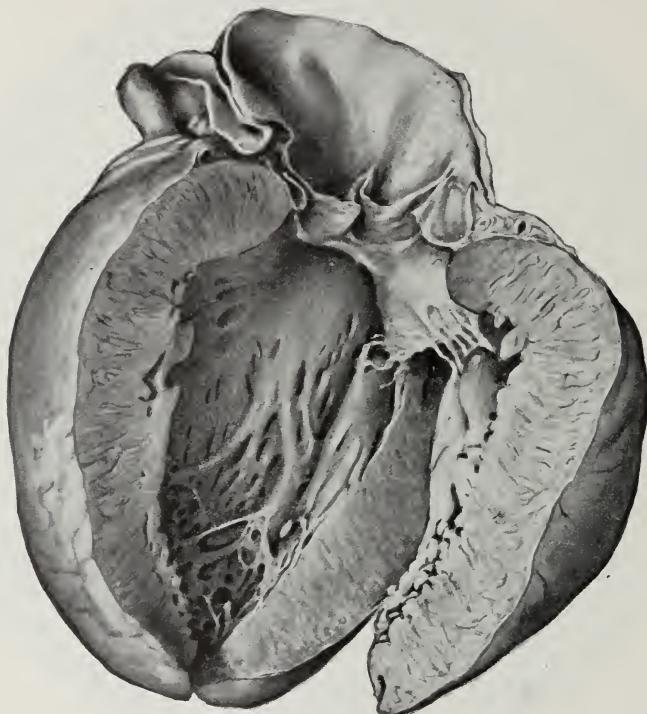


Fig. 153.—Great hypertrophy of the heart affecting especially the left ventricle in chronic nephritis without valvular lesion.

would as completely prevent their function as though they had been removed. It is quite probable that much of the retention of substances which should be excreted depends upon this reduction of the amount of secreting tissue to a level below that capable of coping with the task as though one kidney and most of the other had been removed. But it is also probable that less severely injured glomeruli and tubules may function even though in abnormal fashion, and be responsible for the qualitative changes in the secretion. It must be remembered, however, that *nothing* of the process of secretion, whether normal or perverted, can be seen under the microscope, and we have probably always drawn

conclusions as to the reasons for the abnormal function of the kidney from the appearance of glomeruli and tubules which have long since ceased to function at all.

It must be made clear, however, that it is not always possible to recognize and classify a case of chronic nephritis definitely as chronic glomerulonephritis or chronic arteriolosclerotic nephritis. These conspicuous features are often so prominent that we are content to group such cases together, but classification is no more than this. There are many other cases in which the microscopic study leaves one puzzled. There are advanced alterations in all the elements of the kidney, glomerular changes and arteriolar changes, too, and there may be added an amyloid deposit and extensive alterations of the epithelium. Indeed, every combination of lesions may be expected, and if we emphasize those with glomerular, those with tubular, and those with arteriolar changes it is only because we crave some sort of division, and the aetiological division upon which alone we can finally stand is still lacking.

Changes in other organs are often found in association with chronic nephritis, and to a rather less extent with acute and subacute forms.

The ordinary termination, especially in the chronic forms, is in the profound disturbance of the nervous system which we call uræmia. Nothing definite is known as to the nature of the poisoning which must be at the bottom of this, but the student is referred to Ascoli's book for a most comprehensive review of the endless symptoms that may make their appearance. Most common are drowsiness, stupor and coma, often with convulsions, but the opposite extreme, delirium and maniacal excitement, may appear for a time. Pericarditis without demonstrable infection may appear as a terminal event, and a severe diphtheritic colitis is not uncommon under the same conditions. Cardiac hypertrophy is, of course, the constant result of long-continued arterial hypertension, and one may readily recognize the association in the appearance of the heart which is thick-walled and firm, without any dilatation or scarring such as one commonly finds when valvular or coronary disease is associated with hypertrophy. Blood-vessels elsewhere than in the kidney are not necessarily sclerotic. Occasionally they show the hyaline thickening in the arterioles of spleen and pancreas or adrenal, but hardly elsewhere, although the cerebral arterioles are sometimes affected. Indeed, Bordley and Baker, applying Starling's experimental results, have tried to show that insufficient blood-supply to the medulla oblongata may be the cause of general hypertension, and have demonstrated sclerosis of some of the vessels there.

Blurring of vision and temporary or even complete blindness are associated with striking changes in the retina and in the optic nerve. The so-called albuminuric retinitis shows haemorrhages and shining deposits of cholesterol and hyaline materials in the retina. Arteriosclerotic distortion of the retinal vessels is also frequent, and in some cases the vessels are accompanied by deposits of fat.

We are left as we began, with only rudimentary ideas as to the cause of nephritis, clear only in the case of a few infections and poisonings, with no definite knowledge of the relation between general metabolic

processes and defects in the function of the kidneys in the explanation of the chemical changes in the blood and urine in nephritis, with no comprehension of uremia and only the vaguest notions of the causes of arterial hypertension.

LITERATURE

The literature is so overwhelming, especially in recent years, that only the most useful papers and reviews will be mentioned.

- Blackman, Brown, and Rake: Bull. Johns Hopkins Hosp., 1931, xlviii, 74.
 Dunn, J. S.: Brit. Med. Jour., 1922, December 16th.
 Epstein, A. A.: Amer. Jour. Med. Sci., 1917, cliv, 638; 1922, clxii, 167.
 Fahr: Frankf. Zeitschr. f. Path., 1912, ix, 15; Virchow's Arch., 1919, ccxvi, 119; Klin. Woch., 1934, xiii, 609.
 Fishberg, A. M.: Arch. Int. Med., 1927, xl, 80. Hypertension and Nephritis, 2nd Ed., Lea & Febiger, 1931.
 Friedenwald, H.: Doyne Lecture. Retinal vessels in arteriosclerosis and hypertension, Trans. Ophth. Soc., 1930, I, 452; Bull. Johns Hopkins Hosp., 1929, xl, 232.
 Gaskell: Jour. Path. and Bact., 1911-12, xvi, 287.
 Gull and Sutton: Medico-Chir. Trans., 1872, Iv, 273.
 Harvey: Proc. N. Y. Path. Soc., 1912, xii, 154.
 Janeway: Amer. Jour. Med. Sci., 1913, cxlv, 625; Trans. Cong. Amer. Phys. and Surg., 1913, ix, 14.
 Jores: Dtsch. Arch. f. klin. Med., 1908, xciv; Virch. Arch., 1916, ccxxi.
 Lölein: Ergebn. d. inn. Med. u. Kinderh., 1910, v, 411; Arb. a. d. Path. Inst. Leipzig, 1907, Heft 4; Ziegler's Beitr., 1917, lxiii, 570.
 Longcope: Northwest Medicine, February, 1924; Bull. Johns Hopkins Hosp., 1929, xlv, 335.
 MacCallum: Bull. Johns Hopkins Hosp., 1934, lv, 416.
 Marshall, E. K.: Secretion of Urine, Physiol. Rev., 1926, vi, 440.
 Muller, Fr.: Verh. Dtsch. Path. Ges., 1906, ix, 64.
 Oberling: Ann. d'Anat. Pathologique med. chir., 1924, i, 217.
 Oliver: Jour. Exp. Med., 1915, xxi, 425; 1916, xxiii, 301.
 Ponfick: Verh. Dtsch. Path. Ges., 1906, ix, 49.
 Richards: Amer. Jour. Physiol., 1922, lix, 144; 1924, lxxi, 178.
 Schlayer: Beihefte zur Med. Klinik, 1912, viii, 211; also several papers in Dtsch. Arch. f. klin. Med., xcix, ci, cii, civ, etc.
 Schürmann and MacMahon: Virch. Arch., 1933, ccxcii, 47.
 Volhard: Handb. d. inn. Medizin, Mohr. u. Staehelin, Berlin, 1918, iii, 1149.
 Volhard and Fahr: Die Brightsche Nierenkrankheit, 1913.
 Weigert: Volkmann's Samml. klin. Vortr., 162, 163.
 Ziegler: Dtsch. Arch. f. klin. Med., 1880, xxv, 586.

Functional Changes:

- Christian and others: Amer. Jour. Med. Sci., 1915, cl, 655. Jour. of Urology, 1917, i, 319. Cleveland Med. Jour., April, 1917. Prog. Med., 1918, iv, 135.
 Fitz: Amer. Jour. Med. Sci., 1914, cxlviii, 330.
 Frissel and Vogel: Arch. Int. Med., 1918, xxii, 56.
 Frothingham: Amer. Jour. Med. Sci., 1915, cxlix, 808; 1916, cl, 72. Arch. Int. Med., 1918, xxii, 74.
 Geyelin: Arch. Int. Med., 1914, xiii, 96.
 Mosenthal and others: Jour. Amer. Med. Assoc., 1916, lxvii, 933. Arch. Int. Med., 1917, xix, i, 329; 1915, xvi, 733; 1914, xiv, 844.
 O'Hare: Arch. Int. Med., 1916, xvii, 711.
 Peabody and others: *Ibid.*, 1916, xvii, 980.

CHAPTER XVI

INJURY WITH INFLAMMATORY REACTION AND ATTEMPTED REPAIR (Continued).—INJURY AND REPAIR OF THE LIVER

Structure of the liver in relation to disease. Direct injury to liver-cells. Acute yellow atrophy, eclampsia, and infections. Repair and compensatory hyperplasia. Cirrhosis: its various types. The alterations in architecture involved. Obstruction of portal circulation. Collateral circulation. Biliary and hypertrophic cirrhosis. Wilson's disease.

INJURY AND REPAIR OF THE LIVER

As in other organs, injury is possible in the liver in all sorts of ways, but we shall discuss here more especially those changes which are caused by the introduction of the destructive agent by way of the blood-stream or bile-ducts. Poisons or infections may enter in these ways, and produce all degrees of injury to the liver tissue with many types of reaction. On the other hand, the lack of some nutritive substance in the blood, or even the mere extreme sluggishness of its course, may be sufficient to disable or even to kill some of the liver-cells. As in other organs, the elements which make up the liver tissue are not all equally resistant, and it is constantly evident that the highly specialized liver-cells are injured or killed by poison, which leaves the less delicate gall-duct epithelium perfectly intact and capable of growth. The connective-tissue framework and blood-vessels are even more hardy, and show little effect from injuries that ravage the liver-cells.

Since in many of the cases which we are about to consider, the noxa reaches the tissue by way of the blood, it is clear that if there are any peculiarities in the way the blood-stream is distributed there may be corresponding variations in the concentration with which the poison reaches the liver-cells.

Structure of Liver.—The surface of the living organ is uniformly red, but on the death of the animal, and especially if the blood be allowed to escape from the large veins, a distinct fine lobulation becomes visible because the blood is pushed on in every arteriovenous communication to the venous end. On this account the portion about the efferent vein normally looks red, while the rest is paler, showing the brownish color of the liver-cells. If all the blood be washed out, the liver is uniformly light brown.

These lobules are not sharply marked off from one another, but anastomose in such a way that, from the arrangement of the cells alone, it is not easy to say where one begins and another ends. Naturally, the lobule should be, as suggested by Sabourin, the unit mass of tissue which pours its secretion into a terminal branch of the bile-duct, but even there it is difficult to determine how much of the bile-duct shall be adopted as belonging to one lobule, and the lobule tends to be a branched mass, forming a mantle around the end ramifications of the duct. It has exactly the same relation to the portal vein and hepatic artery. This relation is made very distinct in chronic passive congestion when the parts of the liver tissue most distant from the portal vein, that is, nearest to the efferent vein, are destroyed (*cf. Fig. 156*). Unfortunately, the efferent veins which receive capillaries from adjacent lobules become so conspicuous from the radial way in which these capillaries

enter into them that they are almost irresistibly attractive in a single section, as the centre of each mass which they drain. A purely artificial lobule, set up around the central (efferent) vein, has become the time-honored lobule of the liver, and the more so because in the pig that mass is sharply outlined by fibrous tissue. Doubtless we should break away from this conception and speak always in terms of the true lobule, but it would cause great confusion and add little of great value. Wherever greater clearness can be reached by considering the liver on the basis of Sabourin's lobule it will be done.

The great supply of blood is brought in by the portal vein, but from the capillaries of the hepatic artery which unite with those of the portal where they enter among the liver-cells, blood under higher pressure gives impetus to the venous stream, driving it forward toward the efferent vein. The portal vein may be ligated

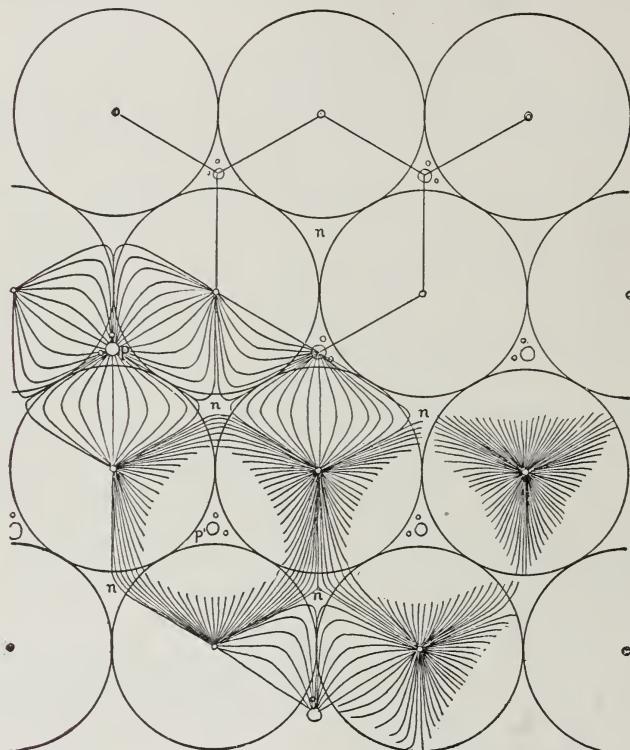


Fig. 154.—Diagram of the liver lobule (Mall).

and its blood diverted into the vena cava without causing the death of the liver tissue, and so, too, the hepatic artery may be obstructed without effect, but if the smaller branches of the portal vein are occluded where the hepatic arterioles join them, the blood-supply is cut off from the liver-cells and they die. Capillaries once formed, after the union of portal and hepatic terminals, run in part directly to the efferent veins, but some take a more roundabout course, so as to supply liver-cells not lying in that direct line (Fig. 154). The disadvantageous effect of this longer course becomes apparent in chronic passive congestion.

The bile-ducts branch minutely so as to connect with the end of each complex cord of liver-cells, the bile capillary, bounded on all sides by liver-cells, forming the continuation of their lumen. The bile-duct epithelium, although of the same origin as the liver-cells and presumably endowed with the same potentialities of

specialization, has not become so differentiated and remains as less highly organized but more hardy cells, with the simpler function of lining the ducts.

Recently there has been emphasized the great importance of the Kupffer cells which are highly phagocytic cells, related to the large mononuclear phagocytes or clasmatocytes of other tissues, and which hang as though suspended against the endothelium of the capillary sinuses of the liver and in very intimate relation with the liver-cells. Particulate matter introduced into the blood-stream is greedily taken up by these cells and bacteria and colloid substances, too. They seem to have, in a sense, a protective rôle, and the student should read Opie's review of their relation to intoxication and infection (Jour. Amer. Med. Assoc., 1925, lxxxv, 1533). It appears that the formation of bile-pigment is carried on by these cells, and that they transfer it to the liver-cells, which, as far as this particular material is concerned, have only the function of secretion into the bile canaliculi. Other related phagocytic cells elsewhere can also produce bile-pigment, but the Kupffer cells seem to be placed in the most advantageous position for this function.

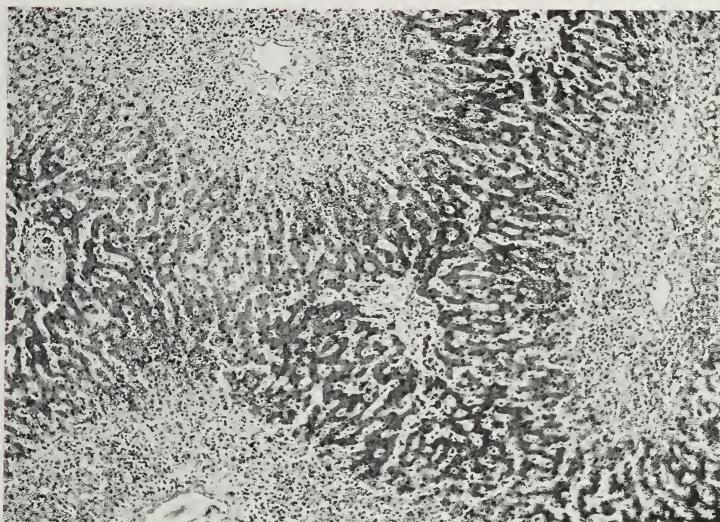


Fig. 155.—Necrosis of liver cells about the efferent vein in each lobule.

Direct Injury to the Liver-cells.—With such a distribution of the circulation it is not surprising that injuries to the cells are often zonal in their arrangement. It is true that in many infections practically all the cells may appear turbid and cloudy, and in extreme accumulations of fat in the liver all the cells may contain globules, but usually such alterations are not so uniform. The fat may be lodged especially in the cells nearer the portal vein, or, on the contrary, especially in those about the efferent vein. When there is actual injury sufficient to kill the cell, it may affect the cells of the zone nearest the portal vein, as in eclampsia gravidae, or the zone farthest from the portal vein, and therefore encircling the efferent vein, as in chronic passive congestion, chloroform poisoning, many acute infections, especially those in which generalized peritonitis (Fig. 155) or other extensive and intensive inflammations occur, and in all that ill-defined group of cases known as acute yellow atrophy of the liver. Sometimes, as Opie points out, in

intense infections, and especially where a toxic injury is combined with bacterial infection, a zone midway between portal and efferent vein may be picked out for necrosis. Yellow fever in which there occurs a distinct midzonal necrosis of the liver is a peculiar example of this. One assumes the determining influence of the blood-stream in producing these differences of distribution, although it is not always easy to understand it. Opie has shown that colored materials injected into the hepatic artery or portal vein during the normal circulation tend to lodge in the middle zone, and one might imagine that a peculiarly acrid



Fig. 156.—Chronic passive congestion; liver tissue is alive close to portal veins but is first fat-laden and then necrotic as the distance is increased.

poison could destroy the first cells it impinged upon, as happens in eclampsia, but how explain the extensive and often sharply limited necrosis of the cells farthest from the entrance of the blood, which is so frequently seen in the conditions mentioned above? In the case of chronic passive congestion it is probable that those cells which receive the blood last are poorly nourished by the stagnating stream, which becomes less able to supply oxygen as it reaches the neighborhood of the efferent vein. It is interesting that, in this case, as in many infectious and toxic injuries, the cells along those capillaries which take a

long course to empty into the efferent vein suffer throughout a region everywhere equidistant from the portal vein and artery, but not everywhere equidistant from the efferent vein. Therefore in these cases the necrotic tissue does not merely encircle the efferent veins, but extends from one to another. If we accept Sabourin's lobule, the whole periphery of the lobule in necrotic; if we regard the efferent vein as the centre of the lobule, the necrotic area occupies the centre of each lobule, and stretches across to join that about the centre of each adjacent lobule (*cf.* Fig. 156).



Fig. 157.—Midzonal necrosis in the liver.

But although injury and destruction of liver-cells may often be distributed in a zone of each lobule, it is very frequently focal. In numbers of infectious diseases, such as typhoid fever, diphtheria, malaria, smallpox, and in poisoning with diphtheria toxin, ricin, abrin, and similar things, one discovers small groups of cells, situated anywhere in the lobule, which have been killed and coagulated. Why those cells should have been picked out for destruction it is not easy to say. Some authors, including Mallory, believe that emboli of cells or agglutinated red corpuscles, often supplemented by fibrin thrombi, so oc-

clude the capillaries about a tiny group of cells as to deprive them of their blood-supply and thus produce an anaemic necrosis. In spite of the difficulty of finding another satisfactory explanation, there is much that seems hardly plausible about this. It is true that such cell emboli are often found, but it is hard to believe that they could so completely surround a group of cells in the liver as to render it anaemic. Even then it would seem that such a small mass of tissue might absorb enough nutriment by diffusion to keep it alive. On the other hand, if a mass of liver-cells did die, one might expect its capillaries to become thrombosed.

It would seem that injection of granular material into the mesenteric vein ought to decide this question at once. In my hands such injection (corn-starch) does rarely produce focal changes which will probably lead to necrosis of the liver-cells, but these are in the beginning areas of tearing of the tissue by haemorrhage evidently as the result of plugging of the capillaries. In those areas stretched and dismembered cords of liver-cells are found; the remainder are pressed back and flattened, but none are necrotic. This is very different from the familiar appearance of most focal necroses, in which the tissue is not in the least disarranged, but each cell has died where it stood. In all the rest of the experiments the grains lodged singly or in groups in the capillaries, without producing the least change in the liver-cells. (See further discussion under Typhoid Fever.)

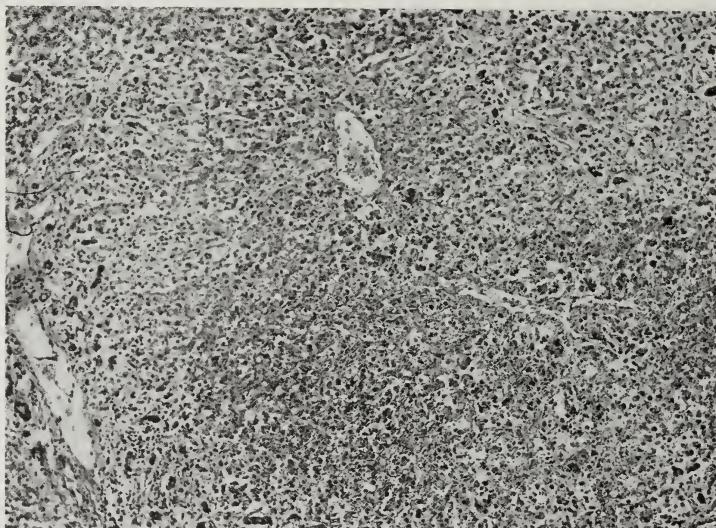


Fig. 158.—Complete destruction of liver-cells by arsphenamine.

If chloroform be administered to an animal for an hour or two and its liver examined after a time, marked changes are to be found in the liver-cells nearest the efferent vein. In case the chloroform has acted mildly, these are chiefly evident in the great accumulation of fat, but in other animals where it has acted longer or more intensely, these cells are quite dead, their nuclei failing to stain, while the cell-body is coagulated and deeply stained with eosin. This may be ascertained by excision of a small piece of the liver tissue shortly after the poisoning, the animal being left alive. After three weeks the liver is found re-

stored to practically its normal condition, so rapid is the removal of the dead cells and the regeneration of new ones from those which remain. By combining bacterial infection with chloroform poisoning Opie has produced much more profound injuries which are not so readily repaired. In the zonal necroses which accompany intense septic infections a similar anatomical condition is produced. All the liver-cells most distant from the portal vein, that is, encircling the efferent vein and stretching to the region of the next, are necrotic. Nevertheless, in these areas of cell death the endothelial cells, Kupffer cells, and connective tissues remain alive. Nearer to the portal vein in each lobule is a zone of cells distended with fat-globules, and still nearer the liver-cells seem intact (Fig. 155).

Extreme Necrosis of the Liver.—The name acute yellow atrophy has for many years been loosely given to those cases in which some destructive agent produces necrosis of liver-cells so wide-spread that signs of acute insufficiency of the hepatic functions appear. It has been observed in children and in young people and often in pregnant women, but recently, since the war, as shown in a review of the sub-



Fig. 159.—Complete destruction of every liver-cell by arsphenamine. See Fig. 158.

ject by Seyfarth, it seems to have occurred far more frequently. In that discussion there was much talk of some possible infection or of syphilis as the cause, but we have been especially impressed by the idea that the reckless use of salvarsan, arsphenamine, and other arsenicals given intravenously is responsible for this wholesale destruction of the liver tissues. Possibly other poisons such as have come into use in munition factories and other industries may have played a part, but the violent arsenical remedies seem especially to blame.

Sudden malaise, symptoms of indigestion, nausea, rapidly deepening jaundice, vomiting of blood, delirium, mental dulness, and coma lead to death. The urine is deeply jaundiced and contains amino-acids, such as leucin and tyrosin, in crystalline form. At autopsy the liver is found very much decreased in size and very soft, of an opaque ochre-yellow color often with areas of red. In each lobule all the liver-cells, with the exception perhaps of those nearest the portal veins, are reduced to a necrotic débris. The endothelium of the sinuses and the Kupffer cells seem to escape. The extreme jaundice is probably to be explained on the ground that if the Kupffer cells are still able to produce bile-pigment, the liver-cells are no longer in a position to receive it, and the bile canaliculi are destroyed so that it is absorbed by the lymphatics and poured into the blood. The necrosis of the liver-cells easily explains the hepatic insufficiency of every sort, and the amino-acids no longer deaminized there pass on unchanged in the blood and appear in the urine. Hæm-

rhaiges into the mucosæ and elsewhere are doubtless related in part to the disturbed power of coagulation of the blood which results from jaundice, and in extreme cases there is, no doubt, such hypoglycæmia as would follow the operative removal of the liver.

But still, in many cases the person survives for a time and, as we shall see, various stages in the removal of the dead cells and the regeneration of liver tissue are to be found at autopsy. Indeed, life may go on for a long time, and when it is ended by some other disease the liver is found most extraordinarily distorted with tumor-like nodules of the liver tissue which has escaped and grown through a compensatory hypertrophy, while all the rest is merely collapsed framework (Fig. 164).



Fig. 160.—Hæmorrhagic necrosis in the liver in puerperal eclampsia.

Eclampsia Gravidarum.—Eclampsia gravidarum is a condition appearing before, during or after childbirth, as part, perhaps, of the so-called toxæmia of pregnancy and is accompanied by the most violent convulsions. Nothing is known of its cause although theories of every sort have been put forward to account for it. It is very often fatal and at the autopsy the liver is found sprinkled with hæmorrhages which may become confluent into great patches (Fig. 160). These hæmorrhages correspond with areas of necrosis of the liver-cells in the periportal region of each lobule but often becoming confluent (Fig. 161).

LITERATURE

Stander: Medicine, 1929, viii, 1; Amer. Jour. Obst. and Gynæc., 1934, xxviii, 855.
Strauss, M. B.: Amer. Jour. Med. Sci., 1935, exc, 811.

In other infectious and toxic processes mentioned, in which scattered focal necroses occur (typhoid fever, diphtheria, etc.), one finds anywhere in the lobule circumscribed areas in which the liver-cells are dead. Here, as in the zonal type, delicate hyaline thrombi are common in the capillaries, entangling the many wandering cells which hurry there and which are active in dissolving and removing the débris of dead cells.

Repair and Compensatory Hyperplasia in the Liver.—The liver possesses very great powers of repairing losses of its substance. Whipple

has shown that destruction of the liver-cells throughout two-fifths of each lobule in the dog can be repaired in a few weeks by the removal of the dead cells and their accurate replacement without any distortion of the lobule. Thus the necroses so constant in typhoid fever are healed without an appreciable scar. This power belongs not only to the highly specialized liver-cells, but also to the epithelium of the bile-ducts which, if they become disconnected from their liver-cell strands by the destruction of some of the cells, quickly bridge the gap and reestablish the connection. All these cells multiply by mitotic division, and are guided in

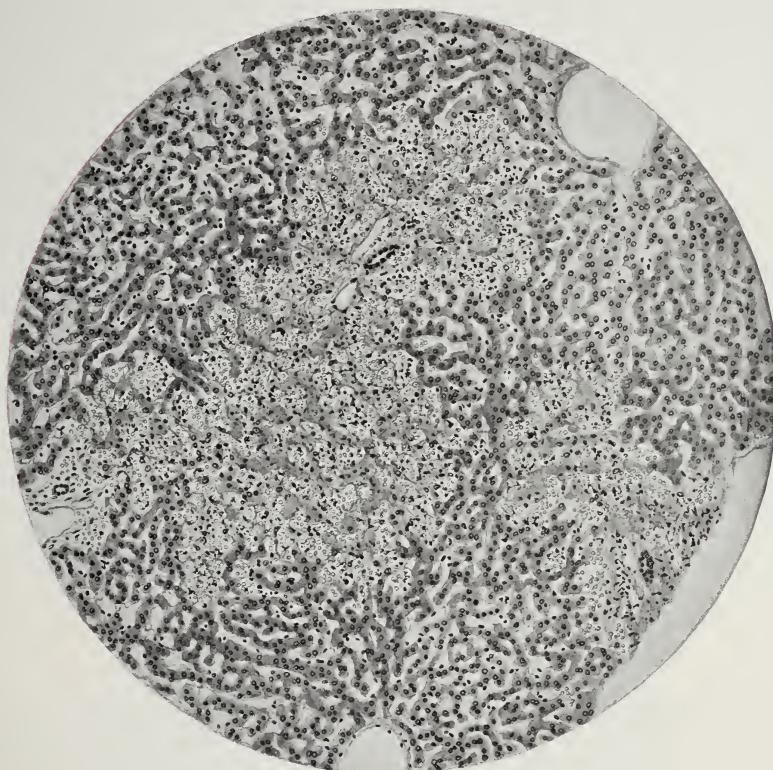


Fig. 161.—Eclampsia gravidarum. Peripheral focal necrosis with haemorrhages.

the direction of their growth by the persisting liver framework. Thus, when all the liver-cells about the efferent vein of the lobule have been destroyed, numerous karyokinetic figures can be found in the cells of the adjoining zone, where they are so loaded with fat-globules, but are rather fewer in the better preserved cells immediately about the portal veins.

Often recognizable as young cells by their pale, clear protoplasm and convex outline, these fresh liver-cells, together with some of the older ones, push their way along the spaces formerly occupied by those which were killed, unless those spaces are collapsed and obstructed. If

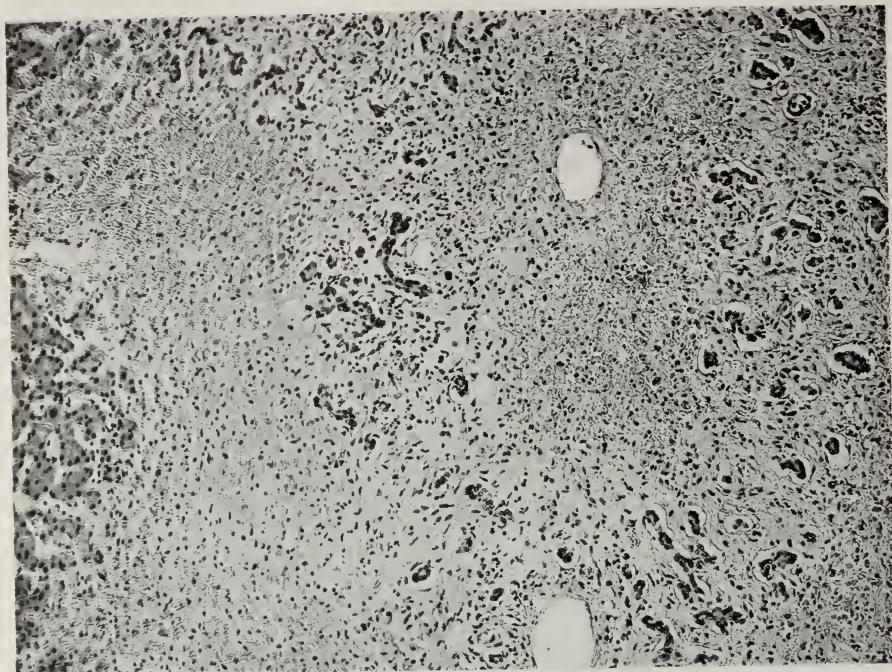


Fig. 162.—Beginning repair of the liver by sprouting bile-ducts after destruction of all the liver-cells in a lobule.



Fig. 163.—Formation of liver-cells by bile-ducts, a rare occurrence.

all the cells of the lobule are annihilated, the framework remains, and is often held open by the rigidity of the tissue about it (Fig. 162). Then there is no source for new liver-cells. Broken ends of bile-ducts which formerly connected, one with each of these strands of liver-cells, remain uninjured in the portal spaces and now grow out with bulbous ends into the framework of the lobule toward the efferent vein, that is, in the Sabourin lobule they sprout out from the central bile-duct. In the lobule in which the efferent vein forms the centre these bulbous bile-ducts appear to grow centripetally. There has been much dispute as to whether they can actually produce new liver-cells. I believe they can to a limited extent, as shown in Fig. 163, where the club-shaped masses were unquestionably liver-cells and new, since they contained none of the pigment which was so abundant in all the older liver-cells. That they can thus become differentiated seems certain, but probably they do



Fig. 164.—Coarse cirrhosis of the liver with large nodules of regenerating liver-cells. Arsphenamine treatment a year previous to death.

so but seldom, and then produce very few liver-cells. Melchior thinks this process very important, but it seems that he assigns to it cells that are otherwise produced.

Thus healing or readjustment of breaks in continuity may be easily carried out by the liver-cells and the bile-duct epithelium. It must not be supposed, however, that the framework of the liver is always left undisturbed, so that repair can proceed so easily and accurately. It may collapse when the liver-cells are gone, and become consolidated into a scar-like band. Then bile-ducts may push their way into it and new liver-cells may be formed there, but their arrangement will not be that of the normal lobule.

Perhaps the simplest available example of repair in an extensively injured liver is furnished by a case studied some years ago, that of a boy who had gone through a severe illness, which may have been acute yellow atrophy of the liver, six months before his death. In the mean-

while, up to his death from an infection, he had been fairly well. The liver was greatly reduced in size, but contained a tumor-like mass in the right lobe, composed of dark green lobules like swollen liver lobules. Throughout the general liver substance every liver-cell had been destroyed; the framework had remained intact with the bile-ducts and blood-vessels, and from every bile-duct branching sprouts were growing into the old framework, although nowhere producing definite liver-cells. In the right lobe a portion of liver tissue had evidently been left intact, and this had become the tumor-like mass by the symmetrical enlargement of each remaining lobule. This mass, which was finally about the size of a small orange, must have been very much smaller at first, and yet it sustained life and prevented any serious symptoms of hepatic insufficiency. This exactly corresponds with Ponfick's experimental results, in which he found that, after removal of a large part of the liver, the remainder enlarged by a symmetrical growth of each lobule, new liver-cells being formed everywhere by division of the old ones. No rearrangement of liver-cells, bile-ducts, or blood-vessels was necessary in this case, and we have the effects of a single great injury before us. Similar cases, in which many large nodules of liver tissue are found embedded in a scar-like organ, are probably also due to a single injury (Fig. 164).

CIRRHOSIS OF THE LIVER

This is a term applied to an extensive diffuse scarring of the liver which has followed the destruction of much of the liver substance. It is regularly accompanied by wide-spread regeneration of the functional liver tissue, usually sufficient to prevent the appearance of any signs of hepatic insufficiency.

There are great difficulties in classifying all the different types of cirrhosis, because, except in about three or four, we are ignorant of their causes. The rest we have to classify, then, on the basis of the anatomical and functional disturbances, which is not very satisfactory. We know that syphilitic and tuberculous infection can produce scars throughout the liver, with profound distortion of the organ, and that obstruction of the bile-duct will in the end set up a peculiar type of scarring about the bile-duct branches, with deep jaundice—but with regard to all the other cases of cirrhosis in which these things are readily excluded we are still rather at sea. Of course, in the lay mind the abuse of alcohol is held responsible for cirrhosis of the liver in a quite unprejudiced way, but although it may well play some part, its influence is undoubtedly greatly exaggerated.* LongCOPE's recent experiments, which show that lesions resembling those found in cirrhosis may be produced by repeated anaph-

* It is misleading to try to determine this relation by estimating the percentage of the cases of cirrhosis of the liver in which there has been abuse of alcohol. If, instead, we study a great number of chronic alcoholics, we find (Simmonds) a relatively small percentage of cases of cirrhosis of the liver. On the other hand, great accumulation of fat in the liver is common in alcoholics. Experimental administration of alcohol to animals produces no cirrhosis, even when enormous doses are given over a very long time.

ylactic shocks caused by injections of egg-white or other protein, are most suggestive of an origin through protein sensitization and intoxication. But the most accurate approach to this anatomical condition has been made by those authors (Opie and others) who have combined bacterial infection with various poisons, such as chloroform, which destroy liver-cells. Probably it is in some such protracted and complex injuries that we shall find the actual cause of the disease, but undoubtedly, as in any scar, the same commonplaeæ result may have a great variety of original causes. The anatomical condition of the liver, and the occurrence or absence of certain associated disturbances, such as jaundice, obstruction of the portal blood flow and ascites, enlargement of the spleen, etc., form the further basis for classification of the cases, and we find that the following types may be separated:

1. The Ordinary Nodular Cirrhosis (Laënnec's Cirrhosis; Atrophic or Portal Cirrhosis; Hobnail Liver; Alcoholic Cirrhosis, etc.).—Liver rough and nodular, tends to be smaller than normal, no jaundice, marked portal obstruction, with ascites and enlargement of the spleen. Ætiology obscure.

2. Obstructive Biliary Cirrhosis.—Liver enlarged, smooth, or granular. Jaundice. Clay-colored stools. Scars following bile-canals. Usually no portal obstruction nor ascites, but spleen may be enlarged. Ætiology: Obstruction of bile-ducks, usually accompanied by infection.

3. Hanot's Cirrhosis, or Primary Hypertrophic Biliary Cirrhosis.—Liver large, smooth, diffusely and finely scarred. Jaundice, with no gross obstruction of bile-ducts; bile-stained stools; no portal obstruction; splenic enlargement. Ætiology obscure, possibly an infectious process.

4. Syphilitic Cirrhosis, Congenital or Acquired.—In the congenital form the liver may be large, smooth, and diffusely scarred, or it may present gummata which later become scarred. In the acquired form gummata heal with large scars, producing deep grooves and lobulations in the liver. No jaundice; no marked portal obstruction.

There are unquestionably many other types, for any injury recovered from and healed may leave its trace in the form of a cirrhotic process.

1. Diffuse Nodular Cirrhosis.—In the ordinary cirrhosis one finds the liver hard and stiff—sometimes larger than normal, but generally shrunken and deformed and roughened all over by projecting nodules of a yellowish-brown or chestnut-brown color (Fig. 165). The capsule is generally thickened and sometimes finely granular, but through it one can see that the shrunken tissue between the nodules is gray and translucent, often showing little veins in the depths of the depressed areas. It is hard to cut, and in extreme cases creaks or cries under the knife. The cut surface shows just the same appearance—rounded or irregular nodules of liver tissue of variable size projecting as little plateaus from the gray, translucent groundwork (Fig. 166). Every kind of variation in the appearance of these nodules may occur; sometimes they are all quite small and uniform, more often some of them are larger, and these tend to be pigmented or bile stained; occasionally they are all very

large—even as large as marbles—and widely separated by a rather loose, vascular connective tissue. In some cases the liver substance forms the great bulk of the organ, so that scars can be traced through it with



Fig. 165.—Diffuse nodular cirrhosis of the liver.



Fig. 166.—Nodular cirrhosis of the liver. The rough outer surface shows both above and below. Some rather large masses of liver tissue project on the cut surface.

difficulty; in others the whole organ seems to be composed of solid elastic fibrous tissue, with only scattered pockets of greenish or brown liver substance embedded at intervals through it. The liver tissue itself

may be made up of quite normal-looking cells, or the cells may be loaded with fat or pigment, or be actually on the way to necrosis and disintegration.

All these variations are of subordinate importance though, and further study shows that in principle these cases are all very similar. Large isolated masses of liver appear when only widely separated groups of cells have been spared and have been allowed ample time to regenerate as much liver tissue as possible. Small, closely packed nodules result when destruction has occurred in smaller foci, and some portion of nearly every lobule has survived. Even the most casual examination shows that these nodules have no longer anything like the normal arrangement of the lobules. They are not, as a rule, isolated nodules, for reconstruction of serial sections shows that they are almost all connected together into an irregular network, but they have lost their



Fig. 167.—Cut surface of the liver; nodular or Laënnec's cirrhosis.

regular relation to the original portal veins, bile-ducts, and hepatic veins. They no longer even approach uniformity in size, nor can one find a central vein in each. Instead, they generally appear in section as smooth, finely granular, almost velvety, solid masses of liver-cells and nothing more.

Microscopical study confirms all this (Figs. 168, 169). Everywhere in the section there are found patches of liver-cells arranged in a most disorderly fashion. All bear evidence of having been enlarged by the multiplication of their cells, so that the arrangement with reference to portal and efferent veins is all that will tell us whether we have the enlargement of a whole lobule or of an isolated group of cells. In the latter case the patch will have no portal and no efferent vein immediately connected with it, but is merely a conglomeration of liver-cells with intervening capillaries which have grown into a perfect labyrinth, and allow the passage of blood with some difficulty. The whole lies sur-

rounded by vascular connective tissue, in which there are many wandering cells, and in which one can see numerous tortuous bile-ducts. Very often one can make out in this tissue what must have been the efferent vein which originally drained the lobule of which we have just considered the hypertrophied remnant, and, indeed, this vein doubtless still drains that overgrown remnant (Fig. 170). Portal veins are also visible, but they are commonly in no clearly recognizable relation to the liver-cells, but lie quite far away in the intervening tissue. So, too, the original bile-ducts can be seen, but there are many other sinuous chan-



Fig. 168.—Nodular cirrhosis of the liver. The low-power drawing shows the irregular arrangement of the remaining liver tissue and the distribution of the newly formed bile-ducts.

nels lined with epithelium which branch abundantly and which one may trace into connection at one end with the bile-duct, at the other with a strand of liver-cells in one of the nodules (Fig. 171).

There has been much dispute as to their nature, and they have been thought by many to be compressed liver-cells, but everything goes to show that they are bile-ducts, for the greater part newly formed from the stumps of those which were left, and now growing to re-establish connection with the liver-cells. The slight part they play in the new formation of liver-cells has been mentioned. Of course, in any such

strand of tissue as we find between the nodules of liver-cells a great many bile-ducts, portal veins, etc., are concentrated together through the collapse of many lobules whose skeleton framework goes to form a large part of the strand, but the newly formed ducts can usually be recognized.

One might trace out the fate of any isolated portion of a lobule which remained after the devastation of the rest in this process, but the process of reëstablishment of relations is the same no matter how much or how little of the original lobule remains. It is as though groups of liver-cells were transplanted into a vascular tissue rich in bile-ducts. They acquire the best vascular connections possible for their situation, and the



Fig. 169.—Nodular cirrhosis showing atypical arrangement of liver-cells in each nodule.

ends of the strands unite with the sprouts of bile-ducts which approach them, after which the liver-cells multiply as fast as possible to produce a larger nodule, which will compensate in function for the cells which were destroyed. There is no evidence of the compression of the liver-cells by the fibrous tissue in which they are growing—rather one might say the fibrous tissue is pushed aside and compressed by them. Nor is there any justification for the term lobular cirrhosis, since, as we see, it is by no means a question of the enveloping of lobules in fibrous tissue. Although many conflicting views have been held, it seems clear enough that the injurious agent effects the destruction of the liver-cells

in the first instance, and that the scarring and the hyperplasia of the epithelial remnants are reparatory processes.

Very commonly the liver-cells are quite normal in appearance and function and doubtless they are so for weeks and months at a time. If the attacks of the injurious agent could be stopped, there is no reason why compensatory hyperplasia should not go on until the organ had once more its full complement of cells in an abnormal arrangement. But they are, of course, as always, susceptible to injury, and for that reason they are often found at the death of the individual, loaded with fat or injured in some other way. Some of these injuries may be of the series



Fig. 170.—Nodular cirrhosis with very great hyperplasia of the liver-cell nodules. Observe the distorted relation of portal and efferent veins to the liver tissue.

which is still at work, adding to the changes which bring about the cirrhosis, but others may be independent, and we might expect to find focal necroses in the liver-cells of a man who has long had a cirrhotic liver and who dies of typhoid fever.

The whole condition is brought about in exactly the same way as the scarring of the kidney with compensatory hyperplasia. The liver-cells are killed in patches—whole lobules and groups of lobules at a time, or only parts of lobules. There remain irregular masses of liver tissue partly disconnected from their bile-duets. The framework of the rest of the tissue collapses and shrinks, and is kept in that position by the

growth of new fibrous tissues, but through that tissue blood still streams readily. The bile-ducts which were interrupted by the death of the liver-cells send out sprouts which attempt to connect again with liver-cell strands. The masses of liver-cells quickly increase in size by multiplication of their cells, new capillaries are formed in every direction, and this labyrinth of cells expands, pressing the stroma away on all sides. For a time the liver-cells are normal, but the whole process may be repeated, and not only once, but many times. It is clear that

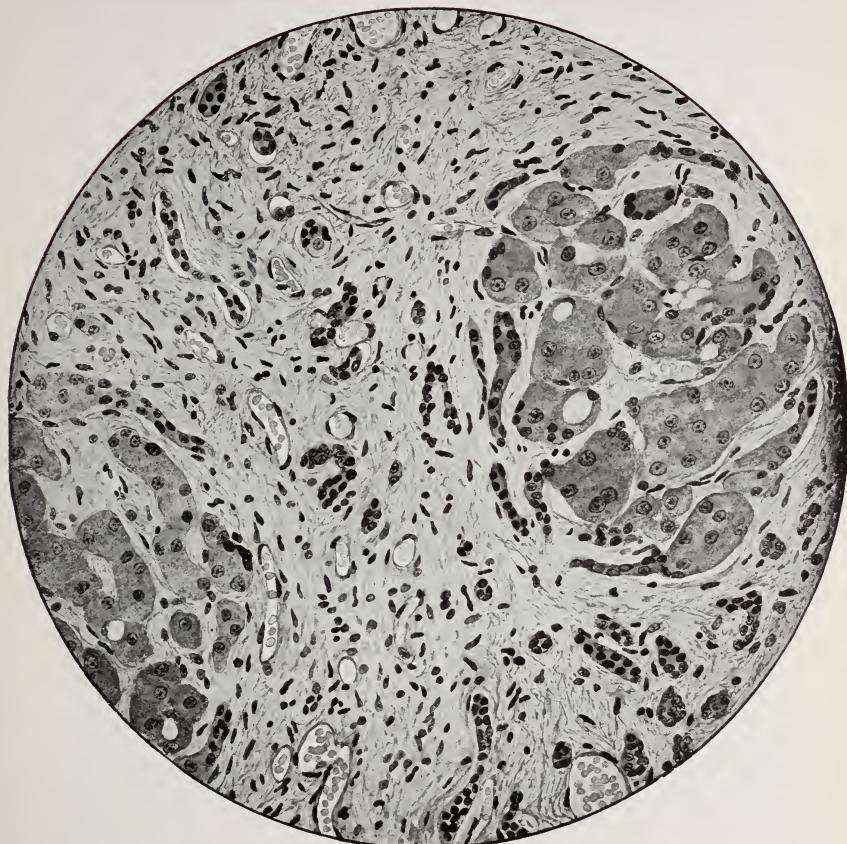


Fig. 171.—Cirrhosis of the liver showing the reunion of bile-ducts with the liver-cells.

this must lead to an extraordinary distortion of the liver's structure. There are no longer lobules, but only nodules produced by the hyperplasia of smaller groups of cells which were left intact. Nevertheless it seems probable that in many cases the cirrhosis is the late result of a single wide-spread injury.

Obstruction of the Portal Flow.—With advancing cirrhosis of the liver it becomes difficult for the portal blood to pass through, and all the branches of that vein come to be distended, sometimes even to the point of bursting. The organs which are drained by them are swollen and blue from the stagnation of venous blood,

and their function is disturbed. Digestion is impaired, and the spleen becomes greatly enlarged. Fluid filters through into the peritoneal cavity, and the ascites accompanying cirrhosis may be of the most persistent.

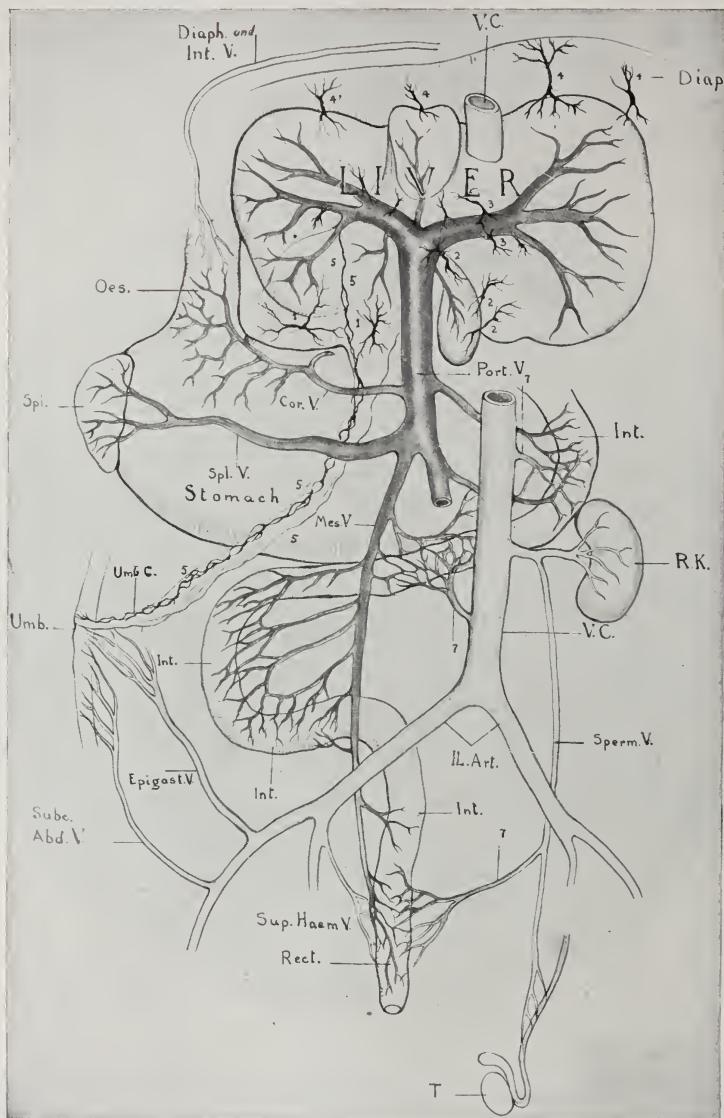


Fig. 172.—Diagrammatic representation of the collateral circulation established in cirrhosis of the liver (from Charcot): 1, 2, 3, 4, 5, Accessory portal veins of Sappey; 7, 7, 7, veins of Retzius. The organs are viewed from behind.

Why so much obstruction should occur is not as simply explained as might appear at first sight. With the great reduction in the size of the liver much of the stream-bed is doubtless obliterated. The rigidity of the scarred organ may prevent the normal distensibility of the blood-vessels, but the capillaries of the scarred bands

are still more easily injected than those of the regenerated nodules of liver tissue. In the liver nodules, on the contrary, the tortuous course of the new capillaries offers an increased resistance to the flow of blood.

Herrick* has offered the explanation that the communications between the hepatic artery and the branches of the portal vein become far wider than normal in the cirrhotic liver, so that the high arterial pressure is communicated directly and obstructs the outflow from the veins, much as it does in an arteriovenous aneurysm.

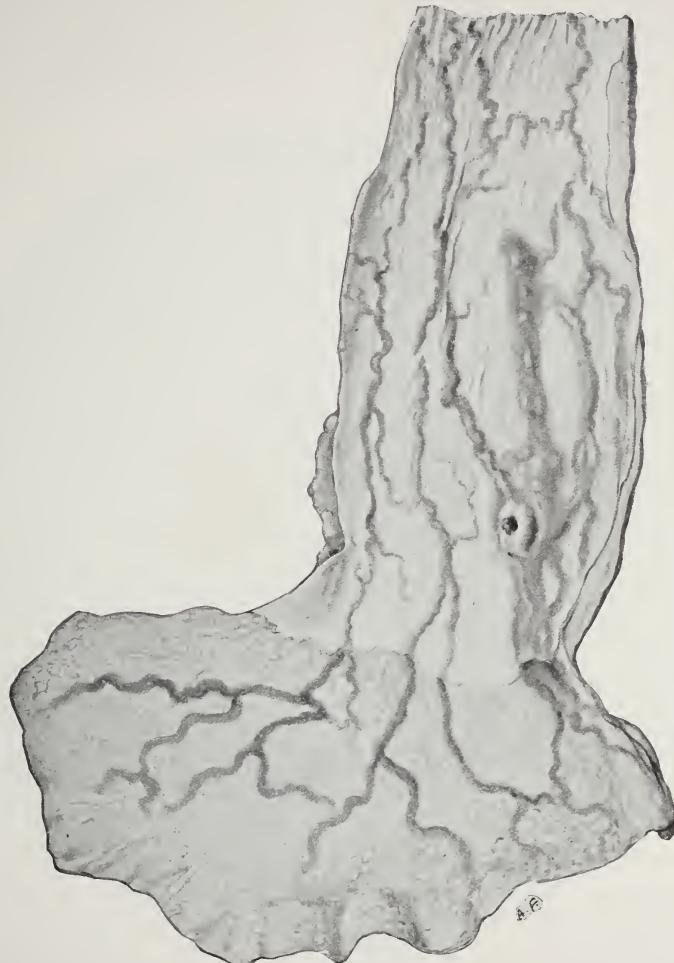


Fig. 173.—Collateral circulation in cirrhosis. (Esophageal varices with rupture and fatal haemorrhage.)

The long-continued overdistension of the portal branches is sometimes partly relieved by the widening of certain communications between the portal system and the branches of the vena cava, which always exist but are normally too small to be of any use. These are well described by Charcot† and are diagrammatically shown in Fig. 172. They are:

* F. C. Herrick: Jour. Exp. Med., 1907, ix, 93.

† Charcot: Maladies du Foie, Paris, 1882.

1. Anastomoses between the left coronary vein of the stomach and the œsophageal veins which open into the azygos or intercostals. These communicating channels often become enormously enlarged (œsophageal varices), and may burst into the œsophagus, with fatal results (Fig. 173). The coronary vein may also anastomose with superior or inferior diaphragmatic veins.

2. Anastomoses exist between branches of the inferior mesenteric vein, the superior haemorrhoidal, and branches of the internal iliac veins, the inferior haemorrhoidal. These are apparently not especially efficient, and haemorrhoids are said not to be common in cirrhosis.

3. The veins of Retzius, which originate in the walls of the intestines and through a little trunk empty into the vena cava or one of its branches.

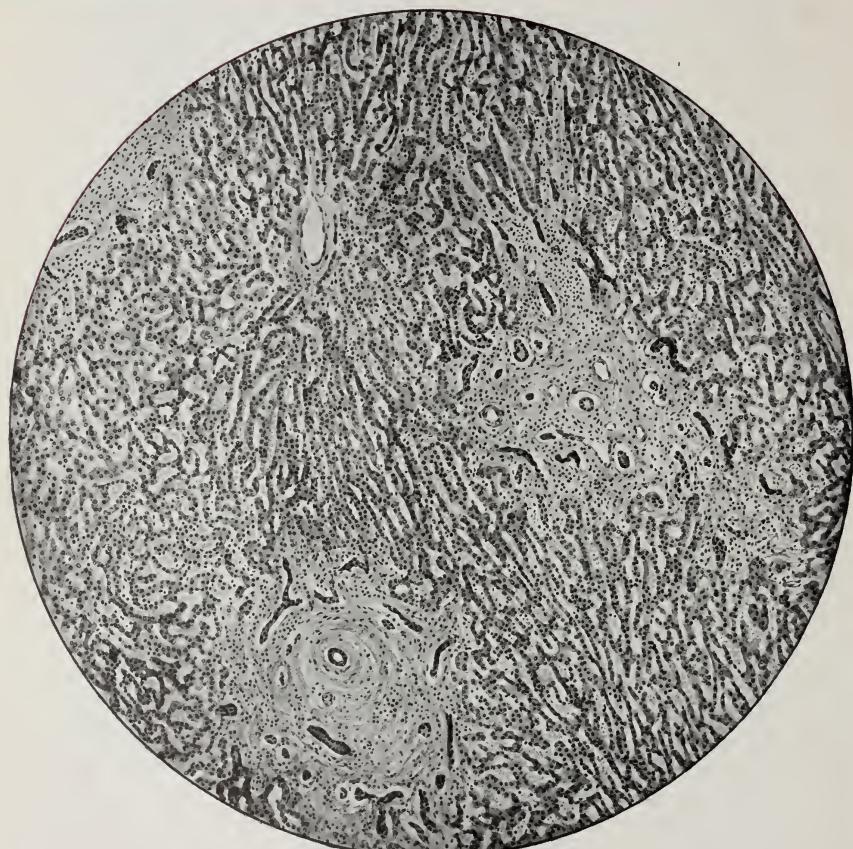


Fig. 174.—Biliary cirrhosis.

4. The veins of Sappey, or accessory portal veins, which originate in some organ other than the digestive tract, and, after forming a trunk, reach the liver and ramify in its substance. Some of them are quite useless in establishing a collateral circulation, as, for example, those which connect the omentum or the gall-bladder with the liver, or those which constitute the vasa vasorum of the portal vein, hepatic artery, and bile-ducts. But the veins of the suspensory ligament which unite with those of the diaphragm are useful. So, too, are the para-umbilical veins (*Umb C*, Fig. 172), whose roots communicate with the epigastric, the internal mammary, and the subcutaneous abdominal veins. They enter the liver along the obliterated

umbilical vein, and are distributed to the lobules along the longitudinal groove, to the portal vein to the left of the umbilical ligament, or to the still permeable part of that ligament. They are important channels of communication, and sometimes appear in their swollen state under the skin of the abdomen radiating from the navel (*caput meduse*).

Of course, other collateral channels arise through the formation of adhesions between the abdominal organs and the walls of the abdomen, and they are often intentionally produced for this purpose by an operative procedure (Talma's operation).

At times the collateral circulation reaches an efficiency which allows the patient to live on without ascites or symptoms of chronic passive congestion, but usually it is not so complete. Jaundice in the type of cirrhosis described is rare, and when it does occur, is probably due to some accessory cause.

2. Obstructive Biliary Cirrhosis.—It has been shown experimentally (Vaughan, Harley, Ogata, and others) that, in certain animals at least, the occlusion of the bile-ducts results in the destruction of some of the liver-cells and in the formation of scar tissue in their place. This is especially striking in zones about the portal veins and bile-ducts, and in these zones numerous new bile-ducts sprout out. The addition of infection to the mechanical stasis of the bile intensifies the process. The same thing is true in human beings when the hepatic or common duct becomes obstructed by a gall-stone or by a tumor growth. Jaundice results promptly, and the liver becomes swollen and deep green in color. After this obstruction has lasted some time slight irregularity of its surface arises, and on section delicate scars can be seen. There is rarely time for the development of any such extreme changes as have been described for the diffuse nodular cirrhosis. The spleen becomes enlarged, but there is, except in advanced cases of long standing, no obstruction to the flow of portal blood. In a man aged fifty-five jaundice appeared and quickly deepened to a dark, greenish bronze color. At the autopsy several jack-stone-shaped black gall-stones were found in the gall-bladder, at the fundus of which a small cancer had developed. A secondary growth from this lay embedded in the liver in such a way as to surround and compress the hepatic ducts as they left the liver—below this the ducts were normal; within the liver they were distended to a phenomenal degree. The liver was deep green, flabby, and coarsely lobulated, although only slightly wrinkled on the surface. Even on section there was no great departure from the regular lobulation. Microscopical study showed each larger bile-duct twig and portal vein surrounded by a loose scar tissue infiltrated with leucocytes, and rich in young, sprouting bile-ducts, evidently growing out to join the remaining liver-cells after the destruction of many of those nearest the portal space (Fig. 174).

Apparently in the cases of longest duration a great deal more distortion of the liver may occur, but it does not approach that seen in the previous type.

3. Primary Biliary Hypertrophic Cirrhosis (Hanot's Cirrhosis).—There exists much confusion as to what Hanot actually meant to include in his type of hypertrophic cirrhosis with icterus and without ascites, but Heineke describes it as a change resulting from the inflammation

of the minuter bile-ducts, and producing a fine, almost intercellular, scarring throughout the liver; with its enlargement—enlargement of the spleen, fever, but no portal obstruction. There are other cases in which there is the same deep jaundice but no evident inflammation of the bile-ducts (Kretz), and still others in which there is no jaundice. Nevertheless, in these too the liver is found greatly enlarged, hard, and smooth, and on section no definite lobulation whatever can be made out. Microscopically there is found a finely diffused network of scar tissue all through the tissue, separating the lobules into little groups of cells (Fig. 175).

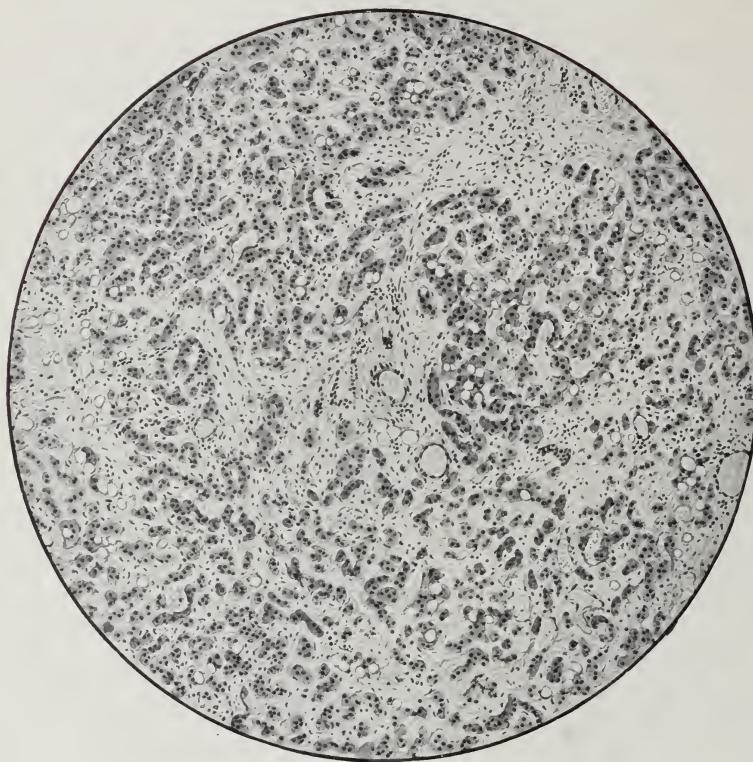


Fig. 175.—Hanot's cirrhosis.

Wilson's Disease.—A peculiar combination of advanced nodular cirrhosis of the liver with degenerative changes and neuroglial scarring in the lenticular nuclei and sometimes with striking pigmentation at the margin of the cornea (Kayser Fleischer pigment). The symptoms are tremor, dysphagia, contractures of extremities and some psychic disturbances but no evidences as a rule of the cirrhosis of the liver. Most authors describe the hepatic changes as peculiar in that they offer little obstruction to the flow of blood and in general they agree that the changes in the liver are primary and those in the lenticular nuclei secondary to the formation of some toxin not more closely defined.

LITERATURE

- Ackermann: Pathol. Bindegewebsneubild. in der Leber, Berlin, 1894.
- Barnes and Hurst: Brain, 1925, xlviii, 279; 1929, lii, 1.
- Ford: Amer. Jour. Med. Sci., 1901, cxxi, 60.
- Heineke: Ziegler's Beiträge, 1897, xxii, 259.
- Howland, J., and Richards, A. N.: Chloroform Poisoning, Jour. Exp. Med., 1909, xi, 344.
- Kretz: Verh. Dtsch. Path. Gesellsch., 1904, viii, 54; 1905, ix, 260. International Clinics, 1905, iii, fifteenth series, 289.
- Lehoczky: Arch. f. Psychiatr. u. Nervenheilk., 1934, cii, 260, 788.
- MacCallum: Johns Hopkins Hosp. Rep., 1902, x, 375. Jour. Amer. Med. Assoc., 1904, xlivi, 649.
- McIndoe: Cirrhosis of Liver, Arch. Pathology, 1928, v, 23.
- Meder and Marchand: Ziegler's Beiträge, 1895, xvii, 143.
- Ogata: Ziegler's Beiträge, 1913, lv, 236.
- Opie: Jour. Exp. Med., 1910, xii, 367.
- Ponfick: Virch. Arch., cxviii, cxix, cxxxviii.
- Ribbert: Deutsche med. Woch., 1908, xxiv₂, 1678.
- Seyfarth: Verh. Dtsch. Path. Gesellsch., 1921, xviii, 255.
- Sjövall: Acta Pathologica et Microbiologica Scandinavica, 1929, vi, 193.

CHAPTER XVII

FURTHER ILLUSTRATIVE EXAMPLES OF DESTRUCTIVE AND REPARATIVE PROCESSES

Structure of arteries. Arteriosclerosis. Anatomical changes in arteriosclerosis in aorta and other vessels. Pathogenesis and aetiology. Sclerosis of peripheral arteries: Thrombo-angiitis obliterans. Arteriolosclerosis. Mechanical and infectious injuries to arteries. Cerebral haemorrhage: Effects.

Structure of Arteries.—The structure of the arteries changes as we pass from the aorta into the branches and finer ramifications. Everywhere, however, there is, as in the case of the veins and lymphatics, a lining membrane composed of a single layer of flattened endothelial cells which offers a smooth surface and acts as a protection for the blood against any contact with other tissues.

In the aorta the outer wall of adventitia is composed of a loose connective tissue carrying blood-vessels, nerves, etc., and containing a loose network of elastic fibrils. The middle coat or media is composed of elastic tissue, smooth muscle, and connective tissue. The elastic tissue which forms the most prominent feature is arranged in a complex of laminae, with fibrils which run obliquely and connect the laminae. In a cross-section one sees the main circular strands of elastic tissue about equidistant from one another, running with a somewhat wavy course around the vessel, and connected by numerous oblique bridge-like fibres; but since in a longitudinal section one sees exactly the same thing, it seems evident that were the elastic tissue isolated, one might discern something roughly approaching the form of a series of imperfect concentric tubes. It seems to be about as though one should paste on a sheet of paper, one after another, pieces of gauze irregular in size and outline, gluing only their edges where they happen to fall, until a uniform thick layer is produced, and then make a tube of the whole, except that each piece of gauze, where it stands away from the underlying and overlying pieces, should be connected with them by many oblique threads. In a tangential section of the media the muscle-fibres, instead of being perfectly circular in their course, form a sort of herringbone pattern, and are surrounded everywhere in the same meshes by loose white fibrous tissue.

There is a vague outer condensation of the elastic fibres which might be called the external elastic lamella, but at the inner margin of the media there is a continuous membrane, uninterrupted except for certain fenestrations, which would correspond to the sheet of paper in the model—the internal elastic lamella. It is difficult to decide whether this should be taken as part of the media or part of the intima, but it is more convenient to consider it with the latter. Blood-vessels, the vasa vasorum, springing from the roots of the intercostal arteries, etc., penetrate the adventitia and extend part way through the media.

The intima of the aorta, which in very early life seems to show little but the endothelial layer resting upon the internal elastic lamella, develops in later life a much more complex structure. Just inside the internal elastic lamella there is a layer composed partly of smooth muscle running longitudinally, and partly of fibres and lamellæ of elastic tissue which are abundantly connected with the fenestrated membrane. This is the musculo-elastic layer inside which a second layer may generally be distinguished, composed of similar elastic structures intermingled with white fibrous connective tissue. Within this is a third layer immediately beneath the endothelium, which is made up of connective tissue alone, the cells of which show beautiful branching processes. Although with the advance of age the intima thus becomes progressively thicker (Jores), it is normally a very thin layer as compared with the media.

The smaller arteries differ from this in their structure in that the medial coat contains practically no elastic tissue. The internal elastic lamella persists and there

is a more evident external elastic lamella with abundance of lamellated or fibrillar elastic tissue in the adventitia, but the media shows only the most delicate branching, cobweb-like fibrils which run in general toward the lumen and not around it (radial fibres of Dürck). This sudden change from the elastic type to the predominantly muscular type is observed everywhere shortly after the branches leave the aorta. The laminated elastic type is maintained by the carotids for a somewhat greater distance, and the pulmonary artery is of this structure, so that it almost seems that the original aorta with its branchial arches had kept to this structure while all the other branches develop the muscular type.

In the smaller arteries the intima becomes simplified until finally, in the very small vessels, the endothelium lies almost directly upon the internal elastic lamella. Nevertheless, in many small arteries, especially in such organs as the kidney, stomach, etc., the internal elastic lamella splits in the third decade into three or four concentric layers, between which are connective-tissue elements. It will be seen that much attention has been devoted to this reduplication of the elastic lamellæ in the discussion of arteriosclerosis. In accord with these differences in structure between the aorta and smaller vessels we may expect differences in their pathological alterations.

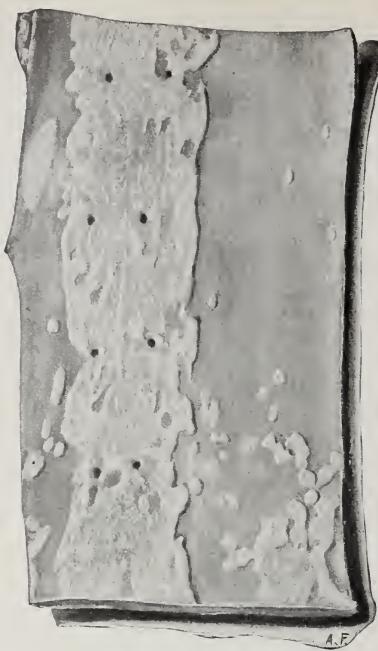
Krogh and his pupils have emphasized the importance of certain contractile cells (Rouget cells) which are applied about the outer surface of capillaries and apparently control their calibre. (A. Krogh, Anat. u. Physiol. der Capillaren, 1924).

Various forms of arteriosclerosis and some mechanical injuries affecting arteries, may be considered here, but syphilitic changes, including most aneurysms, will be described under Syphilis.

ARTERIOSCLEROSIS

Arteriosclerosis is the term in most general use for that disease of the arteries which leads to their loss of elasticity, and changes in the appearance and structure of the intima and other coats which lead to dilatation and deformity of the artery. The condition is sometimes spoken of as atheroma of the arteries, and there is much in favor of the name "atherosclerosis," suggested by Marchand, but the old term, "endarteritis deformans," of Virchow, is now but little used.

The earliest changes recognizable in the aorta as the beginning of arteriosclerosis are found in the form of very slightly elevated, flattened yellow streaks, which usually run on the posterior wall of the vessel, longitudinally, between and about the openings of the intercostal arteries, although they are not by any means confined to this position (Fig. 176). With further advance of the disease these yellow patches are to be found diffusely distributed among the older lesions. Sections passing through them show that, while the artery is normal elsewhere, the elevation is due to a distinct thickening of the intima produced by a new formation of connective tissue, with small and large wandering cells (Fig. 177). Both the original branched connective-tissue cells and the wandering cells are found to be loaded with fat. Such fat is by no means lodged only in the deeper layers of the intima, but extends up to the surface, where the fat-laden wandering cells lie free in crevices. If the upper layer of the intima be stripped off and laid flat under the microscope, the branched connective-tissue cells with their fine fat-droplets can be well seen.



A.F.

Fig. 176.—Fatty streaks and patches in the intima of the aorta.

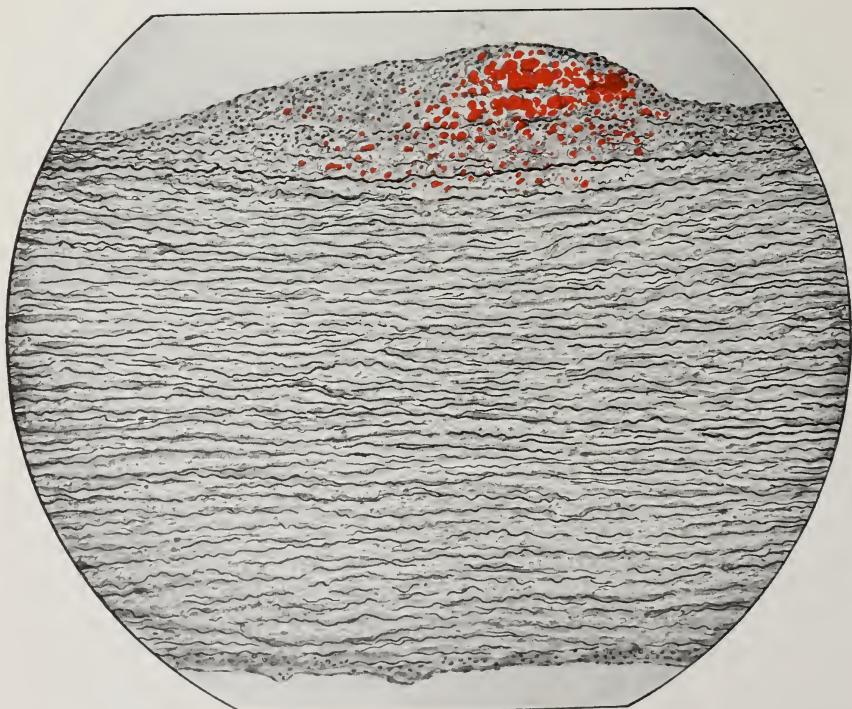


Fig. 177.—Section through a fatty streak in the aorta. (The fat is stained red with Sudan.)

In a later stage the hillock of thickened intima becomes more extensive and thicker, and the tissue becomes hyaline or necrotic about the most abundant accumulation of fat. The superficial or innermost layers become very much thickened, and are now composed of a dense, homogeneous connective tissue (Fig. 178). Rarely do the *vasa vasorum* penetrate from the media to take part in this new formation of tissue, and generally they can be found only in the later stages, although it is stated that injections reveal an increased richness in the vascular supply about the patches of disease. Nor is there any invasion of wandering

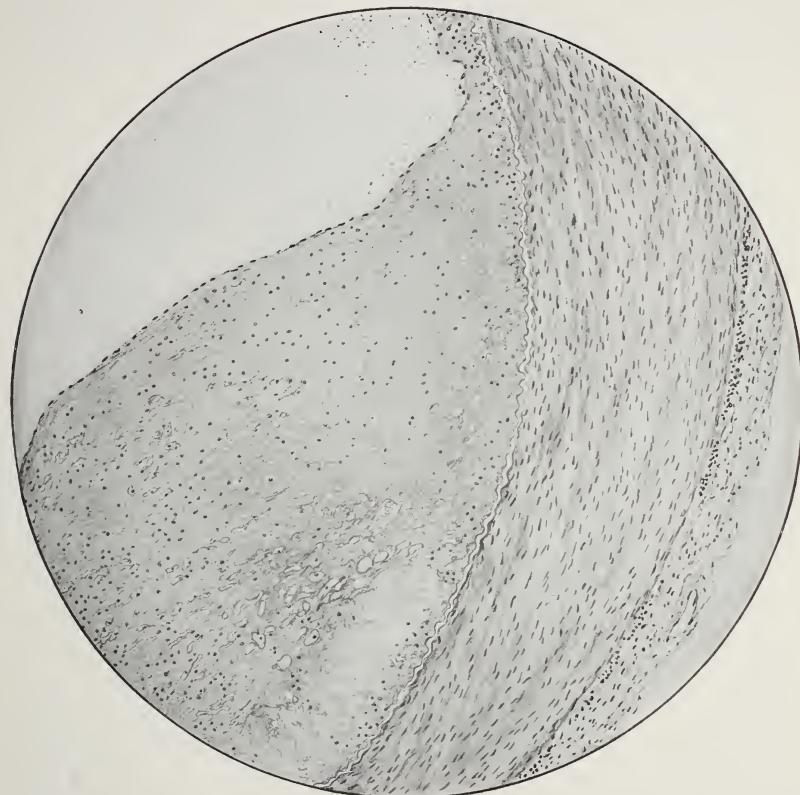


Fig. 178.—Margin of a relatively fresh arteriosclerotic plaque.

cells at all commensurate with the new formation of tissue. The dense connective tissue formed over the mass of fat-containing tissue is bluish white and translucent. It covers the yellow, opaque, fatty material, so that it now appears to lie in the depths of the intima, encroaching on the musculo-elastic layer and the internal elastic lamella. When such an aorta is opened, the most common and characteristic appearance of arteriosclerosis is revealed (Fig. 179). Elevated rounded or irregular plaques or patches stand up from the intimal surface like solidified drops of paraffin. They are often about the orifices of the intercostal

arteries, but may occur anywhere. They seem hard and homogeneous, but on cutting through them there is always to be found the mass of opaque, yellow, fatty material hidden in their depths. From the cut edge this yellow mass can be expressed or dug out, and its soft, mushy character was the origin of the name atheroma. Often the fat extends so as to form a yellow halo about such a plaque, the opaque material shining through the relatively thin surrounding intima.

At this stage the internal elastic lamella underlying the plaque generally shows fragmentation or interruptions, or it is frayed out into several thin laminæ which again unite at the other edge of the plaque. This is best seen in the smaller arteries (Fig. 180), but is visible also in the aorta, and is regarded by Jores as the most characteristic feature of



Fig. 179.—Arteriosclerotic plaques in the aorta about the intercostal arteries.

true arteriosclerosis. Usually the longitudinal muscle-fibres of the musculo-elastic layer are involved in the necrosis in the depths of the plaque, and in great part destroyed. Delicate elastic fibrils appear in the new tissue which forms inside the musculo-elastic layer, and are thought by Jores to arise independently of the lamellæ of that layer. They are, he thinks, more characteristic of such changes as occur in the obliteration of vessels in inflammatory processes or in the organization of thrombi than of the true arteriosclerotic changes.

The media under the plaque, which, for the sake of the various theories which have been put forward, has been studied with especial care, generally shows surprisingly slight alterations. Very definite thick

plaques may form in the intima, while the underlying media seems practically intact, although we realize, of course, that ordinary staining methods may well fail to reveal qualitative changes in the elasticity of the elastic tissue or the contractility of the muscle. Nevertheless, there are often slight accumulations of fat in that layer, and it is generally thinner under the plaques than in neighboring regions. Indeed, such thinning out may, especially in the smaller vessels, proceed almost to the complete disappearance of the coat, leaving us to determine



Fig. 180.—Sclerotic plaque in the mesenteric artery, showing reduplication of elastic lamellæ. Lipoid substances are stained red with Sudan.

whether this is the primary injury to the vessel-wall which is compensated for by the formation of the plaque, or the result of pressure from the plaque itself. Again, we have to determine whether the necrosis which occurs in the substance of the plaque is due to malnutrition of the central part of that mass of tissue, or to primary injurious processes affecting the newly formed tissue. The time-honored explanation has been that nutrition from the *vasa vasorum* on the one side, and from the blood in the main vessel, on the other, kept alive the outermost and innermost layers of the plaque, while allowing the centre to perish

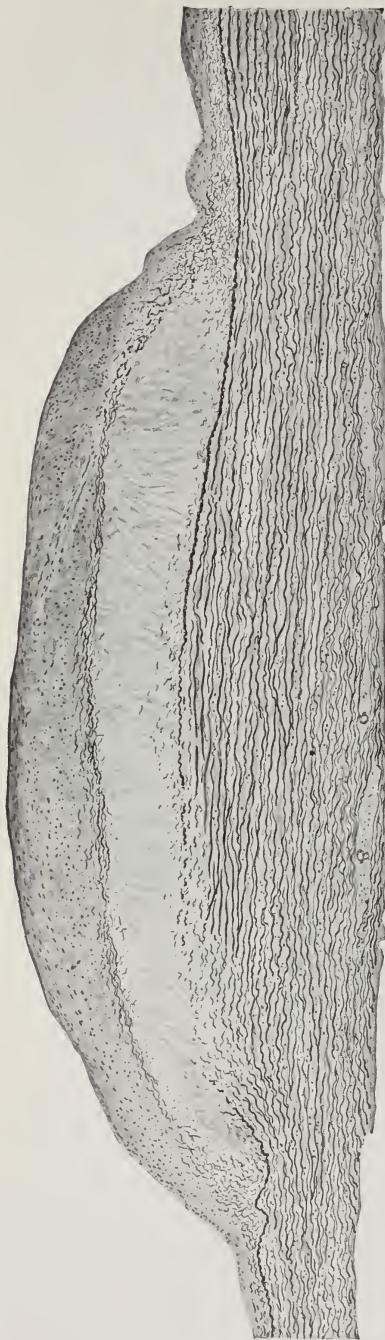


Fig. 181.—Section of an older sclerotic plaque in the aorta, showing cholesterine crystals in the necrotic atheromatous substance.



Fig. 182.—Late stage in arteriosclerosis of the aorta: ulceration and calcification.

(Fig. 181). At any rate, the central mass often becomes very soft, so that if the inner wall or roof of this sac gives way, the contents are washed out into the blood-stream and the ragged edges and base of such an "atheromatous ulcer" are exposed to the circulating blood, often with the result that a thrombus forms in that situation.

The soft material is found to be rich in crystals of cholesterine as well as globules of fat, some of which are evidently cholesterine esters,



Fig. 183.—Arteriosclerosis of the renal artery showing fat-laden wandering cells in the thickened intima.

since they are doubly refractive, while others are neutral fats. Granules or little spherules or larger, irregular masses of calcium and magnesium phosphates also appear, and, indeed, the deposit of calcium salts may be so great that the whole plaque becomes converted into a solid plate of stony material which will crack with a dry snap, like a scale of oyster-shell (Fig. 182). Such plates correspond, of course, fairly well with the contour of the artery, although they project awkwardly when the vessel is laid open. Usually they are smoothly covered

with a delicate layer of intimal tissue and endothelium; otherwise they form a base for the deposit of thrombi. Actual bone formation may occur, with marrow cavity and marrow rich in cells, either in calcified plaques in the vessel wall or in old calcified thrombi which adhere to it.

The sequence of events which leads to the presence of crystals of cholesterine, granules and masses of calcium, etc., has been explained by Klotz and others as follows: Glycerin and cholesterine esters are deposited in the tissue of the plaque, but readily split up and become saponified, with liberation of the soluble glycerin and crystalline cholesterine. Of the soaps formed, with the resultant fatty acids, calcium soaps are insoluble, and remain where they are formed until the advent of phosphates in the circulating fluids, whereby another reaction occurs which leaves the calcium in the form of hard calcium phosphate.

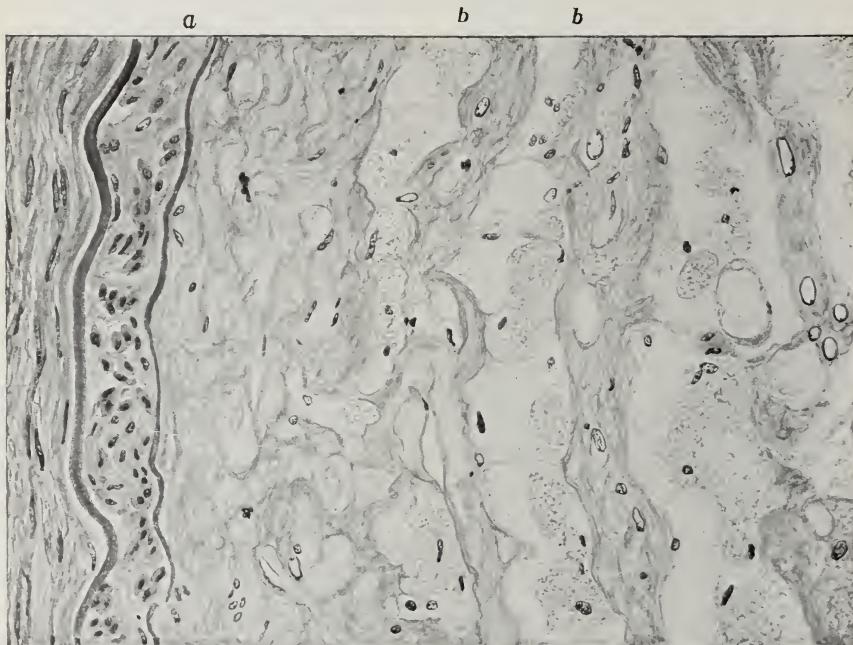


Fig. 184.—Lower layer of the intima from Fig. 183, showing the musculo-elastic layer (*a*) and the fat-holding wandering cells in crevices (*b*).

It must be obvious, from this description, that since all these stages may and frequently do occur at one time in the same aorta, the most variegated appearance is produced. Smooth, rounded, gray eminences scattered along the aorta, and especially about the orifices of the intercostal and other arteries, are interspersed with irregular yellow patches of staining of the relatively unthickened intima, while atheromatous ulcers and sunken, calcified remnants of former atheromatous plaques occur side by side with them. Sometimes the calcification is so extensive that the aorta is converted into a rigid tube.

In all cases there is very great diminution of the elasticity of the artery wall, although its rigidity may be increased. Usually the aorta in advanced sclerosis is dilated and lengthened so that it curves from

one side of the vertebral column to the other, and bulges irregularly at different points. Distention of such an artery reveals the rigidity and inelasticity of the affected parts of the wall, while other places may still be quite elastic.

Exactly the same processes in the same sequence are found in the branches of the aorta (Fig. 183, 185). In these branches, in comparison with the calibre of the vessel, the intimal plaques may be far thicker, so that they go far toward obstructing the channel. It is by no means rare

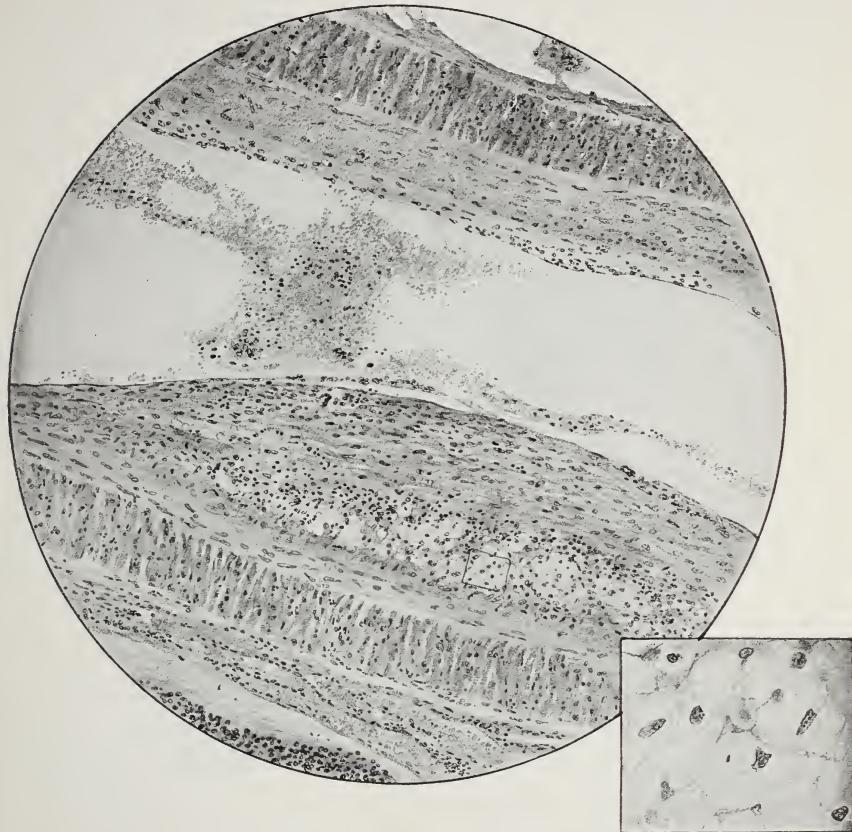


Fig. 185.—Coronary artery encroached upon by a thick arteriosclerotic plaque.

that the lumen of such an artery as the superior mesenteric or the splenic is reduced to a mere slit for a short way as it passes the projecting mass. A cross-section at such a point reveals the misshapen lumen crowded over the one side of the artery, and bounded on one side by the normal wall of the vessel, with its wavy internal elastic lamella, on the other by a great mass of tissue over the outer side of which the media stretches as a thinned-out layer and the internal elastic lamella as a tense straight line. The blood-pressure in the distal part of such a vessel must be greatly reduced, and yet one may find a series of

plaques of this kind ranged along its course. The smaller ramifications of the arteries in the organs often show particularly well such relatively huge masses of new tissue bulging out one wall, and encroaching greatly upon the lumen. The endothelium accommodates itself to the decreased surface it must cover, and is seen to be intact until, through its injury or otherwise, a thrombus completes the occlusion of the vessel. Calcification of the necrotic and fatty plaques occurs, exactly as in the aorta. Arteriosclerosis of this type is very common and important in the coronary arteries of the heart where so much depends upon the instant supply of blood to the heart muscles (Fig. 185). It must be discussed in detail later.

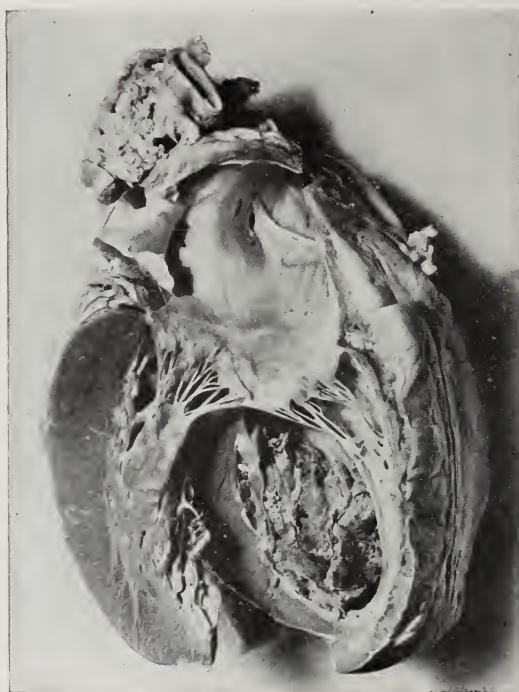


Fig. 186.—Occlusion of coronary, myocardial scarring with thrombus formation.

Pathogenesis and Aëtiology.—We are at present, in spite of numerous theories, practically ignorant of the cause of arteriosclerosis. Rokitansky thought the plaques deposited from the blood; Virchow regarded the whole process as inflammatory, whence his designation, "endarteritis deformans"; Köster also regarded it as inflammatory, but rather in Cohnheim's sense, as an exudative process, because he traced the formation of a cellular exudate in the vessel-walls from the vasa vasorum. Thoma elaborated a theory based on the idea that the cutting off of the placental circulation at birth must necessitate an adaptation of the calibre of the blood-vessels to the changed amount of blood. This, he thought, was effected by a thickening of the intima of the vessels, especially

those which lay in the course of the old umbilical blood-stream. To this process there might be compared the thickening of the intima in arteriosclerosis, which evidently occurs at those points, where, owing to some primary weakening of the musculature of the media, there arose a local bulging of the vessel-wall. In such a bulging area the passing blood-stream would eddy and be retarded, whence the intimal growth, which should be just sufficient to compensate for the bulging out of the media and thereby reinstate the original level of the intimal lining of the vessel. Naturally, such a patch would be thrown into relief by the elasticity of the arterial wall after it is laid open. It is evident that many criticisms of this theory may be offered.

Ranke has, like Thoma, applied mathematical and physical considerations to the explanation of the localization of arteriosclerotic changes and perhaps confirms Thoma's ideas with regard to compensatory processes in the arterial wall. One has the impression, however, in spite of the attempts of Zinserling and others to plot out the distribution of these lesions, that they are really irregularly placed, and that instead of their position being determined by the laws of pressure in the arterial tree, these laws must be coped with after the lesion is developed. The statement that arteriosclerotic plaques are localized about the orifices of the branches of the aorta because the pressure at these points constitutes a more severe test of the strength of the wall than at other points in the aorta, seems labored, and, at any rate, the plaques are just about as likely to develop at any other point.

Marchand defined arteriosclerosis as a nutritive disturbance of the arterial wall with degeneration and hyperplasia. Aschoff, too, emphasizes degenerative changes in the intima. They regard it as a wear-and-tear process, with increase in the connective tissue to maintain the strength, if not the elasticity, of the wall. Hueck, who recognizes the fact that many dissimilar changes are loosely grouped as arteriosclerosis, states that they have in common progressive degeneration with disorganization or, perhaps better, reorganization of the vessel wall.

All these definitions bear very little upon the cause of the disease, and it is unsatisfactory to believe with Jores that it is natural for the intimal layer to increase in thickness with age and thereby to become especially prone to degeneration.

It seems more probable that, as the French have so long maintained, arteriosclerosis is the effect of some injurious or poisonous agent acting upon the intima of the arteries as it might upon any other organ, with destruction, fat accumulation, and repair. What this agent can be is still uncertain. Every sort of poisonous substance has been experimentally administered to animals, either by mouth or by injection into the blood-stream or tissues, but without any very constant results. The ætiological factors most commonly held responsible, alcohol, lead, nicotine, etc., have occasionally given rise to changes comparable to those of arteriosclerosis, but not constantly—indeed, with alcohol and lead the experiments have generally proved negative. More stress has been laid recently upon bacterial infections which may produce lesions only later leading to recognizable arteriosclerotic changes. But it is practi-

cally impossible in an analysis of any large series of cases of infections, or of arteriosclerosis, to show any particular association of the two, although conditions such as diabetes mellitus are with great frequency accompanied by arteriosclerosis.

It is clearly of the very first importance that we should learn the cause or causes of arteriosclerosis, now so completely obscure, since it results in so many disabling and fatal conditions, especially as it affects the coronary arteries, renal arteries and those of the brain. But, so far, the experimental studies have led to no very acceptable results.

Anitschkow and his students have attempted to show that the essential cause is a disturbance of cholesterine metabolism, and their work has been repeated and elaborated by a host of others. It was found that if rabbits be fed for a long time with cholesterine dissolved in oil, great accumulations of the substance are found in the tissues with depositions in the wall of the aorta producing changes like those in human arteriosclerosis. But rabbits and a few other animals are peculiar in this respect and no such results are obtained in dogs or cats, or other animals in which the cholesterine content of the blood is normally higher than in rabbits and in which cholesterine and other lipoids are evidently more easily disposed of. It seems therefore that such results cannot be applied directly to the explanation of human arteriosclerosis. Nor is it clear that in the rabbits the changes in the aorta are primarily the effect of the presence of the cholesterine and its esters. It seems rather that some injury to the vessel wall, possibly the effect of some harmful impurity of the lipoids fed, prepares a place in the tissue of the aorta in which the cholesterine is readily deposited as it is in some other tissues.

In human cases there is seldom any obvious excess of circulating cholesterine in the course of arteriosclerosis and there, too, it seems that a search for the injurious agent which prepares a place for the deposit of lipoid material, is most important.

All of the work on experimental cholesterol arteriosclerosis in its relationship with human arteriosclerosis has been carefully discussed by G. L. Duff, in the Archives of Pathology, 1935, XX, 81, 259, and to this the student is referred.

LITERATURE

- Anitschkow: Wesen u. Entstehung der Atherosklerose. *Ergebn. d. inn. Med.*, 1925, xxviii, 1; *Verh. Dtsch. Path. Gesellsch.*, 1925, xx, 149 (Discussion).
- Arteriosclerosis, A Survey of the Problem by various authors, New York, 1933.
- Aschoff: Beihefe z. Med. Klinik, 1908, iv, 1.
- Aschoff: Lectures on Pathology, New York, 1924: *Brit. Med. Jour.*, 1932, ii, 1131.
- Benson: Coronary Arterial Diseases, *Arch. of Pathology*, 1926, ii, 876.
- Hueck: Münch. Med. Woch., 1920, 535.
- Klotz: Ann. Clin. Med., 1926, iv, 814.
- MacCallum: Physiological Reviews, 1922, ii, 70.
- Marchand: Verh. d. xxi. Congr. f. inn. Med., 1904.
- Ophüls: Stanford University Publications, 1921, i, 1.
- Ranke: Ziegler's Beiträge, 1926, lxxv, 269.
- Saltykow: Ziegler's Beiträge, 1914, 57, 415.
- Versé: Dtsch. Med. Woch., 1925, No. 2: *Verh. Dtsch. Path. Gesselsch.*, 1925, xx, 67.
- Ziegler's Beiträge, 1916, lxiii, 789.

SCLEROSIS OF PERIPHERAL ARTERIES

The peripheral arteries contrast so sharply with the aorta in their architecture that we may well look forward to differences in the form of the arteriosclerotic lesions found there. The most striking difference is in the frequent calcification of the media, a thing practically never



Fig. 187.—Femoral artery showing transverse rings of medial calcification (Mönckeberg's sclerosis).

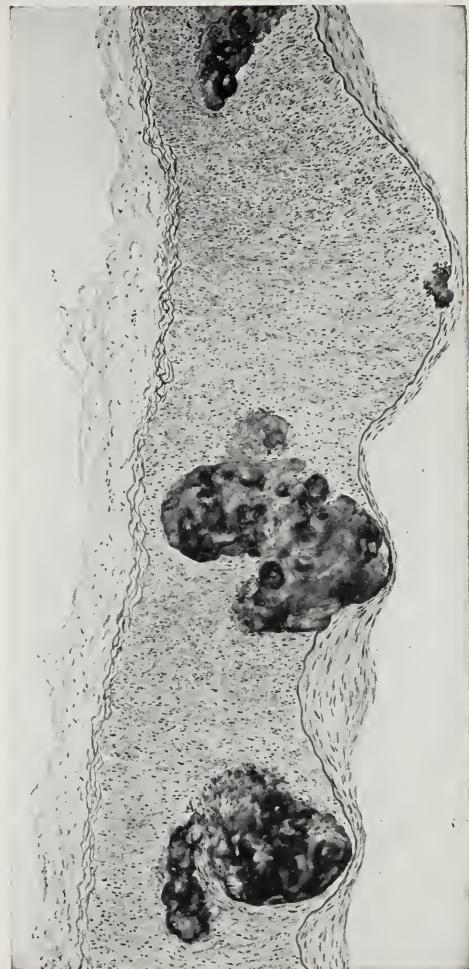


Fig. 188.—Medial sclerosis of Mönckeberg in a femoral artery in longitudinal section. The calcified rings are seen in cross-section.

seen in the aorta except in the most advanced cases of atheroma, where there seems to be an extension or later involvement of the media in the necrosis and calcification that have long been going on in the intimal plaque. But in the femoral arteries one finds rings of hard, calcified material, closely set, so that the artery feels like a trachea. This form,

although known long before, was described in detail by Mönckeberg, and is often called Mönckeberg's sclerosis. When the artery is laid open the calcified rings sink a little below the intervening substance (Fig. 187), and the artery, while rather rigid, often not narrowed by the change. Sections (Figs. 188, 189) show that the calcium is deposited in the substance of the media often very irregularly, but generally in harmony with the arrangement of the muscle-fibres. Indeed, one can see (as Hueck also points out)

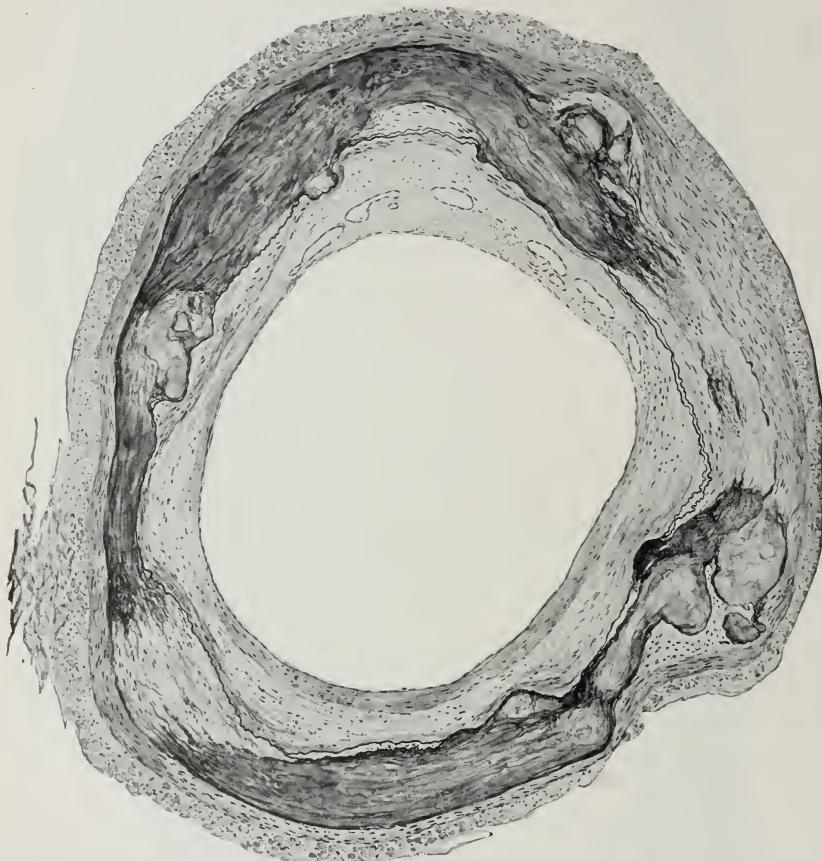


Fig. 189.—Mönckeberg's medial calcification in a peripheral artery.

that the calcium is really laid down in minute granules in the connective-tissue fibrils between the muscle-cells, and it is only when it becomes very abundant and welded together that the muscle-cells finally disappear. The internal elastic lamella is stretched over these stony masses and often interrupted. Actual bone, often with new formed marrow, sometimes appears to replace part of the calcified media. The intima is sometimes not much thickened over these rings in the larger arteries and the lumen may be actually widened. Mönckeberg insists

that such medial calcification should be sharply separated from arteriosclerosis as it occurs in the aorta. It exists independently, and it is not safe to assume that there is arteriosclerosis of the aorta when distinct hard rings can be felt in the radial or in the femoral. But in the smaller branches, such as the popliteal, tibial, dorsalis pedis, etc., thickening of the intima with lipoid deposit exactly like that in the aorta makes its appearance and is so extreme in places that for a short way the lumen of the vessel is reduced to a pin-point opening, only to widen out lower down and again become narrowed. Complete obstruction may

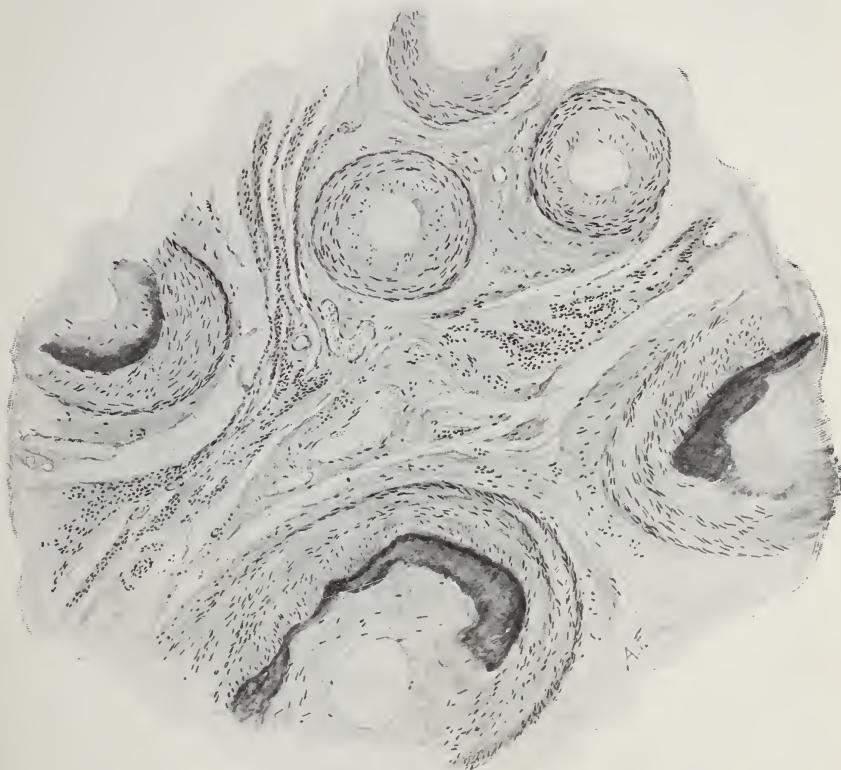


Fig. 190.—Wall of senile uterus: obliterative endarteritis with calcification.

result from thrombosis in some cases. Collateral circulation may be developed to some degree, but amputation of the leg for gangrene is a very familiar occurrence, not only in cases of diabetes mellitus, in which this change is common, but in many other cases in which there is no diabetes. *x*-Ray examination of such a leg shows the calcified vessels very clearly.

In the smaller arteries and arterioles narrowing of the lumen occurs under various circumstances and in various ways. In general, two main processes are concerned which are analogous to those seen in the larger

vessels. Either the intimal layer becomes thickened, often with reduplication of the internal elastic lamella so as to reduce the calibre of the vessel, or the cavity is filled with a thrombus which is then organized and recanalized, so that instead of the original lumen one or more small eccentric channels arise.

The plugging of a vessel by a clot or thrombus often has a protective significance in that it abruptly obstructs the flow of blood. It is the natural method of stanching haemorrhage, and although it may be ineffectual when a large vessel is cut, it successfully closes the torn ends of the small ones. When a vessel is ligated, a clot forms at the point of the ligation and extends to the next branch, where the blood-stream is still active. If the wall of the vessel is injured, the stream may continue until the lumen is filled by the clot which forms on the walls. Since this is formed in the moving blood, it will have the character of a thrombus. When a vessel is obstructed at a point by a thrombus so

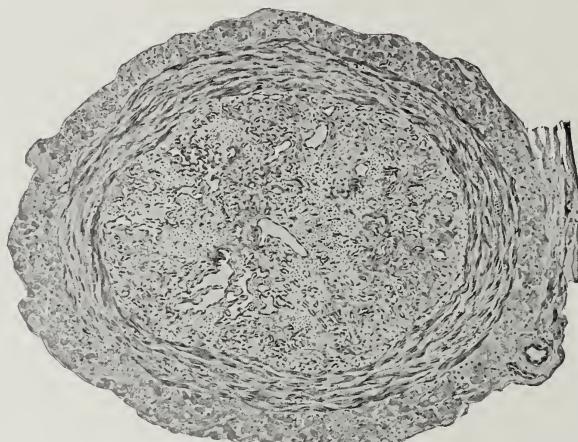


Fig. 191.—Vein with old thrombotic occlusion recanalized by new blood-channels.

that the lumen is open on each side, efforts are made to re-establish the circulation. The thrombus is "organized" by the springing up of capillaries and connective tissue from the vessel wall which replace it with a vascular granulation tissue. Crevices in its substance are lined with endothelium and constitute new blood-spaces. The dilatation and anastomosis of these new vessels and blood spaces may produce new channels which will again carry blood through the obstructed area. They are in time supplied with muscular and elastic coats like those of any other vessel (Fig. 191). A vessel thus reinstated seems like an elastic cord, but from its cut end many fine streams of blood spurt.

The closure of the ductus arteriosus is an example of the first type, and it suggests the idea that the intima thickens and occludes the vessel because the passage of blood through it is no longer necessary. So, too, in disused organs, such as the sexual organs in old age (Fig. 190), the arteries are normally narrowed by such a process. In the uterine wall, however, after each pregnancy the enormously widened arteries are re-

duced to the normal calibre partly by this process, but partly (Goodale) by the formation of new channels within the old. This involves extreme hyaline or vitreous changes in the original elastic lamella and the development of new tissue within it, with canalization and differentiation of elastica and smooth muscle in the walls of the new channels. It seems that this could most readily occur by the organization of thrombi in these vessels. Obliterating endarteritis through the proliferation of the intimal coat is supposed generally to occlude such arteries as are impinged upon by some destructive process. A good example is found in the blood-vessels which lie in the path of an extending tuberculous cavity in the lung. They become almost solid cords and persist as such, stretching across the cavity and only giving rise to sudden haemorrhage when the process is too rapid and they are taken by surprise. When they are slowly eaten through no bleeding occurs. If such a cord is cut across a minute droplet of blood can be squeezed out of the cut end, as might happen if the lumen were gradually narrowed by thickening of the intima, but sections sometimes show that these arteries have been thrombosed and recanalized.

The process of obstruction of arterioles and venules by thrombi with subsequent incomplete reestablishment of their lumen by replacement of the thrombus by vascularized connective tissue is conspicuous in a great variety of inflammatory processes, and is doubtless far more common than anyone suspects in the course of disease and after surgical operations when some transient discomfort is hardly recognized as arising from the injury and thrombotic occlusion of a blood-vessel.

Thrombo-angiitis Obliterans, Buerger's Disease.—A serious affection of the arteries apparently quite distinct from arteriosclerosis, is that which affects young adults between the ages of twenty-five and forty and is found usually in Russian Jews. This was described by Buerger in 1908, and has since been widely recognized.

The symptoms begin with coldness and pallor of the extremities, pain and a peculiar tickling or burning sensation with inability to walk more than a short way without rest. Finally, gangrene of the toes appears and may extend to involve the whole foot or leg. The inability to walk, which is called intermittent claudication, is explained by the fact that the arteries of the extremity are practically pulseless and merged into a firm cord in which they are bound together with veins and nerves. Not enough blood reaches the muscles to allow them to keep up their contraction, and the excruciating pain is probably caused by the involvement of the nerves in this cord. *x*-Ray pictures show no shadow of the vessels because they are usually not calcified. On section, too, (Fig. 192) they present an extraordinary contrast to those found in senile and diabetic gangrene in as much as there is little change in the media although it and the surrounding tissue may be infiltrated with wandering cells and indurated by the new growth of fibrous tissue. Nor is the internal elastic lamella stretched, distorted and frayed out as in the arteriosclerotic process. Instead, it maintains its contour around the original lumen of the vessel but is thrown up into close folds. The lumen is filled with vascular granulation tissue, generally with numerous

endothelium-lined spaces through which a little blood may flow. These result from the organization of the thrombus which has caused the occlusion of the artery. In very early cases before gangrene has set in, obvious thrombi are found there and even in the old cases the process is progressive and at the upper end of the occlusion the canalized connective tissue may give place to a propagated thrombus. The associated veins are generally thrombosed and even the branches which are

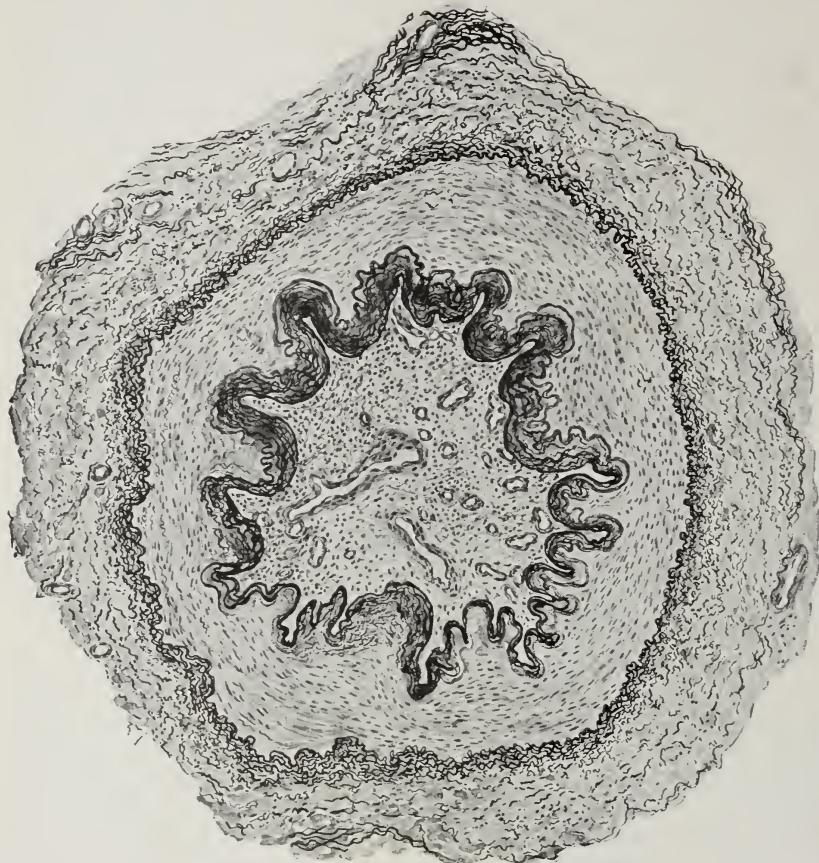


Fig. 192.—Obliterating endarteritis (thrombo-arteritis obliterans) with shrinkage of the walls and partial recanalization.

widened in forming a collateral return channel for the circulation become obstructed. The attempt to produce a collateral arterial circulation widens the small arterial branches with an apparent increase in the arterioles as shown by injection but this is generally inadequate to maintain the nutrition properly.

It appears from the studies of Jager, Sprunt and others that this process may also affect the arteries of the internal organs producing changes in the brain, kidneys and even in the digestive tract.

The affection is not limited to Jews and is occasionally recognized as

following in point of time, at least, some infectious process, such as encephalitis. No actual knowledge of the causative factor is in our possession as yet, and although the ordinary bacterial infections may probably be excluded, it is fairly evident from the inflammatory reaction about the arteries, veins and nerves that some infectious agent has been concerned. It is generally thought, too, that smoking and especially cigarette smoking, goes far to intensify the disease. Lewis suggests that the pain is due to arterial spasm like that in angina pectoris.

LITERATURE

- Buerger: Amer. Jour. Med. Sci., 1908, cxxxvi, 567; Jour. Amer. Med. Assoc., 1909, lii, 1319; Surg., Gyn. and Obst., 1914, xix, 582.
Goodale: Studies from the Royal Victoria Hosp., 1910, ii, No. 3.
Jager: Virchow's Arch., 1932, ccxxxiv, 526.
Lewis: Jour. Amer. Med. Assoc., 1926, lxxxvii, 302; Arch. Surg., 1927, xv, 613.
Mönckeberg: Virchow's Arch., 1903, clxxi, 141; 1914, cccix, 408; Klin. Wochenschr., 1924, iii, 1473.
Sprunt: Southern Med. Jour., 1934, xxvii, 698.

Arteriolosclerosis.—It is perhaps questionable whether arteriolosclerosis should be separated from arteriosclerosis since the same type of metabolic disturbance involving the lipoids, probably associated with some direct injury, seems to be its cause. But these changes in the minute arterioles have come into such prominence in relation with high blood-pressure and with renal disease that they should be emphasized separately.

When for a long time the blood-pressure of the patient has stood continuously at a very high level, such as 180 to 250 mm. of mercury, with corresponding symptoms, and especially when evidences of advanced renal disease are present, we may confidently look for arteriolar lesions at autopsy. The question as to the relation of these phenomena to each other is discussed at length later, especially as to whether they are necessarily interdependent. At autopsy there may sometimes be no marked arteriosclerosis of the large arteries although it is common to find their walls slightly firmer than normal, possibly as a response to the long continued high pressure. The changes in the very small arteries or arterioles are found almost everywhere, although we are accustomed to find them most readily in the kidneys, pancreas, spleen, about the adrenals and in the voluntary muscles. They consist in a hyaline thickening of the walls of the smallest arterioles just before they branch to give rise to the capillaries, and it is evident that such pink-staining, hyaline walls are relatively inelastic and that they encroach greatly upon the lumen narrowing it to an extreme degree. Apparently this material displaces, or results from the destruction of some of the muscle-fibers of the wall. Stained with Sudan the thick, hyaline layer shows great quantities of closely packed minute fat-globules so that it looks almost homogeneous red.

It seems possible that this condition may arise locally, especially in certain places, without being associated with great arterial hypertension and, indeed, as will be seen, its rôle in relation to hypertension and renal disease, whether as cause or effect, is still in doubt.

MECHANICAL AND INFECTIOUS INJURIES TO ARTERIES

Other things that happen to blood-vessels are of the most diverse and unrelated character, but in so far as they end in the formation of some

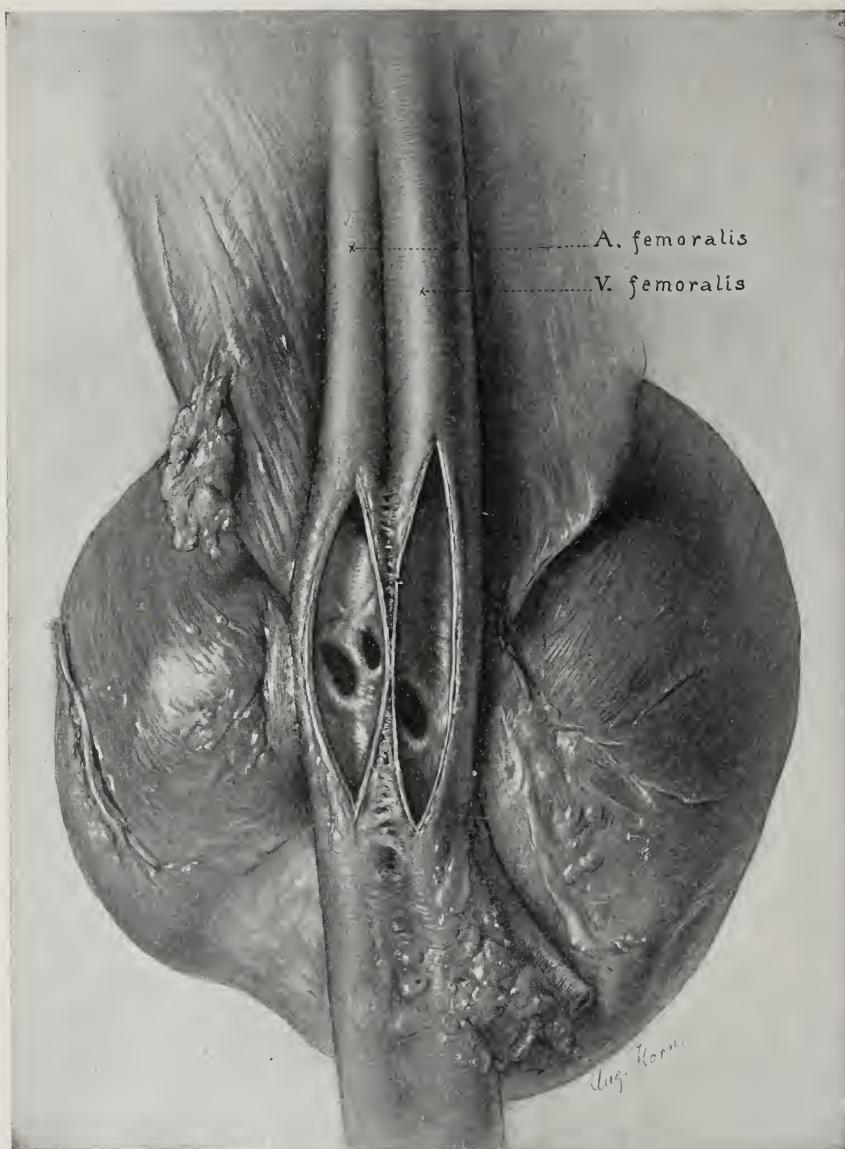


Fig. 193.—Arteriovenous aneurysm caused by a stab wound of the femoral artery and vein.

kind of sac communicating with the vessel they have all acquired the name aneurysm. This of course, originally meant a widening of the

vessel, but since the commonest is the saccular type, which results from syphilitic aortitis, in which part of the wall is so weakened that it is ballooned out by the blood-pressure, this is regarded as a true aneurysm and the others are given qualified names. The syphilitic aneurysms are described under *Syphilis*.

False aneurysms are produced when an artery is torn or ruptured and a haemorrhage outside, it, becoming encapsulated, remains in open communication with the blood-stream, being constantly washed out by an eddy of blood. These must be extremely uncommon except, perhaps, as a continuation and complication of syphilitic or true aneurysms. In one case seen recently there was a saccular aneurysm of the arch with several subsidiary sacculations and a number of tears in the wall of the large sac with haemorrhage outside. It was difficult to say which were true and which false aneurysms, and it seemed probable that some of the sacculations had begun as tears.

Arteriovenous aneurysms are not related to the classical aneurysms except in that a sac is formed in communication with the vessel and receives from it an eddying current of blood. This surprising condition, which is more complicated in that the sac communicates with both artery and vein, arises occasionally when a stab wound or the wound produced in venesection opens an artery and a vein side by side; a haematoma or massive extravasation of blood into the tissue appears and it must be that the outer part clots and is replaced by a dense fibrous wall, while the fluid blood still passes through the cavity from the artery into the vein. A large sac may be formed in this way; in a case seen recently the femoral artery sent a great stream of blood into the vein through such a sac which had, in the course of years, become thin-walled and contained only a pigmented remnant of clot (Fig. 193). There was a loud humming murmur and a thrill over this sac and the pressure of the arterial blood into the vein prevented the return of the venous blood from the leg. On the skin of that leg there were great varicose veins, and a persistent varicose ulcer quite like those seen in old people, although the other leg of this boy was perfectly normal.

In this connection the student should read especially Dr. Halsted's paper on Ligation of the Subclavian, in which he quotes v. Oppel's extraordinary experience with an arteriovenous fistula in the arm. From this it appears that to maintain the life of the tissues distal to such a communication, the easy escape of arterial blood into the venous trunk must be blocked, even if the whole circulation of the arm is left to depend upon collateral channels. The consideration of the mechanical conditions produced by arteriovenous communications is extremely interesting and important, but must be read in the papers referred to.

Dissecting aneurysms are produced by the tearing, under some excessive strain, of the inner coats of the aorta, usually the intima and half of the media. Such a tear is most commonly in the arch of the aorta and has sharp edges as though cut with a knife. In the sclerotic arteries, in which this most often happens, it is easy to split the wall in the middle of the medial coat, and blood presses into the space thus formed and burrows its way far down the length of the aorta and along

many branches, converting each as far as it goes into two tubes, one within the other, the inner formed of intima and half the media, the



Fig. 194.—Dissecting aneurysm of the aorta splitting the arterial wall far into the branches. A haematoma near the bifurcation of the aorta.

outer of the other half of the media and the adventitia (Fig. 194). After this the blood may break through the outer tube and accumulate

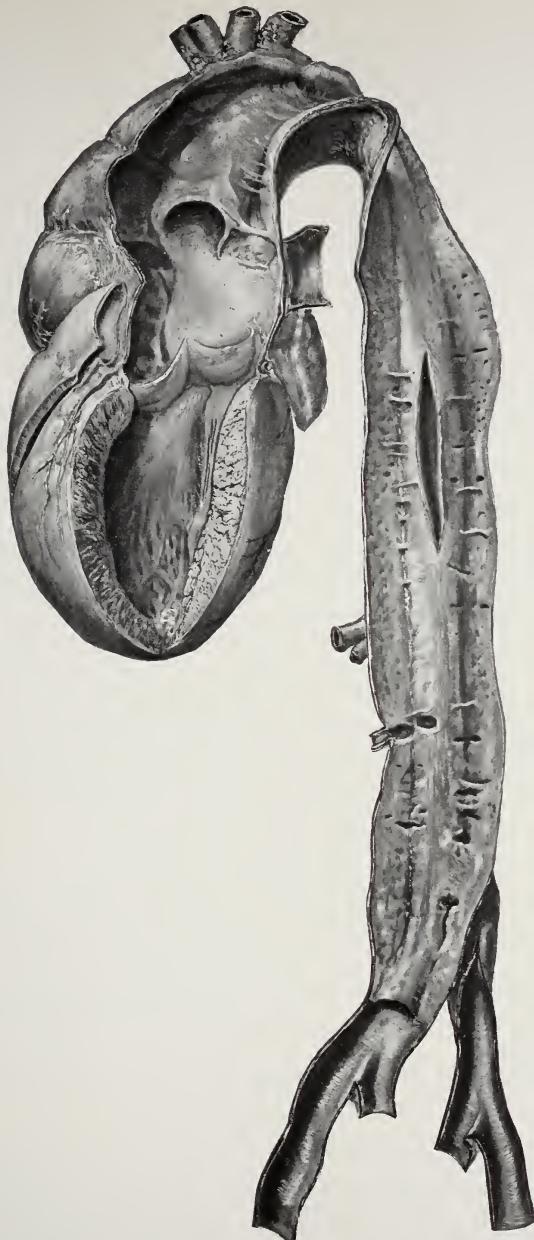


Fig. 195.—Old dissecting aneurysm which has ruptured again into the aorta and established a double aortic channel.

somewhere in the tissues, or back through the inner tube, thus re-entering the regular circulation. The process is really the formation of a haemorrhage or haematoma in the artery wall, but in the last case the

blood actually circulates, and we have seen several cases in which the space in the wall had become lined by endothelium so that something like a double aorta was produced (Fig. 195). It was interesting that the inner tube of each intercostal artery crossed this space and was covered outside with endothelium.

Mycotic Aneurysms.—These are due to infection of the wall of the artery from some abundant source of virulent bacteria such as a vegetation upon a heart valve. It has often been stated that the infection reaches the arterial wall by the *vasa vasorum*, but at least for the mitral valve and the root of the aorta Grant has shown that the bacteria may be directly implanted upon the lining surface from a flapping, torn, aortic valve which bears an infected vegetation. We have seen this many times and the relation is unmistakable. The mechanism of formation of multiple mycotic aneurysms in distal arteries is not quite so evident, but they must be due to infected emboli which lodge against the wall and are perhaps displaced into the sac later. They are, in our experience, most often produced by the *Streptococcus viridans*, although in one case the *gonococcus* was found. The wall of the vessel is eaten through and a sac hollowed out in the tissue outside. Since its lining is so rough and so much infected, the sac is usually quickly filled with thrombus material. In one case caused by the *Streptococcus viridans* the aneurysm springing from part of the circle of Willis pressed upon optic and oculomotor nerves and caused great difficulties in clinical diagnosis.

Erosion Aneurysms.—Encroachment of destructive tuberculous processes may weaken the outer wall of an artery and allow the production of a small aneurysm which may be the source of the fatal haemorrhage from a tuberculous cavity in the lung, just as the advance of a gastric ulcer toward an underlying artery may allow it to bulge and finally rupture in the base of the ulcer.

The small aneurysmal sacs, **miliary aneurysms** of Charcot and Bouchard, which occur in the cerebral arteries and are associated with apoplectic haemorrhage, have been questioned by recent writers, who think them only haematomata, or minute dissecting aneurysms. But they do occur as definite sacculations, and while their structure is clear, little can be said as to their cause. They will be discussed under Cerebral Haemorrhage.

Verminous aneurysms are those produced by certain nematode worms (*Sclerostomum vulgare*) which get into mesenteric and other arteries in the horse.

Finally, to complete the list of conditions for which this name has to serve, **cirsoid** or **racemose aneurysm** is perhaps a sort of tumor—an angioma or haemangioma in which all the tangled wide blood-channels are newly formed as an abnormal and independent growth still fed with blood from the general circulation, or possibly the result of congenital arteriovenous communications.

LITERATURE

Dissecting Aneurysms:

MacCallum: Johns Hopkins Hosp. Bull., 1909, xx, 9.

Arteriovenous Fistulae:

- Callander: Johns Hopkins Hosp. Reports, 1920, xix, 260.
Halsted: Johns Hopkins Hosp. Reports, 1921, xxi, 1.
Holman: Arch. Surg., 1923, vii, 64; 1924, ix, 822. Ann. Surg., 1924, lxxx, 801.
Oppel: Arch. f. Klin. Chir., 1908, lxxxvi, 31.
Reid: Johns Hopkins Hosp. Bull., 1920, xxxi, 43. Arch. Surg., 1925, x, 601; xi, 25.
Rienhoff: (Congenital), Johns Hopkins Hosp. Bull., 1924, xxxv, 271.

Mycotic Aneurysms:

- Grant: Heart, 1924, xi, 9.
Richey-MacLachlan: Arch. Int. Med., 1922, xxix, 131.
Thayer: Johns Hopkins Hosp. Bull., 1922, xxxiii, 361.
MacCallum: Transactions College of Physicians, Philadelphia, 1929, li, 6.

CEREBRAL HÆMORRHAGE

Hæmorrhage into the substance of the brain, except when it is the direct result of violence or associated with infection or tumor growths, is usually dependent upon arteriosclerotic changes in the arteries and may be briefly discussed here. It is often spoken of as apoplexy and the persons suddenly plunged into unconsciousness by this accident are said to have had an apoplectic stroke. Clinically, it is often difficult to say whether such an event is due to haemorrhage or to the sudden blocking of a large artery with infarct formation in the brain, but with the lapse of time these things can generally be distinguished and, of course, at autopsy there is no difficulty.

Cerebral haemorrhage occurs very frequently as a terminal event in persons who have for some time shown a high blood-pressure, generally with evidences of chronic nephritis. Some violent effort or emotional disturbance which still further drives up the arterial tension may be the last straw that overtaxes the diseased arteries, but it is not always so. MacWilliams surmises that people with hypertension who are found dead in bed of cerebral haemorrhage may have had a nightmare.

Of course the occurrence of an intracranial haemorrhage in itself immediately raises the general arterial pressure so that measurements after the event are hardly evidence of the state of tension that may have brought it about. On the other hand, sclerosis of the cerebral arteries and perhaps especially those supplying the medulla may, according to Starling, Bordley, and Baker, provoke the heightening of general arterial pressure, possibly for the sake of improving the supply of blood to the brain. There is thus a sort of vicious circle, in that arteries with inelastic walls are associated with hypertension and exposed to the risk of rupture.

The hæmorrhage may occur anywhere, in the cerebrum, pons, medulla, cerebellum, but it is true that it is most common in the substance of the lenticular nucleus, from which position it tears its way out through the internal capsule, often to burst into the cerebral ventricle (Fig. 196). This site is so well known that Charcot stated that the hæmorrhage comes from the lenticulo-striate artery in such a large proportion of the cases that it might well be named the artery of cerebral hæmorrhage (Fig. 197).

Charcot and Bouchard described small or miliary aneurysms in these vessels from which the hæmorrhage was said to occur. For many years

this was accepted as the general rule, and the great difficulty of finding the exact source of the haemorrhage in the midst of a great clot with torn fragments of tissue contributed to the readiness with which the statement was believed, but recently the frequency of these aneurysms has been seriously questioned and their nature, too, has been interpreted in another way. Ellis and Pick, by shaking the remains of brain with apoplectic haemorrhage in salt solution, isolated the vascular structures, and did, indeed, find small and large nodules attached to the vessels in some cases, but they were generally encapsulated haematoma or dissecting aneurysms. So, too, Shennan, Lindemann, Rühl, and others find that the so-called aneurysms are intra- or extramural haematoma.



Fig. 196.—Apoplexy, both fresh and healed. The large, fresh haemorrhage has burst into the ventricle. The old one is represented by a cavity with pigmented walls in the substance of the opposite hemisphere. There is a small clot in the ventricle of that side.

Nevertheless, in a case recently studied by Forbus, we found several beautifully rounded saccules springing from the vessel walls, the largest of these, which was about 1 cm. in diameter, having ruptured to give rise to an extensive meningeal haemorrhage, while the others were intact. These, however, as described later by Forbus, were sacculations formed exclusively in the superficial arteries and may perhaps throw no light on the source of intracerebral haemorrhage. They were formed at the branching of each vessel where muscular and elastic tissue defects occurred.

The haemorrhage tears its way through the brain tissue, leaving shreds isolated here and there, but most characteristic is the appear-

ance in the neighboring tissue all about the clot of many minute haemorrhages which are found to be about tiny vessels or more often within their lymph sheaths. All recent authors recognize the pretty obvious fact that a haemorrhage in such soft tissue as the brain must tear many other small vessels which not only add their contribution to the general escape of blood, but allow blood to pass into their own lymph sheaths. It seems possible that this blood may even be drawn back into the lymph sheaths from the general pool, but there is generally a little outside this, too, in the tissue about the vessel. All the recent authors emphasize, too, the constancy of arteriosclerotic changes of one type

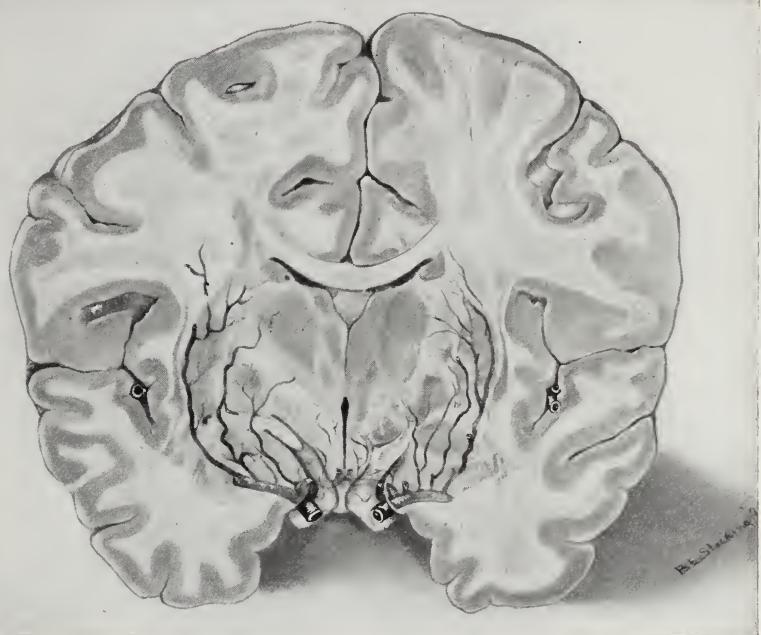


Fig. 197.—Diagram showing the branches of the middle cerebral arteries which supply the basal ganglia. The innermost are the lenticulo-optic, the outer two on each side the lenticulo-striate arteries. The outermost of these which pierces the internal capsule to end in the caudate nucleus is known as the “artery of cerebral haemorrhage.” (Modified from Charcot-Duret.)

or other in these small vessels, and hold these changes especially accountable for the rupture which may be demonstrable in many cases in arterioles with no sign of dilatation or aneurysm formation. But even though many small arterioles may ultimately show ruptures, it seems inevitable that the bursting of one must start the process.

The first result is unconsciousness, with a general flaccid paralysis. Later, when some of the blood has been absorbed and the pressure lowered, the direct effect of the tearing of the nerve-tracts becomes evident, and a clear-cut hemiplegia or one-sided paralysis stands out instead.

If the haemorrhage is not confined to the brain tissue, but bursts through into the ventricles, much freer bleeding may occur, and the blood filling both ventricles and running down through the aqueduct of Sylvius intensifies the effects of increased general pressure.

The distribution of the paralysis depends, of course, on the situation of the destruction of the brain substance. The hemiplegia is complete

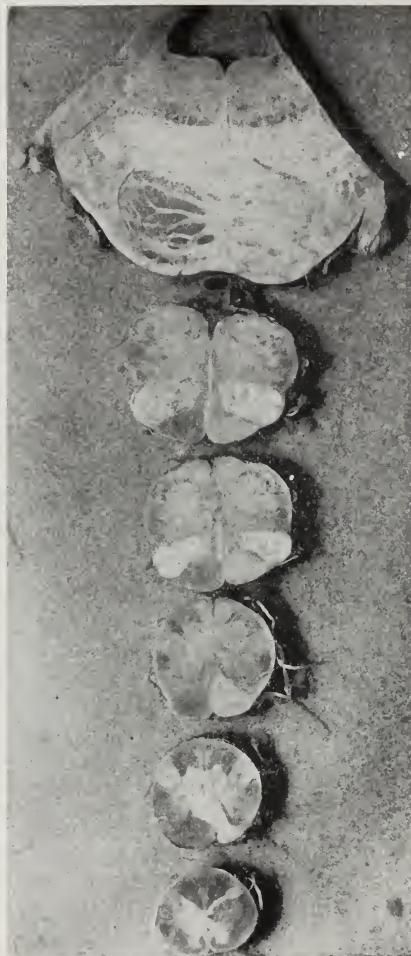


Fig. 198.—Degeneration of pyramidal tract resulting from old cerebral haemorrhage.

when face, arm, and leg on one side are paralyzed, and this arises when the haemorrhage involves the internal capsule and the beginnings of the pyramidal tract high enough to include the origin of the facial nerves. If, however, it is in the lower part of the pons, the nuclei of the cranial nerves may be injured, and then the facial paralysis will be on the side opposite that of the arm and leg (*cf.* Osler's Medicine, 1905, fourth edition, p. 972, Fig. 9).

Healing of the area of hæmorrhage takes place by the disintegration of the blood and its gradual removal by phagocytes. Sometimes a cavity is left, lined by granulation tissue, which is deeply pigmented and contains a clear yellow fluid (Fig. 196). The neuroglia may play a large part in forming the wall of this cavity.

The course of the degeneration is clearly shown in the photographs of successive blocks from the brain stem in a case in which the patient survived for a long time a hæmorrhage which cut across the internal capsule. Even the decussation of the fibres and the exact extent of the pyramidal tracts are quite plain in these sections (Fig. 198). Since this results in the loss of the upper motor segment a certain degree of spasticity may be found in the paralyzed extremities.

It is well known to physicians that in a case of hemiplegia from a hemorrhage which tears through the internal capsule, they may confidently say that the paralyzed leg will recover its usefulness to a considerable extent although the arm remains paralyzed. The reasons for this are not perfectly clear although much is referred to the difference between the automatic character of the movement of the leg, as in walking, and the skilled movement of the hands. Others even derive such automatic movements of the legs from lower centres since dogs from which cerebral hemispheres have been removed can walk after a time. It seems, however, that the recent demonstration by Bucy and Fulton of direct or ipsilateral fibres from the cortex to the pyramidal tract, instead of a complete decussation, may account for the retention of some power on the paralyzed side, although it would, of course, also account for some impairment on the opposite side. The paper of Fulton and Viets gives an excellent discussion of the relations of the functions of the premotor area of the cortex to those of the better known motor area. The tabulation of results which they give is enlightening. A lesion of the pyramidal (motor) area leaves the extremity flaccid with varying changes in reflexes, but essentially a flexor exaggeration with flexion of the leg, while a lesion of the nonpyramidal (premotor) area causes spasticity of the paralyzed leg with increased reflexes, especially causing extension of the leg.

Since in a tear through the internal capsule both may be involved, the symptoms are usually those of a combined motor and premotor lesion. The involvement of the premotor area seems especially to cause disturbance of skilled movements.

Walshe, however, from the clinical study of a case in which at operation the upper part of the pyramidal motor cortex was removed, not transgressing on the frontal limits of this area, refuses to accept Fulton's syndrome of a premotor cortex or extrapyramidal projection system.

In contrast with these forms, a paralysis due to destruction of the lower motor neurons (anterior horn cells of the spinal cord or peripheral motor nerve) is flaccid with abolition of all reflexes, extreme muscular atrophy and with reaction of degeneration to electrical stimulus as seen after poliomyelitis.

LITERATURE

- Buey and Fulton: Brain, 1933, lvi, 318.
Duret: Arch. de Physiol. norm. et pathol., 1874, 2me, Ser. 1.
Ellis: Publications, Jefferson Medical College, Phila., 1915, v, 1.
Forbus, W. D.: Bull. Johns Hopkins Hosp., 1930, xlvii, 239.
Fulton and Sheehan: Jour. Anat., 1935, lxix, 181.
Fulton and Viets: Jour. Amer. Med. Assoc., 1935, civ, 357.
Langworthy: Physiol. Reviews, 1928, viii, 151.
Lindemann: Virchow's Arch., 1924, cccliii, 27.
MacWilliams: Brit. Med. Jour., 1927, i, 125.
Monakow: "Gehirnpathologie," Nothnagel's spec. Path. u. Ther., 1897, ix, pt. 1.
Rühl: Ziegler's Beiträge, 1927, lxxviii, 160.
Shennan: Edinburgh Med. Jour., 1915, xv, No. 4.
Walshe: Brain, 1935, lviii, 81.

CHAPTER XVIII

TYPES OF INJURY: PHYSICAL AND MECHANICAL INJURIES

Mechanical injuries: Pressure, direct violence affecting bones, central nervous system, etc. Gunshot and other wounds. Secondary effects: Complication with infection. Shock. Experimental study and various theories. Effects of heat: Burns, heat-stroke, insolation. Effects of cold: Freezing. Effects of light-rays and radiant energy on skin, blood-forming organs, etc. Electricity: Effects of strong currents.

MECHANICAL INJURIES

THE variety of mechanical injuries is almost infinite, and is constantly increasing and changing with the invention of new machinery. The old swashing blow with the broadsword has given place to the penetrating wound of the high-speed bullet; wounds of encounter with wild beasts are rarer now than those from the fall of an aëroplane. But the principles concerned are relatively few, and with a knowledge of the complexities of organ structure and function the effect of any type of injury can be pretty readily constructed.

In general, mechanical force may be applied to the body in the form either of pressure or of stretching, and according to the shape or character of the instrument, and the rate and violence with which it is applied, different results follow. Thus gradual exposure to a high air- or water-pressure will produce one sort of effect, while a sudden blow with a blunt weapon or crushing between two flat surfaces will have quite a different outcome. If the instrument be sharp or impinge upon the body with great velocity, it cuts or penetrates, separating tissues which might be only bruised or dislocated by a blunter or more slowly moving object.

Distention by gases or fluids, stretching and tearing of extremities caught in machinery, and the dismemberment of the body by the force of an explosion are examples of the application of a stretching force which often involves the exertion of pressure also on some other part of the tissue.

The effects of such violence are not only upon the tissues directly attacked, but since the whole structure of the body is in a state of elastic tension, the severing or destruction of any tissue allows those remaining to gape apart. Especially is this true of the elastic blood-vessels, in which the blood is under high pressure. Any break in the wall of one of these vessels opens more widely and allows the escape of blood. Nor is the effect of any such mechanical injury necessarily limited to its direct result. Here, as elsewhere, it is usually one link in a chain of events which in the end leads to quite unexpected terminations. Thus a man whose back is broken will die from the formation of abscesses in his kidneys, but there is a long series of causes and effects which finally bring this about. It is an example of the far-reaching effects of injuries to the nervous system.

A brief account of some of the common types of mechanical injury will suffice to direct the reader to the literature of the subject.

Pressure.—A diver seen deep in clear water through a glass-bottomed boat becomes perfectly white from the compression of the blood-vessels of the skin. Doubtless this may have some influence upon the general blood-pressure, but when air is supplied through a helmet, no great discomfort is felt if the changes of pressure are gradual enough. The same anæmia, lasting for a long time, if locally produced by the weight of the body on the bed, or by a tight bandage, may be more complete in the area affected, and if the circulation is sluggish, and especially if the nerve supply is interrupted, death of the anæmic areas will follow (*decubitus, bed-sores*). Thus a person paralyzed by an injury to the spinal cord will quickly develop ulcers over the sacrum, heels, etc., if left lying in one position, and the same is true of those bedridden by some disease or infection which greatly lowers their vitality. Violent mechanical pressure on the trunk, as in cases of people buried under an avalanche of coal or grain, or caught under an elevator, may cause death by actual crushing, but short of this it produces an extreme obstruction of the circulation by preventing the movement of the venous blood toward the heart. The head and neck become blue black, and haemorrhages occur from the burst vessels. Slighter pressure applied continually to any tissue over a long time interferes with the completeness of its blood-supply, and prevents or stunts its growth. Well-known examples are found in the distorted feet of Chinese women, the flattened heads of certain Indians, etc. Tumors, pressing in their growth against other tissues, cause the cessation of growth and gradual absorption. This is true everywhere, but becomes especially striking in the case of the rigid bone, which can be hollowed out by an advancing tumor growth. Practically the same thing is seen in the liver as the result of constriction by tight clothing, but also in the form of deep grooves over the upper surface, which correspond with rigid, contracted bands of the diaphragm. Aneurysms which push aside yielding tissues and destroy in their advance bone and anything else which is resistant, afford another example in which the effect of pressure is probably aided by the actual beating of the pulsating sac against the bone, for such eroded bones show not only wasting or atrophy of the tissue, but fragmentation of the bony lamellæ.

On the other hand, intermittent pressure which allows the resumption of the circulation and of the proper metabolism of the cells in the intervals often causes an excessive growth of tissue, as one sees in the case of corns and other callosities, and probably also in the ingrowing toenail.

Heightened air-pressure, to which workers in caissons and submarine engineering operations are subjected, is injurious chiefly through sudden changes in the degree of pressure. The sudden application of a high pressure may cause haemorrhages in the ears. Sudden decompression produces a whole series of phenomena, chiefly dependent upon the expansion of gases which cannot readily escape; the air in the middle ear and the gases in the intestine produce discomfort or injury by being

suddenly released from pressure. Most important, however, is the appearance, in the form of bubbles, of the gases which under higher pressure were dissolved in the blood. These are chiefly nitrogen and carbon dioxide, and if a workman is too quickly "decompressed," that is, if he remains too short a time in the air-locks in which the air is at an intermediate pressure, these bubbles appear in the blood-stream and act as emboli, plugging the arterioles and obstructing the blood-supply until they can be redissolved. In this way the sensitive tissue of the brain and cord undergoes anaemic necrosis in focal areas, and if death does not follow, extensive paralysis and other nervous disturbances appear (the so-called "bends" of caisson workers). Tearing of the tissues by such bubbles seems less important. Exposure to low atmospheric pressure, as in balloon ascensions, mountain climbing, etc., brings with it symptoms that are milder because the change in pressure must be more gradual. Rapid respiration, rapid pulse, and an increase in the number of red corpuscles of the blood are evidences of adaptation to the lowered oxygen tension of the atmosphere. Weariness, nausea, drowsiness, fainting, etc., makes up the condition known as mountain-sickness.

Trauma.—Violence in the form of blows may, of course, have many different results. The commonest is perhaps the bruising of tissues with the stretching and tearing of many minute blood-vessels, from which blood escapes and filters into the crevices round about. If the tissue is soft and loose, as it is below the eye, a blow may cause a very extensive infiltration of blood, while in a denser place a much harder knock will leave no such great black-and-blue spot. At first it is red or purplish red, but with the stagnation of the escaped blood a venous color supervenes which, in the course of the next days, gives place to a series of changing colors as the haemoglobin of the laked blood passes through the stages of the formation of haemosiderin and its gradual removal. Hues of green and brown and yellow finally fade away completely after all the pigmentary remains of the escaped blood have been carried away.

A stronger blow or a twist may dislocate a joint; that is, separate the two articular surfaces by stretching the articular ligaments or by forcing one bone through them. Haemorrhage occurs, as a rule, and unless the bone is replaced properly, new tissue may be formed in such a way as to render the abnormal position permanent. Such a blow may, even though it does not break the skin, cause the rupture of internal organs or the fracture of a bone. In the first case, if the organ is a solid one, rich in blood-vessels, like the kidney or liver or spleen, a great or even fatal haemorrhage may occur. This does not necessarily follow, however, for occasionally there are found evidences of recovery from rupture of the liver in the presence of masses of liver tissue surrounded by, and healed into the omentum.

Fracture of bones can occur in a thousand ways known to every one. It may be only partial, leaving the rest of the bone bent (greenstick fracture), or it may be complete, so that the fragments override and are held in the false position by the muscles. When the bone is shattered into many fragments (comminuted fracture), the dislocation may be

even greater. Occasionally one fragment is driven into the substance of the other, so that it remains embedded there (impacted fracture). When the skin is broken and the fractured bone exposed to contamination from the outside (compound fracture), infection is very likely to occur. Fractures of the skull the bones of which are so intimately associated with infected cavities are also exposed to this danger which, in preantiseptic times, made a compound fracture almost inevitably fatal. Healing occurs by the formation of an abundant new tissue (callus) about and between the ends of the bone. Excessive at first, and composed of vascular fibrous tissue, cartilage, and spongy bone, it later becomes compact, diminished in amount, and consolidated into dense bone, which is gradually modified and adapted to give the greatest strength to the welded point of fracture (Fig. 199).

Blows on the head, besides causing fracture of the bones of the skull, which may be driven into the brain, are capable of injuring the brain either by concussion or by producing a haemorrhage from either or both sides of the dura, or from the pial vessels before or after their entrance into the brain. A blow on the skull frequently produces its greatest injury at a point opposite that upon which it impinges (*contrecoup*).

The mechanism of contrecoup has been variously explained in a vague way as the effect of driving the soft brain substance against the unyielding opposite side of the skull, the concentration of forces passing round the arc, etc., but to me it seems more plausible to assume that the skull, like a hoop struck sharply at one point, takes an elliptical form, so that the side opposite the blow actually approaches that which is struck. At any rate it is common to find laceration of the brain and meninges with haemorrhage, at a situation most distant from the blow.

Concussion is recognized as the effect of a shock to the brain substance, which, although it produces no obvious gross lesion of any sort, does cause unconsciousness of brief or longer duration and many temporary disturbances of the intellect, sensory, or even motor sphere. It is thought to be due to dissociation or disarrangement of the cells, possibly with tearing of many dendrites, axones, and association-fibres.

Meningeal haemorrhage is important above other haemorrhages, not only because it may tear into and destroy the soft brain substance, but because it can, even when it is outside the dura, occupy so great a space within the rigid cranial cavity as to compress the brain, and especially to prevent the access of blood (Fig. 201). A gradually deepening loss of consciousness with flaccid paralysis of the whole body may lead to death—the blood-pressure rises very high, while the pulse sinks. Operative removal of the clot may allow all the functions to return to normal almost instantly. Much greater violence is necessary to wound the spinal cord, but crushing and twisting force may fracture the vertebrae or dislocate them so as to sever or compress the cord. Extravasation of blood in the substance of the cord (*haematomyelia*) extends up and down in the gray matter, destroying much of the tissues as it burrows, but, as a rule, not entering the white matter. The so-called *compression myelitis*, produced by crushing, occupies part or all of the diameter of the cord, and interrupts the course of the fibres. In



Fig. 199.—Healed fracture of middle of femur, shown also in section.

Fig. 200.—Well-healed fracture showing remaining overstrengthening of the shaft.

such an area, débris of cells and fibres remains, together with quantities of phagocytic wandering cells loaded with globules of lipoid material from the disintegrating myeline sheaths.

The effects vary with the extent, and especially with the position, of the injury. Low down in the spinal cord the lower motor neurons are especially affected, and paralysis is flaccid, leading to atrophy of muscles and reaction of degeneration. Higher up a lesion gives rise to a mixture of upper and lower neuron types, while still higher the effect is to produce paralysis predominantly of the type following destruction of the upper motor neuron, such as comes from a lesion of the brain: the muscles retain their tone, do not atrophy, and stimulation of the nerves shows no change of electrical reaction. The paralyzed area may be entirely anaesthetic, or with a zone of hyperæsthesia at the upper limit. Other disturbances of sensation also occur. Reflexes are variable,

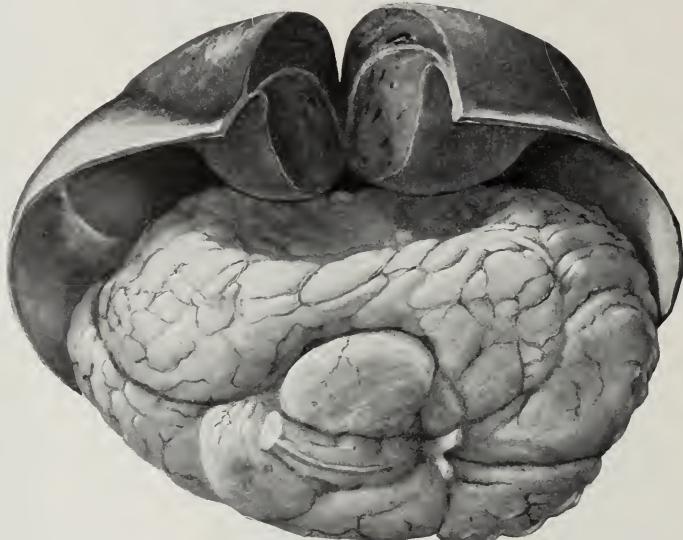


Fig. 201.—Subperiosteal and subdural haemorrhage in new-born child with compression of the brain.

and after a time may be exaggerated, especially with high lesions. The sphincter of the bladder is not paralyzed, although other muscles controlling urination are, so that the bladder becomes greatly distended.

Wounds made with a cutting instrument sever tissues and allow them to gape apart, or in the case of stab wounds, penetrate various organs. They are especially important in that blood-vessels are laid open, nerves cut, and hollow organs punctured, so that their infected contents are allowed to escape. Aside from the direct destruction of the tissues traversed, such wounds are also dangerous because dirt and bacteria are carried into the tissue. In all these respects they are similar to gunshot wounds, which have, however, a special character, depending on the type of missile and the force and velocity with which it passes through the tissues.

Gunshot Wounds.—A hard bullet of very high velocity passes cleanly through the body. A soft bullet spreads and tears the tissue, inflicting much greater damage: either will shatter bones in its course. A bullet almost spent or of low velocity may be deflected by a bone and pursue a most devious course, so that its track is difficult to follow, even at autopsy. The path of a bullet widens as it proceeds, especially in the case of the soft ones, so that the wound of exit is larger than that of entrance. Ordinarily such a bullet brings practically no infection to the tissues unless it carries in with it bits of clothing. It was for this reason that the Japanese in recent actions bathed and put on sterilized clothes.

Immediate Effects.—In all cutting and penetrating wounds the most important immediate effect, unless the brain or spinal cord is injured, is likely to consist in the laying open of blood-vessels. A wound of the heart is fatal not especially because the heart is injured, but because blood escapes into the pericardium (haemopericardium), and by occupying the limited space, prevents the entrance of the venous blood into the heart and stops the circulation. In the case of the aorta or other large vessel, death results rather from direct escape of blood into the pleura or pericardium or to the outside. A vessel, in virtue of its elasticity and muscular contractility, gapes open and allows a maximum escape of blood if it is only partly cut through, while if completely cut across, an artery of moderate size may retract among the muscles, and partly by their compressing effect, partly by its own contraction, the flow of blood may be stopped before a fatal loss has been suffered.

Peripheral nerves may be cut through, or crushed and later surrounded by dense scar tissue formed during the healing process, and in either case the injury may be sufficient to prevent the transmission of impulses. Degeneration of the peripheral portion of the nerve quickly follows, and in a few days lipoid globules are found in place of the myeline sheaths, the axis-cylinders are disintegrated, and electrical stimuli produce no effect (Fig. 37). There may be recovery of the power to transmit impulses if the injury is not too severe, and in the meanwhile the muscle loses its power to contract to galvanic stimuli, but soon recovers it and becomes more excitable than normal. During this period of high excitability, which later passes away, the contraction is, however, not instantaneous, but slow and lazy, and almost without effect (reaction of degeneration of Erb). There are many variations in these relations, depending upon the extent of injury of the nerve and the degree to which the muscle suffers, which must be read of elsewhere. Trophic disturbances, thought by many to be due to the destruction of special trophic nerves, consist in the gradual wasting of the muscle. It is shown that constant fine stimuli are being sent to muscles in health maintaining their tone, and that when the nerve is cut and the muscle becomes flaccid, its metabolic gaseous exchange is far less than that of the properly innervated muscle, even when completely at rest. It seems that this might be the basis upon which atrophy after section of the nerve could be most readily explained.

Secondary Effects.—Many secondary results follow such injuries as have been mentioned, some of which can be avoided by proper surgical

care. Hæmorrhage, as already stated, may cost the person's life through sheer loss of blood or through the compression of the brain or the heart; the perforation of an aneurysm into the trachea may fill the lungs and practically drown the individual. But in another way, especially in the brain and spinal cord, the burrowing of blood in the soft tissues is most destructive. In the walls of the aorta, particularly when the seat of arteriosclerotic changes, a blow or strain may break the inner layers, usually the intima and half of the media, and allow blood to escape into a space which it tears open in the middle of the media, the so-called *dissecting aneurysm*. In one case of this kind the formation of a huge hæmatoma about the roots of the splanchnic nerves was apparently the cause of paralysis of the intestine, with such extreme distention as to tear the muscular coat in many places.

The occurrence of bacterial infection in wounds adds, of course, greatly to their seriousness, and many mere pin-pricks terminate fatally because bacteria have been introduced. This is common in the case of streptococcus and tetanus infections, but it is equally true of syphilis, glanders, anthrax, and a host of other infections. Indeed, it is the very insignificance of the wound, leading to its being neglected, which affords opportunity to the bacteria to gain a foothold. The presence of any foreign body in conjunction with the bacteria helps them greatly in gaining this foothold, and it has been shown repeatedly, in the case of experimental infection, that bacteria which fail to grow when inoculated into an animal alone, will often do so if implanted together with some inert foreign material. Sometimes this acts by merely protecting the bacteria, but at other times it forms a medium upon which they can grow and multiply. This is true of extravasation of urine when the bladder is ruptured, or of accumulations of tissue fluid in the cavity of a wound. Most important in this respect, however, is the presence of dead tissue in a wound exposed to infection. This has been mentioned before, but from a surgical point of view cannot be mentioned too often. No matter how rigid the aseptic technique, the leaving behind in the wound of any considerable quantity of tissue constricted so as to be incapable of surviving, is almost sure to be followed by infection. In other cases the foreign body itself may be irritating and destructive of tissue, so as to furnish a place in which bacteria can thrive. Considerations of this sort became extremely important during the war, when surgeons were confronted with wounds which involved not only mangling of the tissues and extensive soiling but also on account of delay in transportation, actual infection of the injured structures. Whenever possible it became the practice to perform a so-called "*débridement*," which means the wide excision of everything about the wound until healthy, uninfected tissue was reached, after which the whole wound might be closed, and primary healing attained. Of course, it was in the estimation of the extent of the infection and the general state of resistance of the patient that the judgment of the surgeon became of especial importance.

With regard to the bacteria concerned, and especially the anaërobic forms, consult Bulloch and McIntosh, Med. Research Committee, Special Report, Series No. 12, 1917.

Perforation of the stomach or duodenum, which are in themselves nearly sterile, nevertheless sets up peritoneal infection because of the escape of food and of the irritating digestive juices. Perforations of lower portions of the intestine are even more quickly productive of infection because of the colossal numbers of bacteria which pour out with the intestinal contents into the peritoneum. This is one of the chief sources of danger in gunshot wounds of the abdomen, in which several loops of intestine may be pierced.

The crushing or shattering of tissues, involving rupture of blood-vessels, often allows the entrance of groups of cells or single cells of various organs into the blood-stream in such a way that they are swept along and lodge as emboli in the lungs or elsewhere. This is most commonly true of the bone-marrow, where, instead of cells, droplets of fat may enter the blood-current. Practically every fracture of a bone and even severe blows upon bones may produce such *fat embolism* of the lungs. Usually it does no harm, and even at autopsy can be discerned only by the aid of the microscope, but occasionally the amount of oil is so great as to cause death by obstructing too many of the capillaries of the lungs.

Traumatism is, of course, a more serious matter for persons already weakened by disease than for those in full health, and it may be the occasion for the flaring up of an infection hitherto latent. On the other hand, the injury of tissues may produce a point of lessened resistance, where a subsequent infection can be established in a way scarcely possible in an uninjured person. This is doubtless the explanation of the common history of a fall or blow which antedated, by some time, the appearance of a focus of tuberculous infection in a bone or joint. This, too, is doubtless the immediate predisposing cause of the so-called contusion pneumonia of Litten, which follows crushing blows on the chest.

It must be remembered that certain persons suffer directly from slight injuries far more than others, for example, a scratch which would scarcely be noticed by a normal individual may allow a fatal haemorrhage in a member of a haemophilic or bleeder family, while a blow which at most might cause a bruise in one of us, will break the femur of one afflicted with osteopetrosis or fragilitas ossium. And in the same way the sequelæ of injury, such as wound infections, resisted easily by a normal person, will bring about the death of one whose resistance is low, with fulminant symptoms of general septicæmia. This was exemplified recently in the case of a man, apparently in good health, who had his tonsils removed preparatory to a vacation—a streptococcus infection ensued, of which he died in two days, with evidences of acute endocarditis and multiple embolism.

LITERATURE

- Bailey: Diseases of the Nervous System from Accident and Injury, New York, 1909
Henke: Krehl and Marchand, Handb. d. allg. Path., 1908, i, 21.
Hill, L.: "Influence of Atmospheric Pressure," Lancet, 1905, ii, 1865; Proc. Roy. Soc., 1905-06, Ixxvii, 442.
Lagarde: Gunshot Wounds, New York, 1914.
Möbius: Diagnostik der Nervenkrankheiten, Leipzig, 1894.
Stimson: Fractures, Phila., 1912.

SHOCK

This is a peculiar disturbance of almost all the functions of the body, especially characterized by apathy or torpor, dulling of sensibility, failure of the circulation with great lowering of the blood-pressure, irregular gasping respirations, which may be the first thing to fail completely, and subnormal temperature. Fischer's description of such a case may be quoted from Dr. Meltzer's paper:

"A strong and perfectly healthy young man was struck in the abdomen by the pole of a carriage drawn by runaway horses. No recognizable injury was done to any of the internal organs. Nevertheless, grave symptoms made their appearance immediately after the accident. The injured man was lying perfectly quiet, and paid no attention to anything going on around him. His face was drawn and peculiarly elongated, the forehead wrinkled, and the nostrils dilated. His weary, lustreless eyes were deeply sunken in their sockets, half covered by the drooping eyelids and surrounded by broad rings. The eyes had a glassy and vacant expression. The skin and the visible mucous membranes had a marble-like pallor. Large drops of sweat hung on forehead and eyebrows. The rectal temperature was subnormal. The sensibility of the entire body was greatly reduced; the patient reacted slightly, and only to very painful impressions. No spontaneous movements of any sort were made by the patient. On repeated and urgent requests he showed that he could execute limited, brief movements with his extremities. When the limbs were lifted passively and then let go, they fell down like lead. The sphincters were intact. The urine obtained by catheter was scanty and concentrated, but otherwise normal. The almost imperceptible pulse was rapid, irregular, and unequal. The arteries were narrow and of very low tension. The patient answered slowly, reluctantly, and only after repeated urgent questioning. His voice was hoarse and weak, but well articulated. On being repeatedly questioned, the patient complained of cold, faintness, and deadness of all parts of the body. When he shut his eyes he felt nauseated and dizzy. The respirations appeared irregular; long, abnormally deep, sighing inspirations interchanged with rapid and superficial ones, which were scarcely visible or audible."

This is a typical example of shock following traumatism, a condition well known to surgeons to come on immediately or a short time after some extremely painful injury, such as the crushing of a testicle or mangling or laceration of the body in machinery. It is especially common in injuries which involve the exposure and mishandling of the abdominal organs, but practically the same complex appears after extensive burns, and in the case of intense peritoneal and other infections and some intoxications. Possibly the infections and intoxications may be distinct in their mode of action, but in the present confusion of our knowledge the results seem to be practically identical.

An immense amount of experimental study has as yet failed to explain this phenomenon, or even to determine exactly what happens. Keen, Mitchell, and Morehouse, and later Crile, thought the fall in blood-pressure to be the essential feature, and this they explain as due to exhaustion of the vasomotor centre, which allowed relaxation of the

peripheral arterioles and the accumulation of the blood in the large splanchnic veins. Crile advised massage or compression to drive the blood again to the heart. He observed, however, that death in most cases resulted from stoppage of respiration while the heart continued to beat.

Porter, Seely, Mann, and others have shown, however, that the vaso-motor centre is by no means exhausted, but still active, and that the peripheral vessels are distinctly contracted and quite susceptible to vasoconstrictor impulses, which can be elicited by sensory stimulation. Nor is it a fact, as Boise claimed, that the heart is exhausted, for if blood be supplied to it and pressure maintained, it works perfectly well. The nervous control of the heart is intact; so, too, the nervous mechanism which controls respiration is able to respond to various stimuli, although (Mann) it is probably the most easily injured and most seriously damaged of the medullary centres. Henderson ascribes the whole phenomenon to an affection of the respiratory centre following the violent forced respiration which is set up by painful traumatism. This, he states, sets free so much carbon dioxide from the tissues that the condition of "acapnia" arises, namely, a poverty of the carbon dioxide which is necessary for the stimulation of the respiratory centre. Mere lack of oxygen, he says, has no influence in stimulating respiration, and in the absence of carbon dioxide the centre remains inactive, so that in this period of apnoea the individual dies from lack of oxygen. It seems hard to believe that the excessive respiration, which is often so slight, could produce so extreme a change, or that the carbon dioxide produced while the animal was dying for lack of oxygen should not be able to stimulate the respiratory centre, since throughout this time the heart continues to beat. Meltzer regards the whole process as the expression of a preponderance of inhibitory action of the nervous system, which after such extreme stimulation affects even the organs of fundamental importance, the regulation of which is usually so well protected.

Mann emphasizes the predominant part which injuries to the peritoneal contents play in the production of shock, and, finding great increase in the specific gravity of the splanchnic blood and changes in the relation of the blood-cells, thinks the symptoms due to the great loss of cells and fluid from the blood of the splanchnic vessels—a sort of acute inflammatory exudate. The production of shock in cases where such things are easily excluded seems to militate against this idea. Hæmorrhage does aid in the production of shock, and the effects of very severe hæmorrhage are hardly to be distinguished from it. So, too, the effects of such infections and intoxications as are found in general streptococcal peritonitis or in fatal diphtherial intoxication are, as has been pointed out by Pässler and Romberg, in every respect similar. They lay stress on the vascular relaxation and stagnation of blood in the great veins which involves decreased flow in the coronary arteries and cardiac failure, and I could confirm this by showing that if the blood-pressure be maintained by a mechanical device, and the blood driven, regardless of the vasomotors, through the arteries and veins into the heart, the imminent collapse is warded off. Much has been written by Crile and his

assistants about the disintegrative changes in the ganglion-cells of the brain in shock, but it seems that these may be rather the effect than the cause.

H. H. Janeway and E. M. Ewing conclude, from their experiments, that acapnia is not important in producing shock, but that artificial respiration can do so, when forcible enough, by preventing the flow of blood from the veins into the heart. Shock may be produced while the carbon dioxide content of the blood is high. Further, although the early stages of shock produced by the handling of the intestine are due to inhibitory efferent impulses, the nerve centres are not exhausted, but there is a complete local peripheral splanchnic paralysis, so that blood accumulates there, producing in the end a fatal fall in blood-pressure. This permanent loss of vasomotor control is the all-important factor in the development of shock.

These older ideas, while leaving no clear impression of the nature of shock, are not inconsistent with those which have resulted from the very extensive studies made during the war. Various suggestions, such as those which ascribed shock to pulmonary and cerebral fat embolism or to acidosis, have been proposed, only to be abandoned. It has been observed that in most instances several causes have been combined; cold, haemorrhage, crushing and laceration of tissues, and anaesthesia stand out most prominently, and it is found that in many instances the addition of one or more of these factors is decisive in precipitating shock. Ether anaesthesia is far more harmful in this respect than that with nitrous oxide and oxygen. Rich has shown that while extirpation of the adrenals gradually leads to a lowering of blood-pressure, and shock is produced by manipulation of the intestines more rapidly in these animals than in controls, this is not true if the pinching of the intestines follows immediately upon the destruction of the adrenals before hypotension sets in. Then they pass into shock exactly as do the normal controls. He also finds that cardiac failure is not a factor in the production of shock, and that even during deep shock the vasomotor and cardio-inhibitory centres continue to function; further, curiously enough, ether anaesthesia for an hour before the trauma renders the animals very resistant to shock, although this protection disappears if the animal is allowed to recover from the anaesthesia before the trauma is begun.

Distinction is made between *primary shock*, which appears to be the immediate reflex effect of a sudden injury due to the inhibition of the heart through the vagus and dilation of the arteries in the splanchnic area (Goltz's experiment), and *secondary shock*, which is more gradually produced and depends upon other causes.

In secondary shock the blood-pressure drops sharply, then with a temporary constriction of the arterioles rises almost to the original level, after which it gradually sinks to a very low one. When it reaches this level the heart still beats well, but there is very little blood in the arteries or veins and the pulse is not to be felt. By the vital red stain method it has been shown that there is a great diminution in the blood volume (Keith), and it is clear that the arteries and veins are collapsed;

the heart appears to be propelling only a very small amount of blood. The explanation offered is that the enormous capillary stream bed, which under normal conditions is only partly used, is now widely opened to the blood by the paralysis of the capillary walls. It is recognized that the endothelial walls of the capillaries have certain contractility of their own and that they are capacious enough when this tone is lost to receive almost the whole volume of the blood, which thus occupies largely capillaries which are ordinarily collapsed and not traversed by blood. With this comes an increased permeability of their walls so that fluid passes out into the tissues and the blood becomes concentrated. Of course, there is not enough fluid available to give any appearance of edema. Respiration may cease and the patient die with all his nerve centres and his heart inactive from lack of nutrition. It has been found that the introduction of large quantities of blood or of a 6 per cent. solution of gum acacia with salt often relieves the situation by furnishing fluid enough to allow the heart to work and to maintain its own nutrition and that of the nervous system (Erlanger).

Crushing of tissues seems especially likely to be followed by severe shock, and so, too, does the reëstablishment of the circulation through tissues which have long been cut off from their blood-supply; something forms in crushed muscles or injured tissues which is later distributed by the circulating blood and acts as a poison. Dale recognized this, and stated that from its effect it must be a body resembling the histamine or beta-imido-azolylethylamine which he had extracted from ergot. Dr. Abel finds that he can extract histamine itself from practically every tissue and thinks that it may well be the substance actually concerned. The effects of injection of histamine are exactly those of shock. It causes a sinking of blood-pressure through paralysis of the walls of the capillaries which widen and receive most of the blood and become more permeable so that much of its fluid is lost into the tissues. Rich has shown this directly by the injection of histamine into the peritoneum with study of the changes in the calibre of mesenteric and omental vessels. Dale does not claim that this is the only factor in the production of shock, but Cannon, Bayliss, McNee, and others bring greater support to the idea from their observations of the effect of experimentally crushing muscle and other tissues. They speak, therefore, of traumatic toxæmia as the important underlying condition in shock.

(Dale, Wallace, Bayliss, Cannon, McNee, Keith, and others, Report of the Special Investigation Committee on Surgical Shock and Allied Conditions, National Health Insurance, Special Report Series Nos. 25, 26, 27, London, 1919).

All of these studies seem to offer a very plausible explanation for at least some cases of shock.

Since this was written the efforts to understand shock have been continued—even yet without general agreement as to the explanation. All seem to agree that low blood-pressure is the ultimate cause but as to whether this is due to toxic materials derived from injured tissues, or not, there is little agreement. There is a general idea that there is reduced blood volume due to a reflex contraction of splanchnic and

cutaneous vessels but not of the vascular supply of the muscles. This is thought to be a reflex result of pain, cold, fear, excitement and restlessness. It can be produced by injections of adrenalin (Gasser) and Freeman observed that pain, etc., causes hyperactivity of the sympathoadrenal system and splanchnic vasoconstriction. Cannon shows that decorticated cats in sham rage go through this whole process until they die after two or three hours in which their blood volume decreases. Ergotoxin or sympathectomy blocks the vasoconstriction and stops the fall in volume. Since the muscular capillaries are left wide, it is supposed that the fluid escapes into the tissues of the muscle. The capillaries are more than normally permeable to fluid and become packed with corpuscles.

The part played by the sympathetic and adrenal medulla seems important and accounts for the vasoconstriction although the loss of fluid has been hard to explain, except, of course, in the cases of haemorrhage. Now comes Swingle with the statement that loss of adrenal makes an animal far more susceptible to shock but that the cortical hormone relieves this and restores an animal from profound shock. And Heuer and Andrus find that cortin such as Swingle used, will reduce the fall in blood pressure due to plasma loss and combined with saline injection will restore the shocked animal to normal. Just how the adrenal cortex functions there is not yet clear. Moon refers the symptoms and changes in shock to loss of tone in the capillaries, atony of the capillaries being responsible for the weak circulation and the escape of fluid. In his experiments he injected sterile filtrate of normal muscle and produced tissue changes and capillary haemorrhages. Wilson and Roome, on the contrary, find that extracts from traumatized muscles cause a rise in pressure rather than a fall and fail to support the toxic theory of traumatic shock.

It seems possible that if, as stated, there is such extreme contraction of the peripheral arterioles, the changes in the blood volume may be due to the halting of the mass of the blood on the arterial side of the capillaries so that fluid passes into the tissues, leaving the capillaries choked with corpuscles, and not enough blood returns by the veins to the heart to maintain the blood-pressure. The consequent lowering of coronary pressure may contribute to this by failure of the heart's action. But with the best of efforts the difficulty is in explaining the mechanism of the neurovascular changes.

LITERATURE

- Abel and Kubota: Jour. Phar. and Exp. Therap., 1919, xiii, 243.
Brooks and Blalock: Ann. Surg., 1934, c, 728.
Cannon: Traumatic Shock, Appleton & Co., 1923.
Cannon: Ann. Surg., 1934, c, 704.
Dale: Johns Hopkins Hosp. Bull., 1920, xxxi, 257.
Erlanger, Gasser, and others: Secondary Traumatic Shock, Amer. Jour. Physiol., 1919, xliv, 90; 1919, I, 31-119.
Freeman: Ann. Surg., 1935, ci, 484.
Henderson, Yandell: Amer. Jour. Physiol., 1908-1910, xxi-xxviii; Johns Hopkins Hosp. Bull., 1910, xxi, 235.
Heuer and Andrus: Ann. Surg., 1934, c, 734.

- Janeway, H. H., and Ewing, E. M.: Ann. Surg., 1914, lix, 158.
Keen, Mitchell, and Morehouse: Circular No. 6, Surgeon General's Office, 1864.
Krogh: Anatomy and Physiology of Capillaries, Yale Press, 1922.
Mann: Johns Hopkins Hosp. Bull., 1914, xxv, 205.
Macleod: Jour. Lab. and Clin. Med., 1920, v (Editorial).
Meltzer: Arch. Int. Med., July, 1908, i, 571.
Moon: Arch. Path., 1932, xiv, 360.
Rich, A. R.: Johns Hopkins Hosp. Bull., 1922, xxxiii, 79.
Swingle and Parkins: Amer. Jour. Physiol., 1935, cxii, 427.

INJURIES FROM HEAT

Animals can live only within certain temperature limits, which are different for different forms. Lambert has shown, by culture of tissue *in vitro*, that there is a definite temperature at which cells grow, while growth decreases toward certain extremes at which it ceases. Nevertheless, these extremes may be passed without the actual death of the cell. Marchand and others have found that a temperature of 50° to 51° C. (122° F.) is sufficient to cause heat coagulation of leucocytes. So, too, distortion and fragmentation of red corpuscles occur at that temperature, and even the necrosis of epidermis and deeper layers of the skin. Actual haemolysis is produced by a higher temperature—59° to 60° C.—or by longer exposure at the lower point.

Burns.—Actual burning or scalding through exposure to much higher temperatures causes various degrees of alteration in the skin, according to the intensity and duration of the action of the heat; the skin may be reddened, or blistered, or finally it may be actually roasted or charred. Burning of extensive skin surfaces usually causes death within twenty-four hours, but more limited burns and those of slighter intensity may be survived for a longer time or even permanently. The patient suffers the most excruciating pain, becomes delirious or stuporous, but extremely restless, and finally passes into coma which ends in death. The pulse is small, respiration rapid and shallow, and the blood-pressure sinks, producing the whole symptom-complex of shock, such as follows great trauma.

At autopsy nothing is found except congestion of the brain and meninges, and occasional small haemorrhages in the mucosa of the digestive tract. The duodenal ulcers so often mentioned are really rare. Bardeen emphasized swelling and focal necroses in the lymphoid structures, but these seem to be not especially characteristic. There is a good deal of fragmentation of the red corpuscles and some laking of the blood. Haemoglobin is excreted through the glomeruli and precipitated in irregular, globular masses in the tubules of the kidney; but although the haemoglobinuria is marked, it does not indicate blood destruction enough to account for death. The blood is concentrated by the loss of plasma, evidently through great evaporation from the skin. Thrombosis of the minute vessels has been described by several, but others have failed to demonstrate any such occlusion, and it can hardly play an important part. The suggestion has been made very frequently that some toxic material may be absorbed from the burnt skin which could account for the collapse and death, but there is no direct evidence of this. It seems possible that since the symptoms resemble so closely

those of traumatic shock, the same poisons, histamine or related substances, may be concerned. Extracts of such burnt skin have had little or no poisonous effect. In this uncertain state of knowledge it is generally believed that death is actually due to shock produced by the extreme insult to the nervous system.

Injurious Effects of High Temperatures.—The temperature of the so-called cold-blooded animals varies, as does that of any other object, with the temperature of the surrounding air, but in man and warm-blooded animals in general, the heat-regulating mechanism is effective to maintain the body-temperature at a fairly constant level. Clothes and other artificial protections are important in aiding this in the case of man, but even without them the mechanism will suffice for brief periods of exposure to the extremes of heat and cold. There are numerous experiments (Blagden and others) to show that a man may remain for many minutes without any serious discomfort in a room the air of which is heated many degrees above the boiling-point of water (120° C. or 248° F.). Saturation of the air with moisture, so that the cooling evaporation from the skin cannot take place, or a longer stay will finally break down this protection, with serious or fatal results.

Heat-stroke; Heat Prostration.—In very hot weather, especially in places where the air is heavily saturated with moisture, it is not uncommon for persons here and there, to fall unconscious in convulsions, and sometimes to die, as a direct effect of overheating. These are usually debilitated people, or those who make great muscular exertion in clothing which prevents the rapid evaporation of moisture from the skin surface. Occasionally in periods of extreme heat and humidity great numbers of people may be prostrated, as though the affection were epidemic (Alex. Lambert). The mildest effect (heat prostration) consists in headache, moderate rise in temperature, pains in back and limbs, and extreme exhaustion. More severe is the asphyctic form, in which great dyspnoea and cyanosis, with delirium or unconsciousness, are added to these symptoms. Still more severe, and very frequently fatal, is the hyperpyretic type, in which unconsciousness and collapse come on suddenly, or after several days of vague premonitory symptoms. There are convulsions, delirium, or profound coma, with shallow and gasping or very deep respiration, and finally failure and stoppage of the heart. The skin, at first covered with sweat, becomes hot and dry, and the temperature rises to phenomenal levels. Lambert describes one case in which the rectal temperature reached 117.6° F. Another which we observed reached 108° F. before death, but after death continued to rise to nearly 120° F. In that case the most advanced putrefaction with great distention of the body appeared within twenty-four hours after death, and this is a phenomenon regularly observed and worthy of study.

Nothing definite is found at autopsy to explain such a death. There is intense rigor mortis, which sets in at once; the blood is fluid, but thick and dark from the ashytic phenomena of the last hours. No infection nor intoxication has been demonstrated.

We showed in 1920, in a study of gastric tetany, that the obstruction of the pylorus with frequent emptying of the stomach, produces a great

loss of chlorides so that convulsions supervene but can be cured at once by injecting sodium chloride. Recently it has been recognized that a great loss of chlorides can occur in sweat and that convulsions and minor twitchings of workmen in overheated mines where they are drenched in perspiration, can be prevented by taking considerable doses of salt. This seems to be generally known now and even some tennis players prepare for a long match with salt.

Sunstroke or **insolation** must be distinguished from this, since it is the effect of exposure, especially of the head and neck to the direct rays of the sun. Violent headache, with excitement reaching to maniacal outbursts, convulsions, and loss of consciousness characterize the attack, and if it does not end fatally in this acute stage or some days later, there may remain permanent mental and nervous disturbances.

Nothing is found at autopsy except congestion and swelling of the face and scalp, and a similar hyperæmia and oedema of the brain and meninges. It is thought (Schmidt) that it is rather the bright rays of the sun than the ultraviolet rays which penetrate the skull and cause these injuries to the brain—an opinion which seems open to question.

LITERATURE

- Bardeen: Jour. Exp. Med., 1897, ii, 501; Johns Hopkins Hosp. Rep., 1898, vii, 135.
Lambert, Alex.: Medical News, 1897, lxxi, 97.
MacCallum, Lintz, Vermilye, Leggett and Boas: Bull. Johns Hopkins Hosp., 1920, xxxi, 1.
Marchand: Handb. d. alg. Path., 1908, i, 49.
McCrae, J.: Trans. Assoc. Amer. Phys., 1901, xvi, 153.
McKenzie, P., and LeCount: Jour. Amer. Med. Assoc., 1918, lxxi, 260.
Pack: Pathology of Burns, Arch. Path., 1926, i, 767.

INJURIES PRODUCED BY COLD

The heat-regulating mechanism in the case of man is rather less effective in exposure to cold than to high temperatures, and since it works only through retention of the body-heat, it fails when lowering of the oxidative processes reduces the production of heat. Our artificial means of protection have become absolutely necessary to us, since we are not hardened to the exposure of the whole body to cold, and are no longer thickly covered with hair.

With prolonged exposure to extreme cold there are at first excitement and unrest, but later the skin becomes livid or pale, blood is driven back into the interior of the body, the temperature sinks, metabolism is slowed in all the organs, and their activity consequently reduced, the limbs become stiff and weak, the person is overcome by an irresistible desire to sleep, the respiration grows shallow, and the pulse small and weak—the temperature still sinks, and when it reaches 20° to 18° C. the heart stops beating and death follows. Nothing distinctive is found at autopsy, and it seems probable that death is due to just these changes which have been mentioned, just as a perfused heart, beating well upon Ringer's fluid at body temperature, slows down and stops if the fluid is cooled to 18° C. As to the possibility of recovery, it is easy enough to start the perfused heart beating again by warming the fluid, but the resuscitation of a person is a different matter.

There has been much discussion and experiment as to the resuscitation of lower animals which have been frozen, and the most divergent results have been obtained. It seems pretty clear, from many apparently trustworthy reports, that all sorts of animals and plants may be exposed to extremely low temperatures for a limited time, and then resume their vital activities when they are warmed again. But it is generally objected that they are not actually frozen—that is, their fluids do not actually crystallize, for when this occurs, the injury is too great to allow of recovery. Even when freezing does not take place, prolonged exposure to great cold kills. Lambert has shown this accurately with tissue grown *in vitro*; whereas by placing it in relatively concentrated plasma or salt solution it may be kept alive and ready to grow at -4° to -6° C. for five days, it is quickly killed in a less concentrated plasma, in which it actually freezes at this temperature. Even if it does not freeze, it is killed by ten days' exposure and by lower temperatures in a far shorter time, so that it cannot survive exposure to -20° C. for twenty minutes.

The noxious effect of the freezing is explained either as due to mechanical tearing of the cell as the ice crystals are formed, or to the concentration of salt around the crystals, or to the withdrawal of water from the cell to form the ice. It appears that the injury to the cell is the direct effect of the cold, and independent of the rate at which the tissue is thawed out. Rischpler describes in detail the anatomical changes, which consist in vacuole formation in the protoplasm and disintegration of the nucleus, and finally of the whole cell-body. It is easy to see that this must be followed by serious inflammatory reaction or by gangrene. This is indeed the case, but it must be stated at once that the gangrene of extremities which follows such chilling is by no means always directly due to the cold. On the contrary, it is the result of protracted ischaemia from extreme contraction of the blood-vessels or their obstruction by thrombi. Frozen feet or toes become livid or cyanotic, somewhat swollen, and pulseless, and turn purple and finally greenish black. The process is quite like the gangrene described in other connections, and the necrotic areas become sharply demarcated and dry up, or disintegrate or putrefy if they are not removed by the surgeon. Repeated freezing for very short periods at intervals is not so harmful as such long-continued freezing. Instead of necrosis, it tends to produce a remarkable hyperplasia of the tissue, with giant-cell formation in the epidermis.

Exposure to less extreme cold with moisture produces, especially in certain susceptible persons, slighter injuries, evidently largely dependent on the contraction of the vessels and the resulting anaemia. The fingers or toes are livid or cyanotic, and when brought back into the warmth, remain purplish, but swell and become painful and disabled (*chilblains*). After some days the epidermis may peel off in patches, while the normal color comes back gradually. Another exposure to cold will bring on another attack.

It is a matter of common experience with many people that if they sit in a draft or get wet and are chilled they "catch cold." This means

that an infection of the respiratory tract occurs by bacteria which are present there during perfect health, but which gain a foothold and multiply because of favorable conditions produced by the chilling of the skin. Exactly what those conditions are is not clear, although it is generally vaguely stated that chilling of the skin causes congestion of the internal organs. This seems an inexact explanation, since congestion is usually rather inimical, than otherwise, to bacterial invasion (Bier). The investigations of Mudd and Grant have shown, however, that if, when the skin is experimentally chilled, a thermopyle is applied to the mucosa of the nasopharynx it shows a corresponding fall in temperature, indicating that the chilling of the skin causes a reflex vasoconstriction in the mucosæ. This anæmic condition is much more compatible with the invasion of bacteria than the congestion which we formerly assumed to occur. That some definite change is brought about is plain, however, from the fact that the same sort of exposure will cause painful stiffness in the muscles of the neck and back, which must be of inflammatory character ("muscular rheumatism"), while in other persons it brings on an attack of diarrhea. Probably in all instances the chilling acts as a predisposing factor, favoring the invasion of bacteria, but it must be remembered that, although it is common in pneumonia, coryza, etc., it is by no means an indispensable factor, and every one realizes that it is perfectly possible to catch a cold from some one who is already suffering, without having been chilled.

LITERATURE

Lambert: *Jour. Exp. Med.*, 1913, xviii, 406.

Marchand: "Die Kalte als Krankheitsursache," Krehl and Marchand, *Handb. d. allg. Path.*, 1908, i, 541.

Mudd, S., and Grant, S. B.: *Jour. Med. Research*, 1919, xl, 53.

Rischpler: *Ziegler's Beiträge*, 1900, xxviii, 541.

LIGHT AND OTHER RADIANT ENERGY; ELECTRICITY

No attempt can be made here to discuss in detail this subject, which becomes daily more complex with the astounding discoveries in the realm of physics. Reference to recent works which present the subject from its physical aspect are given, so that the student may consult the literature.

Nature of Different Rays.—Radiant energy takes the form of rays moving with the same velocity, but with different wave lengths, according to which its peculiar character varies. Analyzed into a complete spectrum, it appears that the rays of greatest wave length are electric; then follow thermic, optically visible, and finally chemically active, rays, which have the minimal wave length. The atoms of each substance contain electrons which are positively and negatively charged. The vibrations of these electrons communicate electromagnetic vibrations to the ether. These waves, impinging upon other bodies, are absorbed by their electrons, which vibrate at the same rate, and since the electromagnetic vibrations of the negative electrons have the wave length of the ultraviolet rays, the latter are readily absorbed.

Some substances have the power, when thus influenced by certain radiations, of giving forth light-rays of another quality. This so-called fluorescence is of great biological significance.

Other forms of radiant energy, different from the electromagnetic transverse vibrations of the ether, are the so-called corpuscular rays, which consist in an actual

bombardment of negative electrons at a velocity somewhat less than that of light. Where they impinge upon metals, they produce the Röntgen-rays. The positively charged electrons pass in the other direction, and correspond to the α -rays of radium. The shower of negative electrons, the kathode rays, correspond with the β -rays of radium. Where kathode rays strike upon metal or glass, there are produced the γ -rays, which are emanated from radium and are related to the Röntgen-rays. Like the electromagnetic rays, these corpuscular rays may produce electric, thermic, optic, and chemical changes (Aschoff).

Effect of Light Upon the Tissues.—*General.*—Ordinarily we meet with conditions in which the tissues are acted upon by a whole series of different forms of radiant energy at once, and until recently no attempt has been made to analyze accurately these effects, and to experiment with them by separating the waves of different length and allowing them to act alone. Of the visible or optically active rays, it has been said that those toward the red end have the longer waves and are associated with effects of heat—beyond the red rays are invisible rays with long waves, which are merely heat-waves. On the other hand, toward the blue-violet end the waves are shorter, and their photochemical action is intense; far beyond the violet are invisible rays spread out in the spectrum which have the greatest power of influencing chemical action. These very short-waved rays correspond most closely with the vibration of the negative electrons of the tissues, and are quickly absorbed by the most superficial layers, especially when they are colored by pigment deposits. The red and infra-red rays penetrate much deeper.

Little effect is produced by the red rays as compared with the violet and ultraviolet. They are capable of producing an influence upon cells only in the presence of oxygen. The ultraviolet rays have a really intense effect on the tissues, in which they seem to act as catalytic agents. It is not quite clear how they produce their peculiar influence, but it is apparently through inducing intense chemical decomposition and oxidation. Their relation to the lipoid substances is peculiar in that the rays sensitize them and prepare them for oxidation or fermentative decomposition. An intracellular oxidation is brought about without the advent of extra oxygen, through the facilitation of decomposition of the lipoid substances by the action of the light. For this the red-yellow rays require an actual excess of oxygen. Ferments are affected also, but perhaps only secondarily, by way of the altered lipoids, which themselves, under the influence of light, acquire a photoactivity.

Such effects may appear in extraordinarily contrasting forms, according to their intensity, so that at times a new impulse to growth is conferred, at other times the tissues are disintegrated and destroyed. A peculiar influence is exerted by fluorescent bodies, which may depend upon the new ray set free by them when exposed to light or to their acting in some way as sensitizers. In the dark their presence has no significance, but if bacteria in a fluid containing eosin are exposed to sunlight, they are killed very rapidly. Enzymes, haemolytic substances, venoms and toxins, etc., are weakened or destroyed in the same way. The tissues of higher animals seem to be exposed to a new intensity of action of light-rays if they are impregnated with eosin or some similar fluorescent material (*cf.* Flexner, Noguchi).

Sittenfield found, as Tappeiner and others had already observed, that animals injected with minute quantities of haemato porphyrin remained normal when kept in the dark, but died quickly when exposed to sunlight or to the rays of an arc lamp. In the kidneys and other organs of these animals there were to be found distinct lesions in which fragmentation of nuclei and disintegration of cells were conspicuous. The part played by the fluorescence is, however, still uncertain, for some of the most highly fluorescent substances are but slightly toxic under exposure to light. Mrs. Clark, after studying the effect of such a substance as eosin on rennin, inclines to the idea that the inhibition of the action of the rennin is due to the decomposition of the eosin with the liberation of its halogen constituents, but v. Tappeiner showed that paramoecia were killed and disintegrated in an illuminated solution of eosin even when it was neutralized, but maintained their form for hours in a solution in which free acid had killed them. It is evident, as Sellards says, that the subject is as yet comparatively undeveloped.

Effects of Ultraviolet Rays.—The sun's light contains the ultraviolet rays, together with all the others, but they are produced much more abundantly by the electric arc and other artificial light. We may consider their pathological effects and their therapeutic use in pathological conditions.

Exposure to the sun or its reflected rays (from the surface of water or snow) produces the familiar sunburn. This is far more intense upon the tops of high mountains than at the sea-level, where the ultraviolet rays are to a great extent absorbed by the thick layer of the atmosphere.

The effect is not noticed at once, but after some hours there comes on an intense inflammatory reaction which is painful and often accompanied by blisters. The conjunctivæ also become inflamed. Evidently there is definite injury to the skin, for layers of it peel off after the inflammation has subsided. The blisters may leave white, scarred patches with pigmented border. Pigment is increased in the skin, and is recognized as distinctively protective in its function. Every one is familiar with the people who burn, others who acquire freckles, and still others who tan gradually to a dark brown without much suffering. The dark pigmentation of southern races and of negroes is evidently a protective adaptation for those living in hot countries.

Histologically, the epidermis in the sunburned place is found loosened and vacuolated, exudate permeates the corium, blood-vessels are widened, and in every respect the inflammatory reaction is like that produced by some mild chemical irritant. Occasionally the repetition of such sunburn in certain persons produces a chronic condition of pigmentation and excessive keratinization which may lead to cancer formation (the so-called *xeroderma pigmentosum*). In other persons the subject of certain diseases, such as smallpox, pellagra, etc., the sensitiveness to the effects of light is much intensified, and the example of buckwheat rash in cattle seems to make it probable that this susceptibility is due to the existence of a sensitizing or fluorescent substance in the tissues in those diseases.

Therapeutic use of ultraviolet and other rays is made in virtue of their more or less specific destructive influence upon pathological tissue elements. The epithelioid cells of cutaneous tuberculosis (*lupus vulgaris*) are especially susceptible to this effect. Certain rays of short wave length are capable of causing an increase in the number of lymphocytes, and this may be an explanation of their beneficial effect, especially upon tuberculosis of bone. On the other hand, smallpox patients are kept in rooms from which the ultraviolet rays are excluded by red glass in order to protect their sensitized skin. Most interesting is the recently demonstrated power of the ultraviolet rays to cure rickets. In this respect they seem to exert as sure and as specific an influence as cod-liver oil, and further, it appears that the tetany which so often accompanies rickets can also be cured by exposure to these rays.

LITERATURE

Bering: Lubarsch u. Ostertag Ergebni., 1914, xvii, 790.

Clark: Amer. Jour. Physiol., 1918, xlvii, 251. Physiological Reviews, 1922, ii, 277.

Sellards: Jour. Med. Research, 1918, xxxiii, 293.

v. Tappeiner and Jodlbauer: Wirkung fluoreszierender Stoffe, Leipzig, 1907.

The Effects of x -Rays and Radium on the Tissues.—In an x -ray tube the rays which start from the cathode and play on the anode (cathode rays) are really streams of negative electrons which impinge upon the metabolic anode, and there cause the production of electromagnetic vibrations of the ether which are very short, very irregular, and discontinuous. These are the Röntgen-rays. There is a stream of positively charged electrons passing in the opposite direction, which, if the cathode is perforated, pass through the holes and are, therefore, called channel rays. From radium there are given off analogous rays, the α -rays, which, like the channel rays, are really a corpuscular stream of positively charged electrons swung off from the decomposing atom, while the similarly discharged stream of negatively charged electrons constitutes the β -rays, which correspond with the cathode rays. These, through striking on metal or glass, produce γ -rays, in just the same way as the cathode rays produce the Röntgen-rays. They are like the Röntgen-rays, but have a much greater power of penetration.

By the use of adequate filters the effect of the different rays can be analyzed.

Röntgen-rays have little injurious effect upon bacteria, but the α - and β -rays from radium kill them directly, although they do not render the medium in which they grow poisonous to them, as light-rays do. Toxins are variously affected, but the toxalbumins, such as snake venoms, are weakened by radium-rays.

In the case of animals and man, the action of Röntgen-rays and radium-rays is very similar, the β -rays behaving like the cathode rays. Their effects have been studied especially in certain susceptible persons, in whom the so-called x -ray burns have appeared after a relatively short exposure for diagnostic, or therapeutic purposes, and also in radiologists who have been careless in exposing their hands in operating the apparatus. Now that protection is afforded the radiologist by leaden screens, and the patient screened by a thick aluminum plate, the corpuscular rays which seem responsible for the injurious effects are eliminated, and burns are becoming a matter of history.

The Skin.—Although in some cases a reddening of the skin appears at

once, this is usually due to heat, and the real effects of the burn become evident only after a long latent period of about two weeks. Then the skin becomes swollen and reddened, the hairs fall out, and a pigmentation appears. Blisters and excoriations with fibrinous exudate may persist for a time, or the skin becomes a necrotic slough over the affected area. Such ulcers as result from the discharge of this dead tissue show only slow attempts at healing, and repair is never complete, as is pointed out by Wolbach in some of his cases examined many years after the last exposure.

The hands of radiologists show best the chronic effects of long-repeated brief exposure, the lesions dating usually from the early days of radiology, when they neglected or were ignorant of screens. Really dreadful distortion and disfigurement have resulted in many of these men. The skin is dry, reddened, and scaly, with painful fissures and cracks here and there which refuse to heal, or after healing give place to others. The hairs are lost, and with the later atrophy of the skin sweat-glands also disappear. More extensive ulcerations, which are likewise very persistent, occur. The nails are thin and brittle, and are usually badly split and broken.

Wolbach has described the histological changes in many cases, and finds that the epidermis in places produces excessive dense keratinized layers; in other places the cells maintain their plump, deeply staining nucleus, and show no tendency to keratinization. At times vacuolated and evidently in process of downfall, the epidermal cells are often found in active mitosis growing downward into the corium. The corium is indurated in its depths, rarefied in the more superficial layers, where it becomes poor in cells and blood-vessels, and may show areas of necrosis. The capillaries which are there often become greatly distended, and are even so much widened as to give the appearance of telangiectases, through the skin. Such wide capillaries often become thrombosed, and Wolbach describes the invasion of these by the growing epithelial cells. Obliteration of arteries and veins and of capillaries in these layers of the skin by changes in the endothelium and by thrombosis and later organization, seems to him responsible for much of the necrosis in the corium and the inability to heal. With the destruction of the corium in foci, the epidermis is stimulated to grow down, invading unusual positions. It is not surprising, therefore, to find that this brings about actual epithelial tumor growth. There are many cases in which a proliferation of the epithelium, at first indefinite, later becomes recognizable as an actively growing skin cancer, which destroys the tissues in its line of progress and metastasizes into other organs. More will be said of this later, as it offers a point at which the study of cancer development seems promising.

The Blood-forming Organs.—Prolonged exposure to x -rays quickly diminishes the number of lymphocytes in circulation; the other leucocytes are affected slightly, but the red corpuscles seem, if anything, to increase in number. Brief exposure, on the contrary, causes an increase in the lymphocytes. Cases of leukaemia treated with x -rays sometimes show an extraordinary reduction of the white cells in the blood, while the

red corpuscles are unaffected. Doubtless the influence is upon the blood-forming organs, which are especially sensitive to these rays. The spleen is quickly reduced in size and becomes much pigmented. In the thymus the lymphocytes disappear rapidly, and even the framework of epithelial cells is injured. Lymph-glands lose their lymphocytes and become mere skeleton frameworks. In the bone-marrow the red corpuscles do not suffer, but the lymphocytes and myelocytes are destroyed.

An animal thus deprived of its lymphocytes has been shown by Murphy to be far more than normally susceptible to tumor implantations and also to tuberculosis. On the other hand, Sittenfield and Kessel have thought they observed a retardation of the invasion of tubercle bacilli after exposure to *x*-rays.

Genital Glands.—Testes and ovaries are also highly susceptible to the injurious influence of the radiation, the cells of the testicular tubules which produce the spermatozoa being especially affected there, while interstitial cells of Leydig and Sertoli cells are apparently resistant. After sufficiently long exposure the spermatic fluid is found to be devoid of spermatozoa.

In the same way the Graafian follicles in the ovary suffer, although it is less easy to determine whether complete sterility is produced in that way.

Other Organs.—In all the other organs similar, if less definite, changes are produced, destructive when the exposure is intense enough, but rather stimulating to proliferation and cell division when less intense. Experimental radiation of developing eggs and embryos usually produces either death or the development of malformations of all sorts.

Pathological tissues seem to be especially susceptible to destruction by these rays, whether derived from radium or the *x*-ray tube, and a great deal of work has been done upon their application in the case of cancers and other tumors, as well as in the treatment of various skin diseases and in leukaemia, Hodgkin's disease, and other affections of the blood-forming apparatus. This is not the place to discuss the results, but it may be said that while the effects are only palliative in advanced tumors and those in which metastases have already formed, there are some tumors, especially those of sarcomatous or lymphosarcomatous nature, such as occur commonly in the nasopharynx, which melt away as though by magic under their influence. Janeway comments on this and refers to good results in cutaneous epitheliomas. In leukaemia a temporary improvement may be produced, but I saw one case recently in which the irradiation of a mediastinal lymphosarcoma coincided with the appearance of leukaemic changes in the blood, soon followed by death. The destructive changes in the cells of tumors exposed to these rays have been studied by Alter.

LITERATURE

- Alter, N.: Jour. Med. Research, 1919, xl, 241.
Boggs, R. H.: Amer. Jour. Med. Sci., 1918, clvi, 690.
Janeway, H. H.: Surg., Gyn., and Obst., 1918, xxvi, 233.

EFFECTS OF ELECTRICITY

Electric waves, such as the Hertzian waves, are not known to have any effect upon living beings. Most important are the effects of the passage, through the body, of powerful currents of electricity from artificial sources or from lightning.

Judicial electrocution or the accidental contact of the body with the conductors of some light or power current furnishes examples of the former. In electrocution the contact is carefully arranged, so that the current will pass through the nervous system. In accidents it usually happens that the person touches an overhanging conductor and allows the escape of the current through his body to the ground, or forms with his body a short circuit between two conductors. In the case of lightning he becomes in the same way a conductor through which the discharge from the cloud passes to the earth.

Except for the so-called lightning figures, which Jellinek ascribes to paralysis of blood-vessels, and which are branching red lines radiating over the skin, the effects of lightning and the passage of the electric current are the same.

Fatal shocks may be produced by a direct current with electromotive force of less than 500 volts. Alternating currents can produce death with much lower voltage. With alternating currents the effect depends partly upon the rapidity of alternation, and when this is extremely rapid, as in the Tesla currents, its passage may become quite harmless. The effect of such electric shocks depends largely upon the resistance of the skin and of the whole body, and differs in different animals. Horses whose resistance to conduction is very slight are especially sensitive.

The pathological effects are most evident in the skin and underlying tissues, where at the point of contact deep burns are produced, often destroying the tissue down to the bone. At the point where the current leaves the body a similar charred wound may be found, with an appearance almost like that of a gunshot wound, a resemblance which is often intensified by the singeing of the neighboring skin and by the radiating tears in the tissue. These wounds in non-fatal cases are, like *x*-ray burns, extraordinarily persistent and hard to heal. Riehl distinguishes four degrees of severity in the injuries produced by strong electric currents, and states that they are by no means to be confused with the effects of burns. The exact cause of death is not clear, since little is to be observed in the internal organs aside from small haemorrhages and the curious, irregular streaks of contraction and hyaline change in the muscles described by Schmidt. There are great changes in blood-pressure and evidences of shock, but whether these are due to changes in the medulla oblongata or to direct action upon the heart it is impossible to say. Langworthy, from study of the brain after electrocution and from experimental electrocution of animals, finds extreme destructive changes in the nerve-cells in the medullary centers concerned in respiration, and feels that death may result from respiratory paralysis due to these changes.

LITERATURE

- Aschoff: Krehl and Marchand, Hand. d. allg. Path., 1908, i, 144.
Councilman and Magrath: "Xeroderma pigmentosum," Jour. Med. Research, 1909,
xxi, 331. Rich: Johns Hopkins Hosp. Bull., 1924.
Flexner and Noguchi; Noguchi: Jour. Exp. Med., 1906, viii, 1, 252, 268; 1907, ix,
281, 291; 1908, x, 30.
Heineke: Mitth. a. d. Grenz. d. Med. u. Chir., 1905, xiv, 21.
Jaffe: Arch. Path., 1928 (Electropathology Lit.).
Jellinek: Elektropathologie, Stuttgart, 1903.
Langworthy: Jour. Exp. Med., 1930, li, 943; Bull. Johns Hopkins Hosp., 1930, xlvi,
11.
Murphy: Jour. Exp. Med., 1914, xx, 397, and Riehl, G.: Münch. med. Woch., 1923,
1119.
Porter: Jour. Med. Research, 1909, xxi, 357.
v. Schläpfer: Pflüger's Arch., 1905, cviii, 537; 1906, cxiv, 301.
Schmidt: Verh. d. Dtsch. path. Gesellsch., 1910, xiv, 218.
Wolbach: Jour. Med. Research, 1909, xxi, 415.

CHAPTER XIX

TYPES OF INJURY (Continued).—CHEMICAL INJURIES

Nature of poisons: their varying effects. Reaction of organisms; elimination, detoxication, resistance. Auto-intoxication. Poisoning by illuminating gas, corrosive substances, cyanides. Chloroform, alcohol, metallic poisons, etc.

CHEMICAL INJURIES

Nature of Poisons.—Injurious chemical substances or poisons are those which enter into chemical reaction with the tissues in such a way as to injure them. All the activities of the body are based on chemical reactions, and many substances which we regard as foods are necessary and helpful to these chemical processes. Others which prevent them or actually destroy the structure of the cells are poisons.

Many of the substances which derange the activities of the cells do so only temporarily, and are changed into some harmless form or excreted completely before long. It is difficult to say, therefore, in many cases, whether or not we should call them poisons, but in some instances the repetition, through years, of the slight effects of single doses leaves the organs much altered, and we realize, in recognizing this chronic poisoning, that each dose had its own injurious effect.

It is essential to the complete understanding of the action of a poison that we should know its chemical composition, and that of the protoplasm with which it comes into relation, as well as the nature of the interaction. Perhaps even more important is a knowledge of the chemical process through which the cell carries on its function, and in which the poison interferes at some point, but at present it is only in the rarest instances that we possess all this information in accurate detail.

The study of all types of poisons is the province of toxicology, but it is equally interesting to the student of pathology for whom the structural changes and alterations of function form the subject of investigation. These are so manifold that no attempt can be made to describe them here, and we must be content with an outline of the principles involved.

Varying Effects of Poisons.—Without knowing why, we realize that the effects of many poisons vary greatly with their quantity and concentration, so that while small doses stimulate the tissues to intensified biological activity, larger or more concentrated doses have the opposite effect, probably because they render impossible some part of this activity. Often this is effected through making the tissue at first more sensitive, and then less sensitive, to the normal stimuli.

When a poison produces definite structural changes in the cells, its effect, so far as those cells are concerned, is permanent, although the animal may recover in virtue of the great reserve power of every organ, which can, with the remnant of its tissue, carry on the whole function

long enough to tide over the crisis and allow new cells to form and repair the loss. But if, as is so common, the poisoning is repeated frequently, the efforts at compensation and repair finally become inadequate, and the man with advanced chronic nephritis dies from the effects of renal insufficiency.

The extraordinary resources in the face of such attacks, and the long life that may be dragged out with such injured organs, are very striking, in contrast with the sudden violent symptoms and death which follow a rapid and extensive destruction of their tissues. Of course, in the latter case the margin of safety is overstepped, and there is not enough tissue left alive to carry on the organ's function, but in the former, where the destruction is gradual, there is a chance for accommodation to the reduced efficiency of the organ.

Unlike these poisons, there are others whose action is a temporary or invisible one; the functions of the tissue elements are disturbed only while the poison is dissolved in their fluids, and quickly return to the normal when it is washed away. A familiar example is found in the awakening from narcosis, during which the ether or chloroform is thought to be dissolved in the lipoids of the brain-cells.

The body has numerous fairly effective methods of removing poisonous substances, or even of protecting itself against their action. Irritating corrosive substances are vomited from the stomach, which throws out a thick, tough layer of tenacious mucus to protect its mucosa against what remains. Elimination of poisons is hurried by the development of diarrhoea, but also occurs, in the case of volatile substances, through the breath, and in the case of many others through the kidneys or the intestinal mucosa.

In the case of some poisons, such as arsenic, opium, cocaine, alcohol, etc., it is a matter of common knowledge that habitués become able to take far larger doses than other people without any poisonous effect. The explanations attempted for this are very unsatisfactory, especially, perhaps, with regard to the hunger for morphine and alcohol which these people develop when the drugs are denied them, and which often produces such stormy symptoms. No such theory as Ehrlich has devised for the immunity or resistance which comes after poisoning with bacterial or animal poisons will apply here, for the mechanism seems to be quite different and is still to be discovered. In the case of arsenic it is said that the larger and larger doses of the drug fail to poison because the intestinal mucosa acquires the power of refusing to absorb it, so that even in a person able to swallow an enormous dose without any ill effects the subcutaneous injection of the same material is just as poisonous in small doses as it would be to the most unaccustomed person.

The mechanism of resistance to bacterial toxins, snake venoms, and some related plant poisons, such as ricin and abrin, has been detailed elsewhere. (*Cf.* Zinsser.) Its far-reaching importance cannot be overestimated, but even this mechanism may be turned to unfortunate use at times, as it seems to be in producing the anaphylactic poisoning and injury to the tissues (Longcope, Jobling).

On the other hand, there are some poisons, such as strychnine and

digitalis, which have a so-called cumulative effect,, in that successive doses seem to build up their effect upon those which have gone before, and act with increasing intensity.

While rapid elimination and variously acquired resistance thus work toward the warding-off of the effects of many poisons, there are many which are neutralized in other ways by losing their chemical characters under the influence of the body. Inorganic poisons, when they are simple combinations in the form of a salt, are dissociated as electrolytes in the body fluids, and the action is an action of separate ions. Arsenic, mercury, and lead act in this way, as cations, in virtue of their metallic peculiarities, while the anion in sodium bromide or fluoride or iodide is the one which appears as a poison. When the combination is very stable and complex, these metals may be introduced in forms in which they are not easily dissociated, and then fail to unfold their characteristic poisonous effects. It is further true that combinations of atoms, in themselves innocuous, may acquire, in virtue of their peculiar arrangement, toxic characters of the greatest intensity. Therefore it is not surprising that mere processes of oxidation may sometimes be capable of disarranging this fatal combination and rendering the poison inert. Similarly, synthetic combinations may occur with the same result — carbolic acid, in itself a violent poison, becomes harmless in the form of a double ethereal sulphate, while other substances are decomposed, sometimes to render them innocent, at other times only to liberate a more poisonous combination.

Interesting and complex antagonisms between various inorganic substances occur in their action upon cells, and in so far as they are not mere precipitations of the poison, are very hard to explain. Meltzer has shown that the injection of calcium salt will awake instantly, from the deepest coma, a rabbit poisoned with magnesium, and the papers of J. Loeb throw much light upon similar antagonistic action between calcium and sodium or potassium salts, and many others, as tested on developing eggs, muscular activity, etc. He at least proves that it is not merely the neutralization of differently charged ions.

No effort shall be made here to give a classification of poisons; the student is referred to text-books on toxicology and pharmacology. In general poisons are derived from inorganic or mineral sources, from plants, including bacteria and fungi, and from animals. Of the inorganic substances, the most familiar poisons are the salts of heavy metals, such as lead, arsenic, antimony, mercury, chromium, manganese, etc., and the halogen group, fluorine, bromine, iodine. From plants come great numbers of highly poisonous alkaloids and glucosides, oils, terpenes, alcohols, and coal-tar products, as well as all the enormously complex toxins produced by bacteria and moulds, which have the special peculiarity of stirring up resistance and immunity in the poisoned animals. Quite similar in this respect are those other plant poisons of which ricin and abrin have already been mentioned. From animals there originate many venomous poisons, of which those specially secreted in glands for offensive purposes (snake venoms, etc.) are the most interesting. Other animal products, especially the partly digested or disintegrated proteins,

such as albumoses, seem to be poisonous when introduced subcutaneously or intravenously; although they, like snake venoms, are innocuous if swallowed. These protein materials, including the venoms, also, have the power of inciting a reaction of immunity, and, indeed, one can, by injecting frequently the proteins or the cells of one animal into another of a different species, produce in the blood of that second animal a substance which would be distinctly poisonous if now injected into the body of the first. Such cytotoxins, which include haemolytic sera, have already been referred to.

Different in principle is the development of poisonous substances in putrefying fish or flesh. Although part of these familiar sudden and violent poisonings, which may end fatally in whole groups of people who have partaken of stale shellfish, fish, meats, or milk products, have long been ascribed to ptomaine-poisoning, it is possible that in most cases such epidemics are really due to infection with certain bacteria (*B. botulinus* of Van Ermengen, *B. enteritidis* of Gärtnner, and allied forms).

Much is written of *autointoxication*, or the absorption of poison from some place where it is formed in the body itself. In so far as the proper evacuation of the excreta is interfered with by obstruction or disease of the excretory organs, this is easily comprehended. Obstruction of the intestine may be rapidly fatal, and so, too, may such disease of the kidneys, or obstruction to the outflow from ureters and bladder as can stop or greatly decrease the excretion of urine. Uræmic poisoning falls into this latter class. The absorption of bacterial poisoning from the unobstructed and otherwise not diseased intestine has long been widely accepted, but must be taken with caution, while it seems more confusing than helpful to class the alterations of metabolism which follow disease of the organs of internal secretion as autointoxication. Most of these are in reality the effect of the lack of some secretion proper to the injured gland, although, of course, in the imperfect metabolism, toxic substances may arise, as in the case of β -oxybutyric acid in diabetes (*q. v.*).

ABSORPTION AND GENERAL EFFECTS OF POISONS

Most poisons are taken into the digestive tract, although volatile or gaseous poisons may be absorbed in the lungs, and other substances, such as mercury, may penetrate the skin, or, as in the case of snake venom or the drugs administered in a hypodermic syringe, be introduced directly into the tissue or the blood-stream.

They act locally, as when strong acids or alkalies or caustic metallic salts corrode and kill the tissues, or else they are absorbed into the blood and then exercise a more general effect. When poisons are introduced into the streaming blood, they disappear very rapidly and are not to be quantitatively recovered from the blood, nor equally from all organs, but often concentrate themselves in certain tissues with a markedly selective action. Under such circumstances the poison often reaches the nervous system or other vital organs in greater concentration than after the slower absorption from the alimentary tract. Naturally, in the case of bacterial toxins and the less defined products of protozoan

and other animal parasites, the distribution of the parasites determines to a great degree the spread of the poison, although there are, at least, two bacterial infections (diphtheria and tetanus) in which the bacteria grow locally on a mucous surface or in a wound, and diffuse their poison throughout the body.

It has been said that most poisons seem to show a certain selective action in the way they affect especially one organ or another. It would be better to say that those organs exhibit a special affinity for certain poisons, but it is usual to classify poisons as cardiac poisons, renal poisons, blood-poisons, etc. Since there is little in common among the members of such groups, the classification seems hardly rational, and we must believe that the organ absorbs them and is affected by them for different reasons. For example, of the poisons which affect the central nervous system, narcotics, strychnine, and magnesium salts must behave very differently.

Here, if anywhere, it should be easy to carry out the general aim of this book and set in order the pathological results on the basis of aetiology, but the number of poisons is so limitless, and their effects are so variegated, that any classification, to be at all accurate, must include an immense number of headings. For this space at least is lacking, and once more the student must be referred to works on toxicology and pharmacology. It is desirable, however, to discuss briefly the very common forms of poisoning which are found at autopsy, and which occur nowadays usually in cases of suicide or in persons who have worked with poisonous materials in one of the dangerous industries. Doubtless in the old days, when poisoning was a fine art, the subject was vastly more interesting.

Persons committing suicide by poison are generally ignorant of the painful effects of the poison which they choose to take, but are impelled, by the lurid descriptions in the newspapers, to swallow what some other suicide is said to have taken. Hence whole epidemics of poisoning with bichloride of mercury have occurred recently. Many other substances are used because they can be obtained easily, and this is true of carbolic acid and cyanide of potassium, and of the ever-accessible illuminating gas.

Illuminating-gas Poisoning.—The essential factor in this is the carbon monoxide, which is present in greater concentration in the so-called water-gas than in the other types of illuminating gas. Breathed into the lungs, it quickly replaces oxygen in the red corpuscles, by virtue of its very much greater affinity for haemoglobin and the tenacity with which it holds to this combination. It can be gradually washed away by prolonged breathing of pure air or oxygen, so that carbon monoxide haemoglobin is not a permanent and stable combination. The blood, and consequently all the organs, assume a bright, cherry-red color, which is little affected by the condition of asphyxia of the tissues, for it is as difficult for carbon dioxide to dislodge the carbon monoxide as it is for the oxygen. There are usually fever and leucocytosis, but no direct injury to the lungs, nor, as a rule, pneumonia. It is common to find at

autopsy symmetrical areas of softening with minute haemorrhages in the corpora striata and lenticular nuclei of the brain (Fig. 202).

Carbon monoxide in the exhaust gases from automobiles has become a frequent cause of death when persons incautiously remain in a closed garage with the engine running, and sets up symptoms of chronic poisoning in others who breathe it in less concentration (Clemens and Thompson).

Apparently pure carbon monoxide will not produce the symmetrical lesions of the brain, but it is not known what impurity is responsible for them.

Corrosive Poisons.—Strong acids and alkalies and some metallic salts, swallowed usually with suicidal intent, produce deep lesions in the

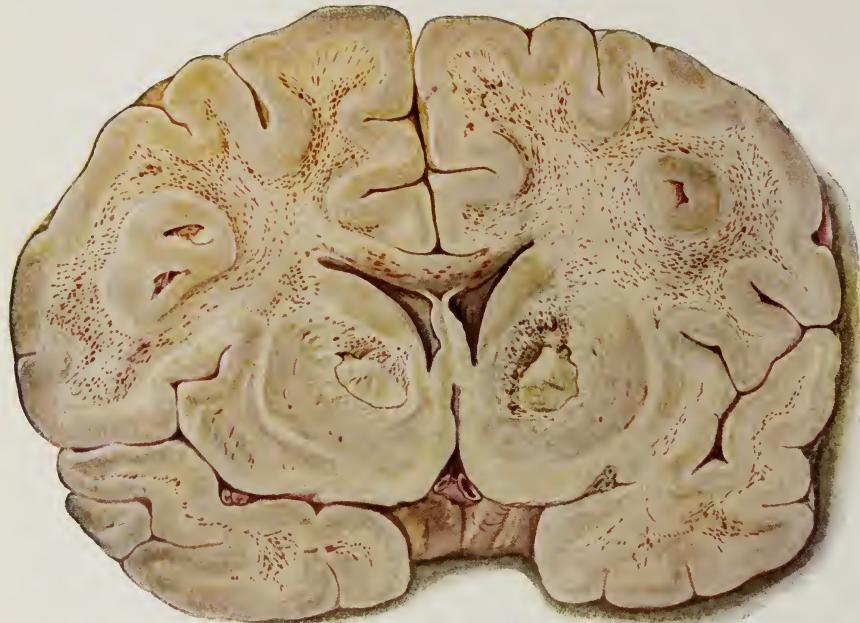


Fig. 202.—Carbon-monoxide poisoning; symmetrical necroses in lenticular nuclei.

stomach wall, which, while very characteristic when fresh, are more difficult to recognize as the typical effect of a particular poison when the persons survive long enough to allow the digestive action of the gastric juice to reduce them all to a similar appearance.

Nitric acid produces deep necroses in the stomach-wall which are discolored and mottled with white and black débris, but characteristically colored in places, at least, by the bright orange yellow of the xanthoproteic reaction. *Hydrochloric acid* fails to produce this color, while strong *sulphuric acid* chars the mucosa into a crumbly black mass.

In all these cases the immediate effect is to make the stomach contract sharply, so that the crests of the folds of mucosa are pressed together and form a smooth surface, while the depths between are protected and secrete much thick mucus for

their further protection. Distention of the stomach tends to make the effect more diffuse, but food, when present, aids in the protection of the mucosa.

Carbolic acid is much favored by suicides, and is usually swallowed in concentrated form. White eschars about the mouth and in the œsophagus prepare one for the appearance of the stomach, in which again the crests of the folds suffer most intensely (Fig. 203). They are covered with a white, opaque layer of necrotic tissue. Carbolic acid is an excellent fixing fluid, and in microscopical preparation these areas of the mucosa seem perfectly normal. The fixation or coagulation may



Fig. 203.—Carbolic-acid poisoning. Coagulation of crests of the folds of mucosa in the stomach.

extend through the wall of the stomach and involve adjacent organs, which look as though they had been cooked. Lysol poisoning produces a peculiar effect in the stomach, and here, as in the case of carbolic acid, the deeper cells of the mucosa, killed but not fixed by the poison, are digested by the fermenters of the stomach (Fig. 204). Uyeno has described extensive changes in the kidney from long-continued carbolic-acid poisoning. These are hardly to be found in the acutely fatal cases.

Caustic alkalies are generally swallowed by mistake, and this accident is especially common among children in the south, where concentrated

lye is sometimes used for household purposes. If they die, the gastric mucosa is found greatly swollen and haemorrhagic, and often rather gelatinous, from the direct effect of the alkali. If they survive, the destructive changes which are commonly produced in the wall of the cesophagus lead to narrowing of its lumen by scar tissue. Such strictures must be dilated to prevent starvation.

Prussic acid and cyanides have no corrosive effect in the stomach, but the mucosa assumes a bright, chestnut-brown color which is characteristic. Here, as in carbolic-acid poisoning, the odor of the stomach-contents and tissue is a very great help in recognizing the nature of the



Fig. 204.—Lysol poisoning. Superficial necrosis and partial digestion of the gastric mucosa.

poison. The cyanides cause death by their action on the nervous system and heart, and by their wide-spread interference with oxidation and ferment processes throughout the body.

Fumes from nitric acid, which, according to Wood, are essentially nitrogen tetroxide, although mixed with other oxides, may be inhaled in accidents, explosions, etc., and may cause death, as in one case which we studied, with extensive desquamation of the lining epithelium of the lungs, with lobular pneumonia and oedema of the lungs. Strong ammonia and chlorine vapors have a somewhat similar corrosive effect, associated with other more general evidences of intoxication.

It is impossible to discuss here all the manifold effects of the poison-

ous gases used in the war, and the student must be referred to the special literature upon this subject. The most important gases used were mustard gas, the phosgene, chloropicrine, chlorine group, and the arsine compounds. In brief, the lesions produced are summarized by Pappenheimer as follows: No data are available on the lesions in human beings from the arsine compounds. Mustard gas (dichlorethylsulphide) produces blisters on the skin after a latent period. Its inhalation causes necrosis of the respiratory mucosa with formation of a diphtheritic membrane extending deep into the bronchi, and followed by purulent bronchitis with regeneration of the epithelium, usually with squamous metaplasia. All types of lobular, haemorrhagic, and interstitial pneumonia follow, sometimes resulting in gangrene, extensive organization, or bronchiectasis. Intestinal and cerebral haemorrhages have been found, and there is aplasia of the bone-marrow resulting in leucopenia. The changes caused by phosgene, chlorine, etc., consist essentially of extreme oedema of the lungs, coming on after a latent period with areas of atelectasis and emphysema. When recovery is not immediate, various types of pneumonia follow. No other visceral changes are observed.

Other volatile substances can be absorbed through the enormous capillary surface exposed in the lungs, and take effect with a rapidity almost as great as though they had been injected into the veins. Among these chloroform, ether, and other narcotics are most prominent.

Chloroform has a distinctly poisonous effect, as is shown by the necrosis of fat accumulation which it produces in the liver. Its more rapidly fatal effects seem to be due to the paralysis of the heart which it brings about when administered in too great concentration. Evarts Graham states that the poisonous effect of chloroform is due to its decomposition within the cell with liberation of free hydrochloric acid.

Alcohol is, of course, the commonest of poisons that affect human beings. Methyl-alcohol in relatively small doses produces coma and death, or recovery with blindness. Its action is in part due to the fact that it is changed to formic acid in the tissues. Ethyl-alcohol has the well-known effect of producing drunkenness, and after protracted habitual use seems to give rise to many anatomical changes in the organs. The proof of this connection is not so clear as it should be, and is questioned by many, especially since such changes cannot be produced experimentally with any degree of constancy. This is true of cirrhosis of the liver, which can be caused by so many other kinds of injury and which is absent in such a large percentage of those who have abused alcohol to the last degree for many years. Nevertheless, it is unreasonable to deny its part in this process, since it undoubtedly has poisonous qualities and seems capable of such a banal effect. Probably it acts in this respect in combination with some other poisons as shown in the recent work of Lamson, who finds that carbon tetrachloride is allowed to exercise its poisonous action especially when alcohol is taken at the same time. The destructive effects upon the brain are more evident in the functional disturbances which are clearly traceable (delirium tremens, alcoholic insanity, etc.). With regard to the relation of alcohol

to chronic nephritis, arteriosclerosis, etc., the same may be said as for cirrhosis of the liver.

Mention may be made of a few poisons absorbed by workers in various dangerous industries. This subject is so broad that the reader is referred to the special literature upon occupational diseases.

Lead.—Chronic lead poisoning (saturnism) among painters occurs in pottery workers, white-lead workers, and many others who constantly deal with dusty operations with lead in various combinations and is so common as to assume great importance among industrial poisonings. Acute lead poisoning is rare.

Anæmia, intestinal colic, a bluish line along the gums of those who neglect the cleanliness of their teeth, paresis of the extensor muscles, resulting in the so-called wrist-drop and toe-drop, and occasionally outspoken mental disturbances are characteristic of this affection. Lead may be found in the brain, kidneys, and liver in proportion varying according to different investigators. But it is especially stored in the bones from which again it is slowly removed at a rate parallel with that of the calcium metabolism. With parathormone or irradiated ergosterol it, like the calcium, can be brought out of the bones far more rapidly and even with the risk of an acute poisoning. Its excretion is chiefly in the faeces although some appears in the urine.

The blood shows anæmia and anisocytosis but especially the presence of basophiles and reticulocytes of which the characteristic stippled cells are apparently a modification. The colic which is very painful is thought by Freifeld to be due to involvement of the solar ganglions and the sympathetic connections. A form of gout associated with chronic saturnism may be partly due to deposits of lead combination with uric acid.

Cerebral disease, the so-called lead encephalopathy with depression, delirium, convulsions and even general paralysis seems to be due to destruction of cortical cells and demyelinization of tracts in brain and cord. The paralysis involves some cranial nerves but more especially the spinal motor nerves.

The cases which have come most often to our attention are those in which children have been poisoned, evidently by paint which they have gnawed off the frame of their cot. These show focal necroses throughout the brain with haemorrhage and clumping of glia cells and even inclusion bodies as found by Blackman. Chronic diffuse nephritis of the arteriosclerotic type, with extensive scarring, obliteration of blood-vessels and glomeruli, is characteristic of lead poisoning, and evidently depends largely upon the effect of the poison upon the smaller blood-vessels.

Recent interest has been aroused by the poisoning with cerebral symptoms and fatal outcome resulting from the use of tetra-ethyl lead in gasoline for motor cars. The recognition of a volatile lead compound in the brain of persons so poisoned perhaps explains the symptoms (Norris and Gettler).

Arsenic.—Once most extensively used for purposes of murderous poisoning and for suicide, arsenic poisoning is now accidental or connected with its absorption from adulterated foods or from various paints

and dyes used in coloring wall-papers, cloths, etc. There may be expected, therefore, acute and slow chronic poisoning. *Acute Form.*—When taken into the stomach in poisonous doses, the effect may be rapid death from direct influence upon the brain and heart, but more often the symptoms are referable to the digestive tract, where the lesions are accentuated by the reëxcretion of absorbed arsenic through the mucosa. Swelling, haemorrhage, diphtheritic inflammation with ulceration are characteristic, and in the mucosa of the stomach crystals or particles of the swallowed arsenic persist. When Paris green or some other brightly colored combination is swallowed, this is a conspicuous feature. Fat accumulation in liver, kidneys, and other intestinal organs is common. *Chronic Poisoning.*—In the chronic forms which may appear late, after even one severe poisoning, the nervous system suffers especially, but conspicuous changes are found in the skin. The cutaneous lesions are manifold, the most extreme being forms of excessive keratinization and deep pigmentation. The nervous changes have the character of a neuritis, with paralyses, followed by muscular atrophy and contractures. There may be also cerebral disturbances of varying degree. Most important, besides the danger of blindness from arsenical destruction of the optic nerves, is the extensive destruction of the liver after the careless use of salvarsan and others of the newer synthetic arsenical remedies. In spite of the statements of Herxheimer and other German pathologists that the so-called acute yellow atrophy of the liver must be referred to syphilis and not to the arsenical remedy, or at least that syphilis is the necessary predisposing cause, we have been profoundly impressed by the frequency of instances in which fatal injury to the liver has followed directly upon such therapy.

Phosphorus.—As an industrial poisoning in those who work in match factories, and as a poison accessible to all for suicidal purposes in the heads of old-fashioned matches, phosphorus is more important in Europe than in this country. *Acute poisoning*, with vomiting, jaundice, haemorrhages, swelling of the liver, etc., may lead to death. Aside from the haemorrhages, which may be widely scattered, one finds intense icterus and great enlargement of the liver, with wide-spread necrosis and autolytic disintegration of the cells. Whatever cells are left are distended with fat and lipoid globules. With recovery, the liver decreases in size and may become greatly scarred. Kidneys, heart muscle, and even skeletal muscles are loaded with fat. *Chronic poisoning* occurs especially in those exposed to vapors of phosphorus, and is particularly characterized by producing necrosis of the jaws. This begins with suppuration at the root of a tooth, which sets free a quantity of pus, when it finally loosens and drops out. The destruction with suppuration does not cease there, but progresses, to destroy the whole jaw or even to extend into the neck. Evidently the aid of bacterial infection is necessary to the process.

Mercury.—Suicidal poisoning with mercuric bichloride is at present in favor, since the public imagination is stirred by the detailed reports of several cases. A few years ago there were cases of the same sort of poisoning due to the inordinate irrigation of wounds with this substance,

which was used as an antiseptic. The poisoning from careless use of mercurial drugs or from the inunction of syphilitics with mercurial ointments is usually milder and more chronic in its course, and since it shows itself in salivation, the loosening of teeth, and foetor from the mouth, is likely to be checked before producing a fatal result. Industrial poisoning with mercury is not uncommon in such trades as mirror making, gilding, thermometer making, etc.

The acute poisoning provokes intense gastro-intestinal symptoms, with pain, metallic taste, vomiting, diarrhoea, etc. The stomach shows various lesions, according to the nature of the poison and the dose. A large quantity of a solution of mercuric bichloride may fix the mucosa so that it appears normal microscopically, although white and opaque to the naked eye. A solid tablet may, it seems, act intensely on one



Fig. 205.—Mercuric-chloride poisoning. Diphtheritic and haemorrhagic colitis and ileitis.

spot and cause the death of the tissue, with subsequent ulceration. If this be survived, the symptoms may practically disappear, but later others ensue—anuria and evidences of inflammation in the colon. Death follows days or even weeks later from renal insufficiency. Since mercury once absorbed is reëxcreted through the mucosa of the intestine, it is not surprising to find at autopsy the most intense diphtheritic and haemorrhagic enteritis (Fig. 205). Mercury can be recognized by appropriate tests in the necrotic mass lying upon the mucosa and in the mucosa itself. The kidneys present most extensive necrosis of the epithelium of the tubules, with deposition of calcium in and about the dead cells. Later, with the liquefaction of these cells or their disintegration by phagocytes, the calcium becomes coalescent in irregular masses within the tubules. The remaining epithelial cells proliferate rapidly, to replace those which were lost, and often become large protoplasmic

masses with many nuclei, which act as phagocytes and engulf those which are in process of disintegration (Fig. 53). (Cf. Heineke.)

It does not fall within the scope of this book to treat of the multifarious effects of poisons of plant and animal origin. They might be classified according to their point of action, as in other text-books of pathology, and mentioned by name, but, except for their discussion in other connections, it seems better to refer the student to works on toxicology where they are satisfactorily treated.

LITERATURE

General:

- Boehm, Krehl, and Marchand: Handb. d. allg. Path., 1908, i, 198.
Ford: "Plant Poisons and Antibodies," Centralbl. f. Bakter. u. Paras., 1913, lviii, 129.
Kobert: Lehrb. der Intoxikationen, 1902-1906, Stuttgart.
Loeb: "Antagonistic Salt Action," Biochem. Zeitschr., 1911, xxxvi, 275. Jour. Biol. Chem., 1914, xix, 431.
Meyer and Gottlieb: Lehrb. d. exp. Pharmakologie, Berlin, 1914.
Peterson and Haines: Text-book Legal Medicine, Philadelphia, 1903.
Welch: Pathological Effects of Alcohol, Boston, 1903.

Lead Poisoning:

- Aub and others: Medicine, 1925, iv, 1; Quart. Jour. Med., 1927, xx, 123; Jour. Amer. Med. Assoc., 1935, civ, 87, 90, 194, 200, 205.
Baker: Amer. Jour. Path., 1934, x, 637.
Freifeld: Virchow's Arch., 1928, ccclxviii, 456; 1933, ccclxxxvii, 549.
Norris and Gettler: Jour. Amer. Med. Assoc., 1925, lxxxv, 818.

Mercury Poisoning:

- Heineke: "Sublimate Poisoning," Biegler's Beiträge, 1909, xlv, 197.

Illuminating-gas Poisoning:

- Clemens and Thompson: Bull. N. Y. Acad. Med., 1926, ii, 402.
McNally: Arch. Path., 1928, v, 43.
Meyer, A.: Klin. Woch., 1927, vi, 145.
Thompson: "Illuminating Gas Poisoning," Med. Record, 1904, lxvi, 41; Occupation Diseases, New York, 1914.

- Chornyak and Sayers: Public Health Reports, 1931, xlvi, 1523.

Carbolic-acid Poisoning:

- Uyeno: "Exp. Carbolic Acid Poisoning," Ziegler's Beiträge, 1910, xlvii, 126.

Arsphenamine Poisoning:

- Hunt: Jour. Amer. Med. Assoc., 1921, lxxvi, 854.

CHAPTER XX

TYPES OF INJURY (Continued).—EFFECTS OF OBSTRUCTION OF THE FLOW OF CONTENTS OF HOLLOW ORGANS. OBSTRUCTION IN THE ALIMENTARY TRACT

Salivary ducts: bilo-ducts (gall-stones, cholecystitis, jaundice). Pancreatic ducts (pancreatic cirrhosis, acute pancreatitis). Obstruction of digestive tract. (Esophagus, stomach (gastric ulcer). Intestine; varying mechanism of obstruction (hernias, intussusception, volvulus, compression or kinking by adhesions, paralysis, stenosis).

THE possession of a duct or canal for the discharge of secretions, or for the reception and transmission of fluid, gaseous, or even solid materials, is an arrangement common to a great many organs. Wherever this plan is made use of, there may arise obstruction of the canal, and the effects which follow are so much alike that it seems desirable to consider them together, and to regard this as one of the types of injury which underlie pathological processes. The mechanical principles are very nearly the same in all, although it may at first glance seem absurd to bring together in any way such processes as bronchiectasis and hydronephrosis. As a rule, an accumulation of material occurs on one side of the obstruction, which causes the gradual widening of that part of the canal, while the part on the other side remains normal or even shrinks together. This and the general behavior of the organ depend, however, very largely upon whether the obstruction is complete or only partial. Some organs can go on secreting for a while, attempting to force their secretion into the duct against a complete obstruction, but in many cases they quickly stop all activity under those conditions and the duct never becomes distended. On the contrary, when the obstruction is only partial or intermittent, secretion or the entrance of material into the canal goes on until it becomes greatly dilated. Examples from various parts of the body will make these principles clear, and show further many modifying influences. These conditions, varying as they do, afford a large proportion of the operable disturbances which may be treated by the surgeon.

RESULTS OF OBSTRUCTION IN THE ALIMENTARY TRACT

Naturally, since the glands of the stomach and intestine open by individual canals, it is rare to find any obvious effect of their obstruction, although it is quite true that in some old inflammatory changes in the mucosa they may be constricted at their orifice or obliterated by healing processes so that their continued secretion distends them into tiny cysts. This is more frequent in the colon than elsewhere. But the accessory glands, which empty into the alimentary tract, are often victims of some form of occlusion of their ducts.

In the salivary glands this is not especially common, but there do occur calculous concretions in the salivary ducts which partly or com-

pletely occlude them and cause inflammation and dilatation of the duct, with gradual atrophy of the gland. Such calculi are rough and irregular and white, and are composed chiefly of calcium phosphate and carbonate.

Bile-ducts.—In the case of the liver, the canal giving exit to the biliary secretion is somewhat complicated by the presence of a reservoir, the gall-bladder, joined on laterally. Obstruction of the canal may, therefore, take place at such a point as to affect the whole system, only the lateral reservoir, or only the liver or portions of the liver. The obstruction may be caused by compression of these ducts from the outside at any point; by changes in their own walls, which, becoming thickened, encroach upon the lumen, or by some solid plug which may lodge at any point in their lumen. Not uncommonly these factors are found combined, as when there arises about an obstructing gall-stone an inflammatory thickening of the wall of the duct or even a tumor.

Much has been said in discussing the rather broader topic, jaundice, about the important part played by various forms of obstruction in its development, and this need not be repeated. The principles underlying such obstruction are, however, well exemplified in the variegated phenomena which are associated with the formation of gall-stones (cholelithiasis).

Gall-stones.—In the first place, it is becoming clearer in later years that the primary formation of gall-stones is itself largely dependent upon stagnation of bile, such as may arise in the gall-bladder if an intermittent or incomplete closure of the cystic duct be brought about by such things as tight lacing, pregnancy, or even the unequal sagging of the abdominal viscera. Then, although some bile moves in and out of the gall-bladder, there is stagnation, and even in the clear, uninfected fluid, cholesterine crystals may separate out and cluster about a central point until there is formed a solitary round or oval, slightly roughened, stone-like mass, which usually lies loose in the neck of the gall-bladder.* This is the first type named by Aschoff and Bacmeister, the *radiate cholesterine stone* (Fig 207, 14), because it is found on cross-section to be composed of coarse, radiately arranged crystals of nearly pure cholesterine, which project to produce the roughened surface of the stone. There is so little admixture of other materials that such calculi are quite clear or only pale yellow. Pure crystalline masses of this sort are not very common, for usually they become covered with yellow, brown or greenish material by a secondary deposit. This happens when, after the stone has lain in the gall-bladder for some time, infection with bacteria arises around it and causes inflammation of the gall-bladder wall (cholecystitis). With the appearance of the inflammatory exudate, which is rich in calcium, there are deposited on the surface layer after layer of a combination of calcium and bilirubin. It may be emphasized that, whereas the cholesterine is a constituent of the bile and crystallizes out from it, calcium appears in appreciable quantities only in the course of inflammation. Such a mixed stone with a nucleus formed of cholesterine and a mantle of calcium bilirubin may be regarded as the second type. The mode of its formation by apposition is shown in sections by the fact that each projecting crystal of the cholesterine nucleus is separately covered by a layer or two of the brown mantle before the depressions are sufficiently filled up to allow the next layer to be laid on smoothly.

There are other types, such as the laminated calcium cholesterine stones, and

* Recent investigations of Stewart, Hermann and Neumann, and others show that, during pregnancy, the blood and bile are rich in cholesterine. Doubtless this is important in the production of gall-stones, which are so common in women who have borne several children. Rothschild and Wilensky support this in their studies of the cholesterine content of the blood in this and other conditions, but there are others who deny the relation.

the soft, blackish-green calcium bilirubin concretions, which are usually formed in the hepatic ducts, and more rarely get into the gall-bladder; but all these are rarer and of less importance than the last form, which is the common mixed calcium bilirubin-cholesterine stone (Fig. 206). These form the great majority of all gall-stones, and occur sometimes in hundreds or thousands in a single case, although there may be only two or three large ones filling up the gall-bladder. These large ones are rounded or barrel-shaped and faceted where they abut on one another. The smaller ones vary in color from pure, silky white through yellow, brown, and green to black. They may be so small as to be almost like sand, or a centimetre or two in diameter. Often a great number of stones of almost exactly the same size may be found together. Usually they are faceted against one another, and fit together by their polished surfaces like dice. Sometimes, indeed, they seem to show the effects of rubbing, for several laminæ may be found exposed. On cutting through and polishing one of these there is found to be a soft, greenish-brown or yellow



Fig. 206.—Subacute and chronic cholecystitis with gall-stones. There is one rounded stone of pure cholesterine, together with nine faceted mixed pigment calculi. The small irregular mass was found in the duct.

central mass which is composed of conglomerate crystals with much organic material and pigment, and then, surrounding this, there are laminæ, often alternating in color, of a much denser consistence, and composed, as stated above, of a mixture of cholesterine with calcium bilirubin (Fig. 207).

Ribbert's interesting study of these stones gives many details of their structure, showing that the central portion contracts upon drying in such a way that sharp clefts extend radially as far as the laminated outer part. He devised a new way of studying them in section, and finds that the part played by the calcium is perhaps less than generally supposed.

All the types of gall-stones described contain a great deal of organic material derived from desquamated epithelial cells and coagulated albuminous matter, as well as pigment. Many of them contain bacteria, and are formed in infected bile and within a gall-bladder which is inflamed, because in this vicious circle the pres-



Fig. 207.—Gall-stones of various types cut and polished. 4, 7, 13, 14 and 17 show primary gall-stones at first composed of almost pure cholesterol, later covered with pigment. 3, 5, 6 and 11 are faceted secondary stones. 9 and 19 show well the thin laminae found under the faceted surfaces.

B.E. Stocking 720

ence of the stone aids in giving a foothold to bacteria, while they in turn, through the inflammation they set up, aid in the growth of the stone.

The bacteria are of many sorts, but the typhoid and colon bacilli are common invaders, and doubtless the pyogenic cocci are important in causing the acuter forms of inflammation. How they enter has been much discussed. Probably the typhoid bacilli, since they are distributed everywhere by the blood-stream, might reach the gall-bladder in that way, but they may also be excreted from the liver, and may be found there for months after convalescence from typhoid fever. There is some evidence that they may, by being agglutinated in clumps, produce nuclei upon which gall-stones may form, but this evidence is not conclusive, since it has been shown that bacteria may quickly wander into such stones. The lower end of the common duct is always infected, so that, especially when calculi lodge in the duct and obstruct the stream, bacteria may wander up in that way. The occurrence of cholecystitis following appendicitis seems to suggest the possibility that bacteria may be carried from the appendix by way of the portal vein, and back into those branches which drain the gall-bladder.

Rous and his co-workers show that minute spherules of calcium carbonate and calcium bilirubinate with an organic scaffolding form in the alkaline bile from the liver of the dog when the gall-bladder is excluded and the common bile-duct intubated. This is in the absence of infection. The bile of the gall-bladder tends to become acid through some activity of the gall-bladder wall, and this tends to protect against the formation of gall-stones, for in infected gall-bladders when the reaction turns to the alkaline side concretions may more readily form.

Cholecystitis.—There is nothing peculiar about the inflammatory process in cholecystitis. The beginnings are seldom seen, but apparently infection takes place in the so-called Luschka's crypts, or under gall-stones which press on the wall. It commonly produces diffuse, abscess-like infiltration of the wall (*acute phlegmonous cholecystitis*), often with extensive ulceration of the mucosa. Gall-stones may come to lie in these deep ulcers, or even to pass through perforations in the wall if the ulcer goes deep enough, sometimes into a neighboring hollow organ, like the colon, if there have been adhesions, at other times into the open peritoneum. I have seen one case in which recovery took place after such a discharge of stones, and long afterward they were found hanging in fibrous capsules from the omentum like so many cherries.

Occasionally the acute forms of cholecystitis heal completely, but usually there are many recurrences, especially when stones persist and bile is stagnant, and the ulcerated mucosa, as well as the whole thickness of the wall, becomes much occupied by scar tissue (*chronic recurring cholecystitis*) (Fig. 208). The remnants of mucosa are thrown up into relief, and attempts at repair on the part of the epithelium result in the formation of distorted, gland-like structures, or even complicated, adenoma-like masses. Enormous thickening with rigidity of the connective-tissue walls may take place, and in these walls accumulations of wandering cells loaded with lipoid substances and bile-pigments give the whole a dull, ochre-yellow color.

The *mechanical effects of the gall-stones* are manifold, for by no means all of them are passed down through the cystic duct to escape into the intestine. Some do make this descent, causing great pain, and may lodge at various points. Occluding the cystic duct completely, they prevent ingress and egress of bile. That which remains in the gall-bladder is soon absorbed, but the sac does not collapse, for it is full of a clear, glairy mucoid secretion from its own walls. When there are

other stones in the gall-bladder, it often happens that its thickened wall shrinks down about them until there is no lumen left, and the whole gall-bladder is reduced to a mass of stones tightly bound in a fibrous covering.

When the calculus passes into the common duct *jaundice* results—a jaundice which may be lasting until the gall-stone is removed by operation, or by its escape into the intestine, or until the death of the patient. In those cases where the stone is not large enough to occlude the duct completely the jaundice may vary in intensity, but usually the accompanying inflammation is enough to complete the obstruction.

When the ampulla of Vater is large and receives both bile-duct and pancreatic duct, and opens by a narrow orifice, the occlusion of this

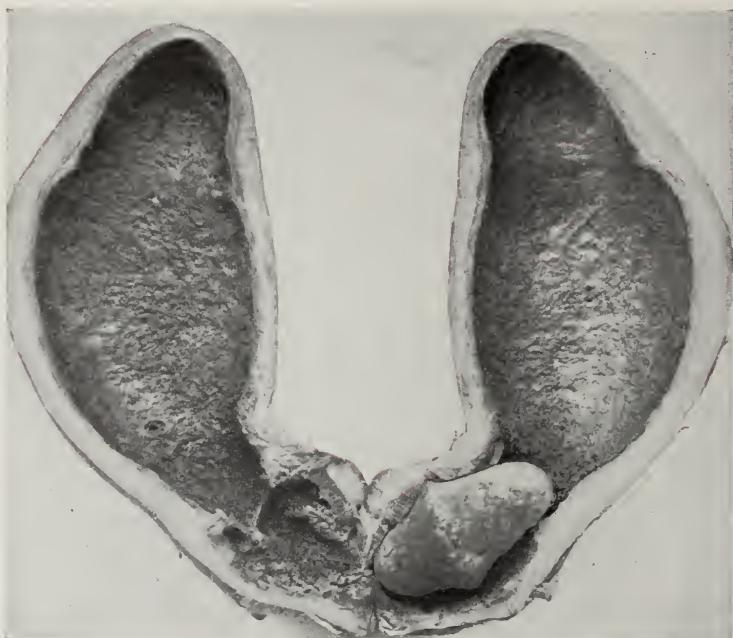


Fig. 208.—Large gall-stone impacted in neck of gall-bladder. Subacute and chronic cholecystitis.

orifice by a small stone may cause the retrojection of bile into the pancreatic duct, an occurrence which is followed by acute haemorrhagic necrosis of the pancreas, with all its sequelæ. Large gall-stones which escape into the intestine may become impacted, and even be sufficient to cause an obstruction of the intestine.

Finally, the persistent presence of the gall-stones in one position in the gall-bladder may stir up a change in the character of the mucosa, so that a cancerous growth appears there and tightly clasps the gall-stone. In one case I saw a round, radiate cholesterine stone held as in a cup in the fundus of the gall-bladder by the thickened cancerous wall, which passed over abruptly into the thin, unaffected wall of the rest of the

sac. One could hardly escape the impression that the presence of the gall-stone had produced this change in the mucosa, although this idea is by no means accepted by every one.

In the liver itself obstruction to the escape of bile soon causes rupture of the walls of the bile-capillaries by destroying the liver-cells which form those walls. This is probably not merely a mechanical effect, but due to the poisonous action of the bile as well as to the enforced inactivity of the cells. Indeed, Steinhaus, Beloussow, and others have de-

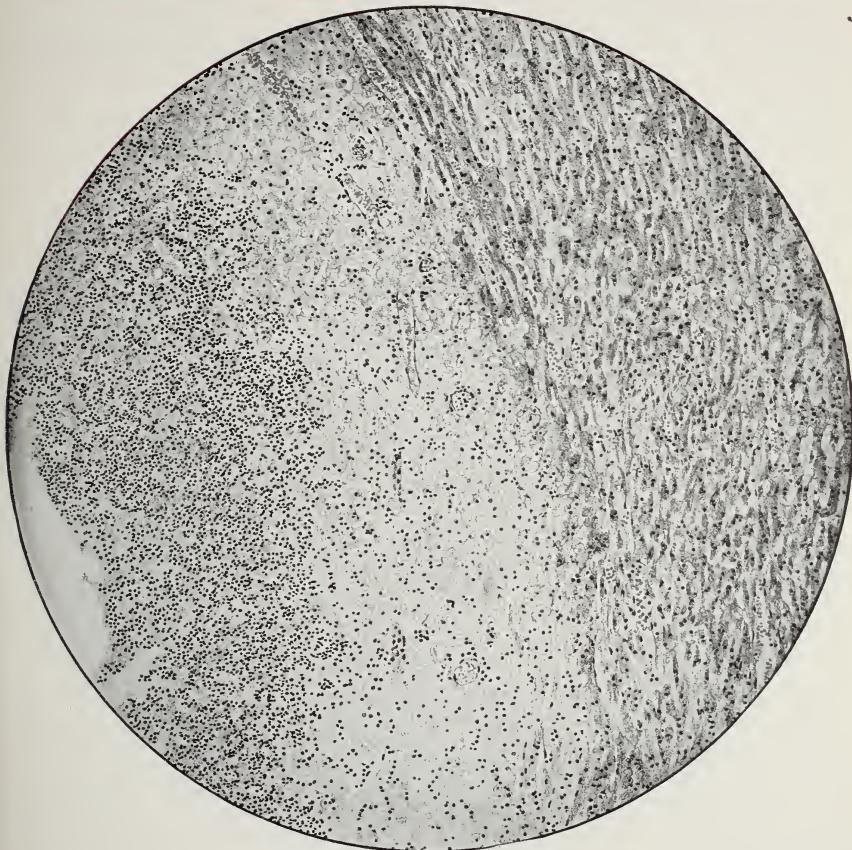


Fig. 209.—Margin of cholangitic abscess of liver, showing compression of liver-cells and layer of fat-laden phagocytes. There were multiple bile-stained abscesses resulting from obstruction by gall-stones and infection.

scribed rather extensive necroses in the liver following in the wake of obstructive jaundice, and think that they may underlie the scarring in the so-called biliary cirrhosis. It is precisely in the liver, however, that obstruction of the ducts may be survived by the organ for a long time in spite of the most intense jaundice. Is it possible that this is because the cells are so actively engaged in carrying on functions which have nothing to do with bile production, so that, even when that is stopped,

they are not entirely inactive? At any rate, the effect of obstruction is far less obvious than in the case of other glands. In those cases in which obstruction of the bile-ducts is accompanied by infection of their stagnating contents it is common to find numerous abscesses (Fig. 209) scattered through the liver and evidently formed about the bacteria which have penetrated into the smallest ducts. These *cholangitic abscesses* may become quite large and contain pus which is deeply bile stained.

LITERATURE

- Aschoff and Bacmeister: *Die Cholelithiasis*, Jena, 1909.
Bacmeister: "Aufbau und Entstehung d. Gallensteine," *Ziegler's Beiträge*, 1908, xliv, 528.
Chiray et Pavel: *La vesicule biliaire*, Paris, 1927.
Naunyn: *Klinik d. Cholelithiasis*, Leipzig, 1892. *Gallensteine*, Jena, 1924.
Ogata: *Ziegler's Beiträge*, 1913, lv, 236.
Ribbert: *Virchow's Arch.*, 1915, ccxx, 20.
Riedel: *Pathogenese, etc.*, d. *Gallensteinleidens*, Jena, 1903.
Rothschild and Wilensky: *Amer. Jour. Med. Sci.*, 1918, clvi, 239, 404.
Rous and others: *Jour. Exp. Med.*, 1924, xxxix, 77-403.

Obstruction of the Pancreatic Ducts.—Usually there are two ducts opening separately, and sometimes hardly anastomosing in the substance of the pancreas. One of these, the duct of Wirsung, which usually opens with the *ductus communis choledochus*, is much more exposed to influences which might block it than the other, the duct of Santorini, which opens separately. Tumors, especially adenocarcinomata of the head of the pancreas, gall-stones in the common bile-duct, aneurysms in neighboring vessels, and pancreatic calculi in the duct itself are the commonest causes of its occlusion, and exert their effect upon that part of the gland which it drains. The rest, which is drained by the duct of Santorini, may remain quite normal. Of all these causes, probably the tumor growths most commonly produce the completer forms of occlusion, while with the passage of gall-stones temporary and incomplete obstruction may arise. Occasionally, whether from infection of the duct or other causes, the mucosa lining the smaller ducts may proliferate into such voluminous folds as to plug the duct and set up the most intense changes in its drainage area (Winternitz). Pancreatic calculi are like irregular, rough bits of marble, and are, as their appearance suggests, composed chiefly of calcium carbonate. Their impaction in the duct may again give a foothold for bacteria, and when they are surrounded by an abscess-like area of inflammation, the obstruction is usually complete. When some pancreatic juice can escape, the duct is apt to become greatly dilated, and even when none can pass, one usually finds that the duct is widened behind the obstruction, perhaps from an earlier stage in which it was incomplete.

When a duct has been stopped up for a long time its drainage territory is usually found extremely shrunken, hard, and leathery, in sharp contrast to the well-preserved, lobulated part, which is still free to discharge its pancreatic juice by way of the other ducts. Microscopically, one finds that the lobules have lost most of their acini and are hardly to be outlined. The remaining acini show a dilatation of

their lumen and a thinning or flattening of the epithelial cells, and the whole of this persisting pancreatic tissue is embedded in abundant scar tissue, which has grown to replace those acini which are lost. It is evident that the damming-up of secretion under some tension and the enforced inactivity have led to the gradual disappearance of the secreting cells and their replacement by scar tissue (Fig. 210). Here and in many other instances it will be observed that there is no evidence that the scar tissue is the cause of the destruction of the pancreatic cells.



Fig. 210.—Chronic pancreatitis following obstruction of the ducts. Fat and fibrous tissue have replaced many lobules of the gland.

On the contrary, there is every reason to regard its presence as an attempt to heal the gap left by the loss of those cells, because the islands of Langerhans, which occur in most of the lobules, and which are not connected with the pancreatic ducts, remain uninjured, and finally stand out conspicuously as about the only intact tissue left. Experimentally, we have ligated the duct of a large part of the pancreas in a dog, and found, after a year, that this portion was reduced to a thin

film—a mere opalescence in the transparent mesentery in which pancreatic acini had disappeared and only islands of Langerhans were left.*

Acute Pancreatitis.—There are several forms of acute destructive changes in the pancreas in which obstruction in some sense plays a part, if only by allowing the introduction of the injurious agent into the gland. These are acute haemorrhagic pancreatitis, with its less common sequel, gangrenous pancreatitis, and the more localized suppurative pancreatitis.



Fig. 211.—Acute haemorrhagic necrosis of pancreas: cholelithiasis and impaction of a small gall-stone in the common duct and in the ampulla of Vater. Abundant fat necrosis.

Fitz in 1889 made clear the existence of these three affections, and described many cases. Since that time much anatomical and experimental work has shed light on their nature, but even yet there are many obscurities.

Acute Haemorrhagic Pancreatitis.—This condition arises suddenly with violent symptoms of pain, collapse, cyanosis, and vomiting. In these respects it resembles rather closely obstruction of the intestines at a high level. Death follows quickly.

* MacCallum: Johns Hopkins Hosp. Bull., 1909, xx, 265.
Kirkbride: Jour. Exp. Med., 1912, xv, p. 101.

with general intoxication in most cases. If the abdomen is opened, there is a blood-stained fluid in the peritoneum, and in the fat of the omentum and mesentery there are found opaque white patches of pasty consistence. These are areas of necrosis in the fat, and are indicative of pancreatic disease. The pancreas is swollen and deep red or purplish-black in patches (Figs. 211, 212). On section, the brown or black patches are found to be rather dry and dull looking, and extend widely through the substance of the gland surrounded by haemorrhage. In places they may be softened. Opaque, white, necrotic patches are found in the fat in the interstices of the pancreas. Microscopically, the dark areas are found to be patches of necrotic pancreas, infiltrated with changed blood, and showing about the margins, at least, an intense acute inflammatory reaction. Sometimes nearly the whole pancreas may have undergone this coagulative necrosis with haemorrhage and inflammation. Occa-

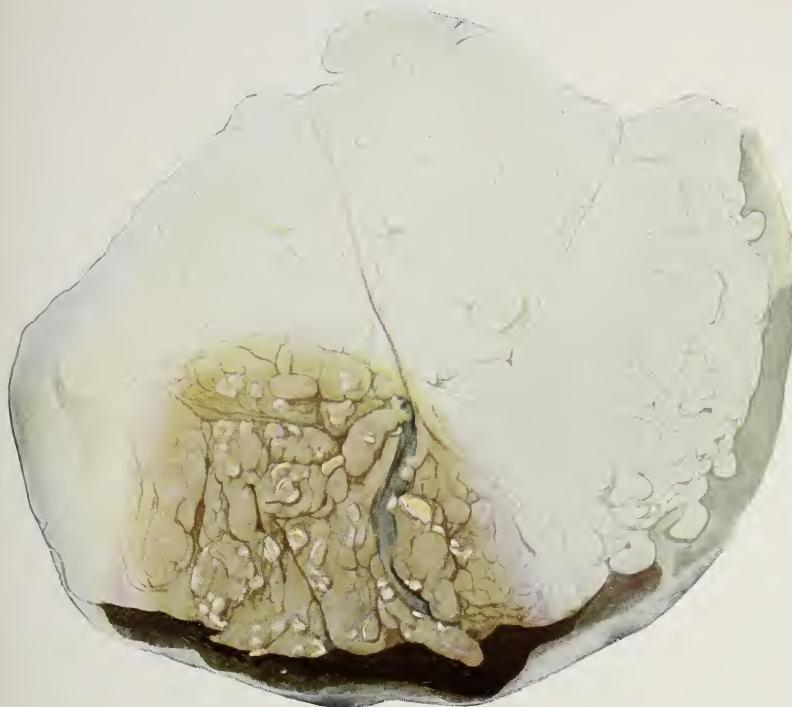


Fig. 212.—Pancreatic fat necrosis in the omentum.

sionally the process is so fresh that there is but little inflammation, and Chiari suggests the name "acute haemorrhagic necrosis" of the pancreas.

The cause of this was quite obscure until Opie discovered a case in which a small gall-stone had become impacted in the orifice of the ampulla of Vater in such a way that neither bile nor pancreatic juice could escape, although bile could run back from the common bile-duct into the pancreatic duct. Naturally, if the ducts had opened side by side instead of into a common ampulla, or if the stone had been too large to obstruct the orifice of the ampulla only, no such access of bile to the pancreatic duct would have been possible. Opie readily showed that injection of bile into the pancreatic duct would produce acute haemorrhagic pancreatitis in animals, and Flexner showed that gastric juice and many other irritating substances would do so too. He found that fresh bile was most effective, that much mucus rendered its action far milder and produced rather chronic effects. Several other cases have been found in which exactly the same unfortunate combination of cir-

cumstances has led to the results found by Opie, but there are many cases in which no such good explanation is to be found.

Rich and Duff find in attempting to explain these numerous cases in which there is no question of retrojection of bile, that the destruction of the tissues is due to the escape of trypsin and that bile injected into the pancreatic duct acts chiefly by distending the ductules with rupture and escape of trypsin. Trypsin injected into subcutaneous tissues or elsewhere is found to produce destructive changes in the walls of vessels allowing their rupture and thus accounting for the haemorrhage, and this change is found in the haemorrhagic pancreatitis. They ascribe many of the cases to obstruction of ductules by metaplasia of the lining cells, but it still seems curious that even ligation of the pancreatic duct, with gradual complete atrophy of all the tissues except the islands of Langerhans, should produce no suggestion of haemorrhagic pancreatitis.

Any injury to the pancreas which causes the death of cells and allows the escape of pancreatic juice into the tissues seems to be capable of causing a little of such haemorrhagic necrosis, and it is probable that this is at the root of the formation of those areas of gangrene which are sometimes found in its substance. Doubtless if the person could live after an extensive haemorrhagic necrosis, infection would follow by way of the ducts, and a putrefactive liquefaction of the dead tissue might occur. Whether such necrosis and self-digestion form the basis upon which localized infection and abscess formation occur in the gland is not so clear. The fact remains, however, that abscesses of considerable size are occasionally discovered there in cases in which intense symptoms point to their existence.

The fat necroses (Fig. 212) are due to the dissemination of the ferments of the pancreas, which are able, by their lipolytic action, to decompose the fat in the fat-cells which they have rendered necrotic. The neutral fats break up into free fatty acids and glycerin, and usually bunches of needle-shaped crystals of fatty acids are visible in these areas. Combinations with calcium salts often produce, in those situations, the insoluble white calcium soaps which add to the whiteness and opacity of the foci. Any injury to the pancreas which tears its tissue allows the dissemination of the ferments. In one case in which a small incision was made into a pancreas by accident in the course of an operation there appeared a crop of fat necroses in the neighborhood. Ligation of the duct usually produces them. In the cases of acute haemorrhagic pancreatitis they are very wide-spread, and in animals in which this condition is produced experimentally they are found in the subcutaneous abdominal fat, and even in that of the pericardium and pleura. Lipases have been demonstrated in these areas, and also in the urine in such cases.

Of course, there is nothing in common between these forms of haemorrhagic pancreatitis and the so-called *pancreatic apoplexy*, which is a rapidly fatal haemorrhage into and about the pancreas from a large diseased artery. In one case at autopsy I found a retropancreatic haemorrhage of almost two litres which came from the rupture of the sclerotic pancreatico-duodenal artery as it passed through the head of the pancreas.

LITERATURE

Dohmen: Dtsch. Ztschr. f. Chir., 1935, ccxlv, 620.

Dragstedt, Haymond and Ellis: Arch. Surg., 1934, xxviii, 232.

Fitz: "Acute Pancreatitis," Boston Med. and Surg. Jour., 1889, cxxi, 607.

Opie: Johns Hopkins Hosp. Bull., 1901, xii, 182.

Rich and Duff: Bull. Johns Hopkins Hosp., 1936, lviii, 212.

OBSTRUCTION OF THE LUMEN OF THE INTESTINAL TRACT

The most extraordinary variety of phenomena based on slight modifications of a few underlying principles occur here, and one might foretell easily enough the effect of obstruction at any given point. The same general types of occluding agent appear, but there are some modifications, owing to the strong muscular character of the wall of the canal. Foreign bodies in the lumen, tumors in the walls sometimes

encircling the canal, constricting scars resulting from healing ulcers, twists and kinks and compression from outside by tumors or by constricting bands, the escape of a loop of intestine through a narrow hole in the abdominal wall, or the telescoping of a part of the intestine into itself—all these things and many others may impede the flow of the intestinal contents in the normal direction. Even the mere lack of propulsive muscular contractions over a length of intestine may be enough to allow the contents to stagnate and give the symptoms of obstruction (paralytic ileus).



Fig. 213.—Achalasia of the œsophagus with great hypertrophy.

Œsophagus.—Two common causes of œsophageal obstruction exist, namely, the narrowing of the lumen by the shrinkage of scar tissue formed in the healing of an ulcer caused by the swallowing of some corrosive poison, such as concentrated lye, and, secondly, the encroachment of a cancerous tumor growing from the mucosa. Other things, such as the pressure of a tumor or an aneurysm from the outside, may have a similar effect, and make it difficult or impossible for food to pass into the stomach. Extreme narrowing, usually at the cardiac end of the œsophagus, may be produced, in the stricture following ulceration, but since the food is easily regurgitated, there is usually no great dilatation of the canal above the closure, nor any very marked hypertrophy of its muscular walls.

On the contrary, in some rare cases, of which we have recently seen one, without any apparent obstruction the œsophagus may be found enormously lengthened and widened, so that it sags and kinks, and food is regurgitated unchanged without ever entering the stomach. Rake and Hurst and Rake have shown that this is the result of a destruction of the ganglion cells of the intermuscular plexus in the wall of the œsophagus which disturbs the proper peristaltic contraction. Therefore, the cardiac part of the œsophagus remains closed, not, as they explain, owing to any spasm produced by sympathetic stimuli but because of the inability of the vagus which acts normally through the ganglion cells of the œsophageal plexus, to produce peristalsis.

We have recently observed a typical case of long duration in which the œsophagus was not only enormously dilated but greatly thickened, evidently from hypertrophy of the muscular wall which would suggest increased peristalsis. The explanation offered seems hardly satisfying and the name achalasia which they give, meaning a failure of relaxation, can hardly be interpreted except either as a spasm or as unyielding rigidity. Quite analogous is the so-called *Hirschsprung's disease*, or *megacolon*—a condition found in children and also in adults, in which the colon is hugely dilated and its wall much thickened. The same arguments are brought forward as may be read in Hurst's recent summary (1934). He points out that there is no palpable spasm of the sphincter—that peristalsis may be active but that gas and faeces accumulate in great quantity in the greatly enlarged colon which fills and distends the abdominal cavity. It is stated that stimulation of the sympathetic connections from the second, third and fourth lumbar ganglia produces relaxation of the pelvic colon and rectum and spasm of the sphincter ani, while stimulation of the parasympathetics from the second, third and fourth sacral nerve roots causes contraction of the pelvic colon and rectum and relaxation of the sphincter. This anatomical relation is clearly worked out by Telford and Stopford. Various authors assume an overactivity of the sympathetics with relaxation of the colon and spasm of the sphincter but the hypertrophy of the colon must be due to overactivity and straining peristalsis and Hurst prefers to regard it as a disturbance of balance between sympathetic and parasympathetic supply to the sphincter which leaves the sphincter closed but not in spasm—again a most unsatisfying explanation. Surgeons cut the sympathetic supply with questionable results—certainly not always with relief to the patient so that it seems that it might almost be better to cut the sphincter.

More localized dilatations are the traction and pulsion diverticula. The traction diverticula are common, and usually small and funnel-shaped; they arise usually from the adhesion and contraction of adjacent scarred lymph-nodes. The pulsion diverticula are the outcome of local weakening of the wall and the forcing out of a hernia-like sac. These may become quite large, and are annoying in that they receive the food until they are full, and may, by their bulk, offer obstruction to the main channel.

Obstruction in the Stomach.—Similar types of obstruction are met

with in the stomach, and the occlusion may be at the cardiac orifice or at the pylorus. In the first instance, in which the growth of a cancerous tumor is the common cause, the individual tends to starve, because food does not easily reach the stomach. In the second case, in which the cause is a cancerous growth or the contracting scar of a round ulcer at the pylorus, the orifice of the pylorus may be reduced to a very narrow channel (Fig. 214). Stagnation and accumulation of the stomach contents follow, with great changes in the gastric juice, which often loses its antiseptic acidity. The stomach may become hugely dilated, so as to be capable of holding four or five litres, and the most incredible mass of material, dating from meals long past, may accumulate there. The wall becomes thick, the muscular coat hypertrophic, in the attempt to drive the contents through the pylorus, and the mucosa seems to hypertrophy by the production of new glands to comply with the necessity for covering all that increased space.

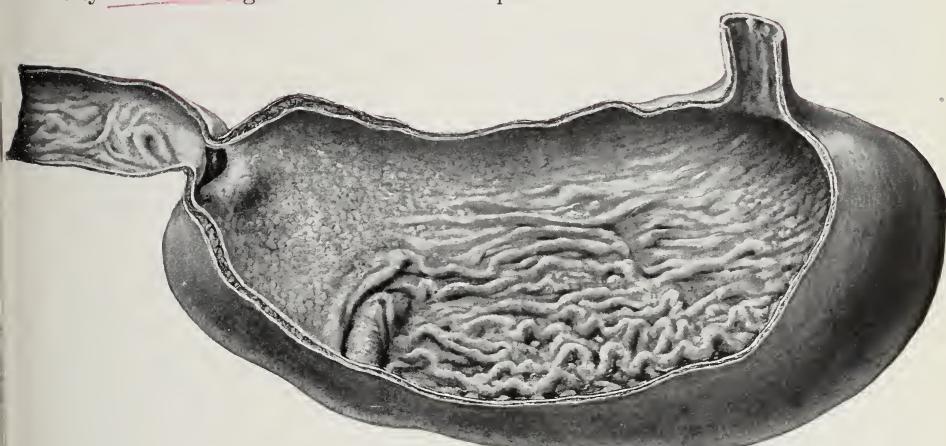


Fig. 214.—Scarred ulcer of the pylorus, dilatation and hypertrophy of the stomach.

But the most striking result in such obstruction is the development of the so-called *gastric tetany*. In its general symptoms this resembles the other forms of tetany with heightened electrical excitability, muscular spasm, and convulsions, but is fundamentally different in that it has been shown (MacCallum and others, Johns Hopkins Hospital Bulletin, 1920, xxxi, 1) to be due not to lowering of the calcium content of the blood, but to a loss of chlorides in the vomited gastric juice. The chloride content of the blood and urine is greatly reduced, the reaction of the blood tends toward the alkaline side, and the condition can be relieved or prevented by the introduction of sufficient chlorides to repair the loss.

Haden and Orr have published twenty-four papers, chiefly in the Journal of Experimental Medicine, which confirm these statements, except in that in most of the papers they feel that loss of chlorides is not responsible, but show that there is a great increase in non-protein nitrogen in the blood which is probably due to a toxic destruction of protein.

White and Bridge find that the fall of chloride in the tissues parallels that in the blood and that since the administration of chloride and water can prevent a fatal outcome, it is this fall and not a hypothetical toxin which is at fault.

There are other ways in which such gastrectasis can be set up, as by the pressure of outside tumors or by the sagging of the stomach and the kinking of the pylorus, but the two causes mentioned above are by far the more common. The symptoms are not acute in these cases, nor do they quickly end fatally, because vomiting is capable of relieving them to some extent.

LITERATURE

- Finney: Surg., Gyn., and Obst., 1908, vi, 624.
 Hirsehprung: Jahrb. f. Kinderheilk., 1888, xxvii, 1.
 Hurst: Guy's Hosp. Rep., 1934, lxxxiv, 317.
 Hurst: Jour. Amer. Med. Assoc., 1934, cii, 582.
 Hurst and Rake: Quarterly Journal of Medicine, 1930, xxiii, 491.
 Rake: Guy's Hosp. Reports, April, 1927.
 Telford and Stopford: Brit. Med. Jour., 1934, i, 572.
 White and Bridge: Boston Med. and Surg. Jour., 1927, exvi, 893.

Gastric Ulcer.—There are several types of ulceration of the gastric wall produced in as many ways, and distinguished by nothing specially characteristic. For while the intact living mucosa resists perfectly the digestive action of the gastric juice, anything like a strong corrosive poison which can kill the tissue, or even anything like a haemorrhage, which may interrupt the circulation of a patch of mucosa for a time, exposes that area to the liquefying power of the juice, and in an incredibly short time there is produced an ulcer which extends to the depth reached by the anaemia or coagulation of the tissue. Even the little ecchymotic haemorrhages which appear after violent vomiting present themselves very shortly as pits of pinhead size in the mucosa. Emboli in the larger vessels have no such consequences, since the intercommunication of the arteries is so extremely rich. If we try experimentally to produce an area of anaemia in the wall of the stomach of an animal, we fail, even though we tie several large vessels. Their current is instantly supplied backward, if necessary, from other arteries. It is only by injecting a suspension of coarse particles which plug all the small vessels, or by causing a spasmodic contraction of the muscular wall, which clamps down the collateral arteries, that we can produce an anaemia of the mucosa serious enough to allow the gastric juice to attack and digest it, and thus form an ulcer. But although many things will produce an ulcer, the mucosa is surprisingly capable of healing it over. I have removed large squares of the mucosa of the dog's stomach, only to find, a short time later, such complete healing that it was impossible to say where the ulcer had been.

Countless experimental researches have been carried out in recent years using every conceivable method of impairing the circulation, or the innervation, traumatizing or infecting the stomach wall, but it may be said that none of these have given a clear explanation of the development and particularly the persistence of chronic gastric ulcers. Most of them do heal, and we find only the scar, but others, although they are the seat of energetic efforts at healing, not only persist, but progress, boring deeper and deeper into the thickening stomach wall. Very similar ulcers are found in the duodenum, where they follow a course much like that of the gastric ones. All the theories as to their origin seem inadequate, from that of Virchow, who thought them to be due to the embolic occlusion of the artery supplying that area, to the more recent ones, which attempt to incriminate bacteria and other parasites, or, as in the case of van Yzeren and Talma, ascribe them to changes in the innervation of the stomach, which maintains part of its wall in a bloodless state through cramp of the muscle.

Cushing has drawn attention to the violent contractions of the stomach that result from operative interference with tumors which involve the basal part of the brain. Such contractions seem to cause haemorrhage and ulceration in the stomach, often with perforation and fatal result. This confirms the idea of Rokitansky who many years ago put forward the statement that gastric ulcers are caused by a nervous disturbance. Cushing recognized the dependence of these effects upon the stimulation of para-sympathetic centres in the hypothalamic region. There, the three nuclear masses, the supra-optic, the tuberal and the posterior or paraventricular, can be distinguished, the tuber nuclei being distinctly para-sympathetic in their relations while the posterior or paraventricular are sympathetic. Cushing showed that injection of pituitrin or of pilocarpine into the ventricle produces the most violent sweating and peristalsis of the stomach with vomiting, evidently a para-sympathetic response. He thought the effect analogous to that produced by the secretion of the adrenal medulla upon the sympathetic. Watts and Fulton have since, by lesions in the tuber nuclei in monkeys, produced profound gastro-intestinal disturbances with gastric and duodenal erosions and perforation, although similar lesions in no other part of the nervous system had this effect. The subject is discussed in Fulton's paper on the hypothalamus and visceral mechanism.

Whether the liberation of such violent para-sympathetic impulses via the vagus to the stomach, causing such acute destructive lesions can also be held responsible for the maintenance of chronic gastric ulcers, seems questionable. One remembers the extraordinary rapidity with which ulcers produced by merely snipping off the mucosa heal in dogs, so that no trace is left, and it seems complicated to imagine the continuous repetition of contractions of the stomach wall in the same place which would be necessary to make the original ulcer chronic.

The matter seems still to require further study. Many recent papers emphasize the injurious effect of cigarette smoking which has such a powerful vagotonic effect and produces pain of contraction and hyperacidity. Cushing states that this is well known to clinicians and fully recognized, if not admitted, by the victims of ulcer themselves.

Ulcers occur in relatively young persons, usually in association with hyperacidity of the gastric juice, and cause a peculiar pain. There may be only one or several. Some of them are irregular in outline, and there are small ulcers, as well as widespread erosions, but the name arises from the fact that the typical ones are quite round and smooth (Fig. 215). Such ulcers look as though they had been cut out with a gunwad cutter, except that their base is terraced and funnel shaped, and may run slantingly into the stomach wall, or else their edges are undermined. All around such an ulcer the wall becomes very thick and hard, so as to be easily recognized from the outside when the stomach is exposed. Often there are adhesions formed over it, so that in case the ulcer extends quite through the wall, it is likely to encounter first the adhesions and then the adherent organ. Most ulcers of the stomach (perhaps 90 per cent) occur on the lesser curvature of the stomach where it is less mobile and is supplied with blood from the right gastric artery. Since they often perforate the posterior and inner curvature of the stomach, the pancreas is likely to be the bulwark and to be rapidly excavated, until, sometimes, the splenic artery is cut into. The liver may sometimes form this buffer, but it is not very uncommon to have the gastric contents emptied through the perforated ulcer directly into the peritoneum. Microscopically, the edge of such an ulcer shows an abrupt cessation of the mucosa. The precipitous walls are lined with a thin layer of formless, hyaline material, and pass through the greatly thickened submucosa, the musculature, and even the thickened subserous tissue. There is often not much infiltration with wandering leucocytes to indicate any active inflammatory process. On the contrary, the ulcer may look as if bored through a dense, hard, fibrous tissue. In the floor of the depression one may sometimes see an artery laid bare, or even find its exposed wall so thinned that the blood-pressure has been sufficient to bulge it out into an aneurysmal sac. It is obvious, though, that one would be more likely, under such circumstances, to find the little sac burst into shreds after an alarming or fatal haemorrhage had called attention to the ulcer.

Aside from these two dangers, the most serious effect of the ulcer may arise in the course of its healing if it happens to encircle the pylorus. It is then that the

contraction of the scar may produce the most extreme narrowing of that orifice, and a consequent enormous dilatation of the stomach.

Surgeons have for a long time been concerned with the possibility that a carcinoma may develop in the margin of a chronic gastric ulcer. Irregular growth of



Fig. 215.—Gastric ulcer, excised by surgeon.

the mucosa does occur there in the attempts at healing, and this probably accounts for the opinion held by some that carcinoma occurs in a very large proportion of the cases. Actually it appears that cancerous tumors have been observed in persons in whom there had been for years a definitely established chronic gastric ulcer, but the proved cases appear to amount to less than 5 per cent of the ulcers.



Fig. 216.—Gastric ulcer in section showing interruption of musculature and extensive scar formation.

Duodenal ulcers (Fig. 217) are similar in their course and even in their general effects, for they may perforate into the peritoneum or into blood-vessels or adjacent organs. They sometimes appear when gastro-enterostomy has been performed, at the point where gastric juice pours into the intestine, and I have recently seen a case in which five ulcers burrowing and connected in the most tortuous way were formed in this manner.



Fig. 217.—Duodenal ulcer with much undermined edges. The pancreas is adherent outside.

LITERATURE

- Beattie: Canad. Med. Assoc. Jour., 1932, xxvi, 278.
 Cushing: Proc. Nat. Acad. Sci., 1931, xvii, 163, 239. Surg., Gyn., and Obst., 1932, iv, 1. Lancet, 1930, ii, 119, 175.
 Fulton: Hypothalamus and Visceral Mechanisms, New England Jour. Med., 1932, ccvii, 60, 94.
 Hauser, G.: Chr. Magengeschwür, Jena, 1883; Med. Klinik, 1927, xxiii, 120.
 MacCallum: American Medicine, 1904, viii, 452.
 Matthews and Dragstedt: Surg., Gyn., and Obst., 1932, iv, 265.
 Payr: Arch. f. klin. Chir., 1910, xciii.
 Schultze: Lubarsch u. Ostertag Ergebnisse, 1922, xx, i, 488.
 Van Yzeren: Ztschr. f. klin. Med., 1903, xlivi, 183.
 Watts and Fulton: Ann. Surg., 1935, ci, 363.
 Welch: Ulcer of the Stomach. Pepper's System of Medicine, 1885, ii, 512.

Intestinal Obstruction.—Although the various ways in which obstruction of the intestine can occur, and all the changes produced by it are clear enough, the actual reason for the extremely violent symptoms that follow has long been a mystery. It is well known that obstructions in the small intestine, and especially when they are high up, are accompanied by far more violent symptoms than those in the rectum or sigmoid flexure. It would seem that if we imagine the symptoms to be due to absorption of poisons, these would be more severe the greater the proportion of the intestine involved, but the fact that impaction of faeces in the rectum with no discharge for days or even weeks may cause nothing more serious than headache is familiar.

The symptoms of obstruction (ileus) are much more severe when to the obstruction there is added strangulation from the shutting off of the blood-supply which is so frequent an occurrence.

In general, the intestine above the point of closure becomes distended with gas and a very foul-smelling fluid which swarms with bacteria. Even when there is no outward obstruction to the circulation its wall is soon so stretched as to be paralyzed and is reddened by obstruction of the venous outflow. Later necrosis and ulceration of the mucosa may appear, often with actual tears in the muscular wall and serous covering of the gut. Kocher has called these ulcers distention ulcers. It would seem that poisonous materials must pass out into the peritoneum from such a sac-like loop of intestine which is practically like a huge bouillon culture of bacteria, and often the bacteria do pass through and produce an acute peritonitis. But in many cases there is no such profound injury to the intestinal wall and no peritonitis or general infection, and still there are extraordinarily violent and severe symptoms.

Sudden pain, thirst, vomiting, complete cessation of bowel movements, continued vomiting, abdominal distention, lowering of the blood-pressure lead to extreme prostration, collapse, and death unless surgical intervention is very prompt. The student should perhaps read the recent surgical discussions, Finney and others, Taylor, Handley and Souttar, Perthes, etc., about this. Their methods are, of course, to bring about as soon as possible after the onset of the symptoms the relief of the obstruction and the establishment of free passage or escape of the intestinal contents.

There remains the difficulty in explaining the severity of the general disturbance. Of course, there has always been the suspicion that some toxic substance may be formed in the intestinal lumen above the obstruction, and many have demonstrated such a poison. Whipple, Stone, and Bernheim were able to extract a substance from the fluid content or from the mucosa of such a loop of intestine which when injected intravenously in a normal dog would kill with symptoms like those of actual intestinal obstruction. This substance they isolated sufficiently to find that it is a proteose which they regarded as the product of the action of bacteria upon the cells of the mucosa. Whipple with other collaborators has pursued this discovery, and has shown that this proteose impairs the function of the kidney so that when it is injected there is a marked retention of non-protein nitrogen in the blood. This explains his observation that, as is now generally recognized by surgeons, an increase in the non-protein nitrogen of the blood is a characteristic accompaniment of intestinal obstruction.

Others, such as Sugito and Copher and Brooks, have also demonstrated toxic substances with the same properties, but there is another aspect of intestinal obstruction which is only beginning to be appreciated. As described above in connection with pyloric obstruction, we found that vomiting caused a loss of chlorides, alkalosis, and tetany which could be prevented or relieved by reintroducing sodium chloride. Haden and Orr found that the same series of events occurs in high intestinal obstruction. They recognized in these cases not only a dis-

pearance of chlorides, but a great retention of non-protein nitrogen in the blood, and thought the loss of chlorides due to protein destruction in some way. Hartwell and Hoguet thought the symptoms of intestinal obstruction due to dehydration. All this is put together clearly by Gatch and his co-workers, who find that dehydration and loss of chlorides is due to vomiting or the accumulation of fluid in the obstructed intestine, that the nitrogen retention and lowered excretion of chlorides by the kidney are due to the same cause in simple intestinal obstruction, but not in that associated with strangulation where a factor of intoxication is added. Administration of sodium chloride with enough water keeps the animals alive until they starve in simple obstruction, but not when there is strangulation.

Further studies by Moss and McFetridge, and especially the experimental work of Schnöhr, show the importance of the loss of chlorides which is followed by a retention of urea in the tissues. The injection of hypertonic salt solution (10 per cent) increases diuresis and lowers the nitrogen retention. Schnöhr leaves it with the statement of his impression that death is due in high intestinal obstruction to "toxæmia."

Now that at least two quite different phenomena are recognized in the disturbance following intestinal obstruction, it seems that light is beginning to dawn on the subject, but there is still much to learn.

Mechanism of Intestinal Obstruction.—Ordinarily the contents of the small intestine are quite fluid, and the musculature of the colon, aided by that of the abdominal wall, is strong enough to expel the more solid contents of that part of the intestine. Still it occasionally happens that a foreign body which was swallowed and has passed through the stomach sticks somewhere in the intestine. This is true, too, of the so-called enteroliths, which may be very large, and partly composed of hair, and of large gall-stones, as well as of the indurated masses of faeces which sometimes become impacted in the colon and obstruct it. Knotted masses of ascarides figure in some countries as a cause of intestinal obstruction.

Tumors or aneurysms outside the intestine rarely compress it enough in the yielding abdominal cavity to produce obstruction unless the tumors have surrounded it and involved it in their growth. After abdominal operation, however, in which the intestines have been roughly handled and displaced, and especially when there exists a focus of infection and inflammation of long standing, such as an abscess around the appendix, or a general infection of the peritoneum, adhesions are apt to bind the intestinal coils together. Then the symptoms of obstruction commonly appear, and the surgeon must separate and loosen and straighten out such loops. Usually in such a case the occlusion is produced by the angular kinking of the gut, but sometimes the most extraordinary long bands of fibrous tissue are found stretching from one point to another, entangling, as in a ligature, a loop of intestine. Doubtless this latter condition is brought about by the peristaltic and passive movements of the intestine, which entangle it in the adhesions.

Hernias.—Quite analogous to this method of obstruction is that found in the various sorts of hernias, where again the movements of the intestines (this time chiefly the passive movements, caused by the press

of the abdominal muscles) forcibly intrude them into compromising situations. The omentum, and in some forms of hernias, even other abdominal organs, may be forced to accompany the intestinal loops. These structures pass through a weak point in the abdominal wall, pushing ahead of them a sac composed of the peritoneum, usually with accompanying layers of tissues which lie outside it in that area. When the violent muscular effort is over and the heightened intra-abdominal pressure is relaxed, the intestine may slip back or be pushed back by the surgeon. But the sac remains, and the intestine is easily forced into it again—the more so as with each time it grows larger and receives more and larger loops of the gut, which may remain there without causing any trouble. Such a sac often contains serous fluid and is subject to inflammations, just as is the peritoneum in general.

Inguinal hernias are those in which the sac is pushed through the abdominal wall just above Poupart's ligament. Those which pass through the internal abdominal ring, that is, outside the deep epigastric artery, pass along the track of the inguinal canal or through the unobliterated inguinal canal, when that has remained open, into the scrotum. They are the oblique inguinal hernias. Those which push through to the inner side of the epigastric artery and likewise project through the external abdominal ring into the scrotum are the direct inguinal hernias.

Femoral hernias are such as arise from the propulsion of a peritoneal sac through the space between the femoral vein and Gimbernat's ligament, beneath Poupart's ligament, to project through the saphenous opening.

Umbilical hernias are often of great extent when congenital, and may contain most of the abdominal viscera. They are acquired in later life through the protrusion of a sac through the weakened scar tissue about the navel, and are common in women who have borne many children. Hernias through the abdominal wall may occur anywhere where a large operation wound has resulted in delayed healing, and the scar has remained as a weak place.

Other hernias which are less conspicuous and far less common occur, and some of these are the so-called *internal hernias*. Thus the left side of the diaphragm may be thinned and stretched into a sac, and in a case which we recently observed nearly the whole of the stomach, the spleen, and the splenic flexure of the colon lay in this sac far up in the thoracic cavity. The most unexpected places may be pitched upon by the intestinal loops for invasion, and extraordinary results follow. For example, the fossæ about the junction of the duodenum and jejunum, which are ordinarily quite small recesses, may become distended into great sacs in which numerous loops of intestine are found ensconced. The same is true of the fossæ about the cæcum and at the root of the sigmoid, and I have recently reported a case in which a notoriously weak place in the root of the mesentery of the jejunum was attacked, and just as a flock of sheep in a street, left for a moment to themselves, will hurry into any open door, the whole of the small intestine had become inclosed in a sac which hung to the right of the midline.

All this seems to have little to do with intestinal obstruction, but it is precisely in these hernias that a common form of obstruction takes place. For although ordinarily the neck of the sac is wide and the intestinal contents circulate through the loop in the sac without hindrance, more intestine than usual may sometimes be forced into the sac. All these hernias tend to grow in this way, and it may even happen that the abdomen is so emptied of its contents and contracted and the sac so large that it is impossible to reduce the hernia, that is, to replace its contents in the abdominal cavity. The formation of adhesions between

the intestine and the wall of the sac may also make the hernia irreducible. Such a condition may exist for a long time.

If, through a sudden violent exertion, a loop of intestine be forced through a very narrow orifice, or if an excessive amount of intestine or too much of the intestinal contents be forced into the sac, the afferent and efferent portions as they pass through the neck of the sac become compressed. Then not only is it impossible to reduce the hernia, but the intestine is obstructed and all the symptoms of an acute ileus, distention of the loops above the constriction, faecal vomiting, etc., make their appearance (incarcerated hernia). This is not all, however, for the compression of the veins of the mesentery of the incarcerated loops soon causes oedema of those loops, and increases still further the bulk of the contents of the sac until the flow of the circulation is quite stopped, and the whole included loop becomes the seat of a haemorrhagic infarction (strangulated hernia). The wall becomes greatly thickened and infiltrated with blood, and dies, after which the bacteria in the lumen pervade the dead tissue and set up an inflammation in the sac. If some time elapses before the sac is cut open by the surgeon, the intestine is found to be purple or greenish black, but if relief is rapid, circulation may be re-established and the loop saved alive.

Somewhat similar in principle to this process is the prolapse of the rectum, in which the relaxation of the tissue in and about the rectal wall allows its mucous surface to be everted through the anus until a considerable length has been turned outside and protruded.

Intussusception.—Higher up in the intestine one portion of the wall may be telescoped into the next section below. This invagination or intussusception is often found after death in normal animals and people who have died of some other cause, perhaps as the result of irregular peristalsis which arises just after death. But it does occur also during life, far more often in children than in adults, and quickly leads to complete obstruction of the intestine and all the acute symptoms of ileus. For, as will be seen in the drawing (Fig. 19, p. 42), the portion which is invaginated drags with it its mesentery, while the portion which receives it is stretched until it constricts its contents closely. Especially at its beginning or upper end, where the mesenteric mass at least is most bulky, it forms a tight ring constricting the mesenteric veins. The result, as in the strangulated hernia, is the production of a haemorrhagic infarction in the two internal folds, which thereby become even more swollen. It is said to have happened that the normal entering intestine, by healing to the upper end of the outer or receiving intestine, allowed the whole of the invaginated portion to be sloughed off and discharged per rectum, but this must be a rare occurrence. In the early stages, before circulation has been interrupted too long, the surgeon may pull out the intussuscepted part and relieve the whole condition. But after the infarction of the invaginated part is complete, a more radical operation is necessary. Irregular peristalsis is held responsible for this process, but sometimes there is a stalked polypoid tumor hanging from the mucosa which is forced along the intestinal canal and drags the wall with it. Once started, the invagination tends to increase rapidly.

Watts and Fulton have shown that the active peristalsis can be produced in a monkey by stimulation of the premotor cortex, the impulse going through the vagi and producing intussusception. Stimulation of the motor cortex failed to stir intestinal peristalsis.

Volvulus.—Volvulus is another type of constriction from without which depends upon the twisting of a loop of intestine through more than 180 degrees, so that the two ends of the loop compress each other as in a knot. For this there must be a long loose mesentery, and the condition is most common in the sigmoid flexure. Complete obstruction occurs, with the isolation of a loop. When the twist is tight enough to embarrass the circulation, the condition comes to resemble closely that in the strangulated hernia.



Fig. 218.—Carcinoma of the colon encircling the gut and producing a stricture, with dilatation and ulceration above.

Paralytic Ileus.—Instances of post-operative obstruction due to adhesions which compress or kink the intestine, or among which the intestine can entangle and strangle itself, are not very uncommon, but almost as common are those cases in which evidences of obstruction arise very soon after the operation, when there has been no time for dense adhesions to form, and in which, at a second exploration, the intestine is found bent on itself at a sharp angle, above which it is greatly distended. These are rather hard to explain, but they seem to be due to a combination of a paralysis of the intestinal wall with any slight mechanical displacement, which after the first handling of the intestines, is maintained even by weak fibrinous adhesions. The capability of mere paralysis of peristalsis in a length of the intestine to produce the symptoms of obstruction is well known (paralytic ileus),

and the inert segment which does not help in the propulsion of the intestinal contents will, if it is long enough, prove to be as effective a barrier as a ligature. It is not always easy to explain how the paralysis is produced. Sometimes, as in a phlegmonous inflammation of the intestinal wall, when the infiltrated wall becomes rigid, the cause is clear, and so, too, are those in which thrombosis or embolism of the mesenteric vessels causes the death of a whole length of the intestine, with haemorrhagic infarction, but at other times we are reduced to the idea that the nervous controlling mechanism is disturbed. I have already mentioned one instance in which a dissecting aneurysm had ruptured into the tissues about the aorta, so that there was a great clot of blood stretching from the upper thoracic to the lumbar region. The most striking symptoms were those of intestinal obstruction, for the relief of which an operation was performed. The man died, and at the autopsy the intestines were distended with fluid and gas to a colossal size, so that from the stretching the muscular wall showed numerous tears, but there was no obstruction except from the paralysis of the intestines.

It seems possible that in many cases this may be the effect of some toxic agent acting directly upon the smooth muscle of the intestinal wall, and as in the case of mechanical obstructions the poison which suggests itself is that derived from the bacterial decomposition of proteins or from the injured tissues themselves.

Stenosis and Stricture.—Finally, obstruction may be gradually produced by the development of a tumor encircling the lumen of the intestine, or by the contraction of a scar produced in the healing of a girdle ulcer. Cancerous tumors of this sort are most common in the large intestine, and they may produce obstruction by their increasing bulk or by the scar tissue formed after their partial degeneration. In the small intestine annular lymphosarcomata, and more rarely carcinomata, may cause the same thing. Ulcers of tuberculous origin rarely heal far enough to cause stricture, but other ulcers, especially in the rectum, frequently do so. All these things produce a gradual narrowing with slowly advancing incomplete obstruction, so that the symptoms are not the acute and violent symptoms of ileus. Instead, the intestine above the stenosis becomes greatly distended and also greatly thickened through the hypertrophy of the muscular wall, which attempts constantly to drive materials through the narrow opening (Fig. 218). Below the stricture the intestine is collapsed and thin walled. An almost continuous stream of fluid intestinal contents is driven through the stricture, and may cause the so-called paradoxical diarrhoea. Above the stricture the mucosa of the distended intestine often presents extensive ulcerations, which are thought to be due partly to its disturbed nutrition, partly to the stagnation of masses of infected faecal material in contact with it (stercoraceous ulceration). Sometimes an acute diphtheritic inflammation of the mucosa of this area is produced in the same way.

Thus, if we look back over this review of intestinal obstructions, we find that no matter what the mechanism by which occlusion of the intestine is produced, the effect is fairly constant, and varies only with the

completeness and situation of the obstruction. It differs from the effects of the occlusion of the duct of a gland on account of the immediate vital importance of the intestine, its circulatory relations, and its abundant content of bacteria.

LITERATURE

- Finney: Surg., Gyn., and Obst., 1921, 402.
 Gatch, Trusler, and Ayers: Amer. Jour. Med. Sciences, 1927, clxxiii, 649.
 Haden and Orr: Jour. Exp. Med., 1923, xxxvii, 365, 377, and many other papers.
 McQuarrie and Whipple: Jour. Exp. Med., 1919, xxix, 397.
 Moss and McFetridge: Arch. Surg., 1934, c, 158.
 Perthes: Arch. f. klin. Chir., 1925, cxxxviii, 303.
 Schnohr: Acta Chir. Scandinavica, 1934, lxxv. Supplement xxxiii. (Very good summary and literature.)
 Stone: Surg., Gyn., and Obst., 1921, xxxii, 415.
 Taylor, Handley, Souttar, and others: Brit. Med. Jour., 1925, ii, 993.
 Watts and Fulton: New England Jour. Med., 1934, ccx, 883.
 Whipple, Stone, and Bernheim: Jour. Exp. Med., 1913, xvii, 286, 307; Ann. Surg., 1914, lix, 715.

DIVERTICULA OF THE INTESTINAL TRACT

In various situations throughout the digestive tract saccular dilatations, or diverticula, may occur. Of these most important on account of the complications which may arise, are those found in the colon. Diverticula are found occasionally in the cesophagus and in the stomach, more often in the small intestine where in addition, remains of Meckel's diverticulum of embryonic origin may persist, sometimes even with small areas of gastric mucosa or of pancreatic tissue in its wall. When



Fig. 219.—Multiple diverticula of intestine.

multiple diverticula of the small intestine are found they are usually rather large, but as a rule they produce no serious effects. The diverticula of the colon are in general smaller but occur in considerable numbers, often along the mesocolon but sometimes near the epiploic appendages. Graser thought that they arose as hernial protrusions of the mucosa and submucosa through the muscular wall along the course of blood-vessels about which the muscle fibres leave a potential space. Others, such as McGrath, offer a series of factors which might favor such a process, emphasizing especially constipation and old age. Faecal material accumulates in the saccules and although this condition may persist for years without any symptoms, there are many instances in

which the imprisoned bacteria produce a severe inflammatory reaction in the lining of the sac, often with perforation followed by generalized peritonitis, or the formation of a localized abscess. Even after recovery from such an event there may be produced scar-like adhesions, often with obstruction and further extension of infection. The condition is well described by Edwards, McGrath, Wilkinson and others.

LITERATURE

- Edwards: Brit. Med. Jour., 1934, i, 973.
Graser: Arch. f. klin. Chir., 1899, lix, 638.
McGrath: Surg., Gyn., and Obst., 1912, xv, 429.
Wilkinson: New England Jour. Med., 1933, ccix, 197.

CHAPTER XXI

TYPES OF INJURY—OBSTRUCTION (Continued).—OBSTRUCTION OF RESPIRATORY TRACT

Nose (coryza, adenoids, etc.). Larynx (œdema, diphtheria, foreign bodies, compression); bronchi (foreign bodies, stenosis). Atelectasis: its causes. Mechanism of bronchial dilatation. Bronchiectasis. Emphysema.

NASAL OBSTRUCTION

IN the upper air-passages, especially in the nose, there are several common forms of occlusion which impede respiration, with peculiar results. Swelling of the Schneiderian membrane in ordinary coryza may make it impossible to breathe through the nose, so that the throat becomes dried from the prolonged breathing through the mouth. More serious, because more prolonged, is the blocking of the nares by certain *polypoid œdematosus fibromata*, which hang down from the septum, or project from the antrum, or by the growths of *adenoid tissue* from the roof of the pharynx. In young persons the latter give rise to a great deformity of the face, with flattening of the features, which, since the mouth is constantly open, gives the person a most vacant expression.

The difficulty in breathing through the nose, with the consequent violent inspiratory efforts, brings about curious deformities of the chest. A lateral caving in of the soft ribs leaves the sternum prominent (*pigeon-breast*), while the tension of the diaphragm at its insertion may cause a furrow-like retraction of the ribs along that line (*Harrison's groove*).

OBSTRUCTION OF THE LARYNX

Spastic closure of the glottis in children, especially in such conditions as tetany, causes a peculiar difficulty in inspiration, with stridor (*laryngismus stridulus*), while paralysis of the vocal cords may produce a similar obstruction in another way. Actual asphyxia may occur. Asphyxia is much more commonly the result of œdema about the larynx or other types of inflammatory exudate there.

Œdema of the Larynx.—This is, in many instances, only a part of a wide-spread œdema of the tissues such as seen in cases of cardiac failure or renal disease, or due to some local disturbance of the circulation, which may be caused by posture, but at other times it is the effect of an inflammation in or about the larynx (Fig. 220). Masser and others have pointed out the existence of an erysipelas-like infection of the larynx and pharynx in the course of which extreme œdema may arise. So, too, abscesses in the neighborhood of the tonsils, and more especially the phlegmonous inflammations starting about the submaxillary glands (*Ludwig's angina*) or from the mucosa, or even the skin, may produce the most intense infiltration of the tissues of the neck, with inflammatory œdema of the especially loose structures of the larynx. The epiglottis swells into a balloon-like mass, and each aryepiglottic fold assumes huge dimensions, so that the opening of the larynx may easily be closed and suffocation ensue.

Diphtheria, by blocking the larynx and trachea with a tough, inflammatory pseudomembrane may also asphyxiate a child, and it is to obviate this that tracheotomy is sometimes necessary. Exactly the same sort of asphyxia arises when a foreign body, such as a piece of meat, is drawn into the opening of the larynx (Fig. 221). Incredible as it may appear, it is not uncommon to find, in the autopsy upon drunken per-

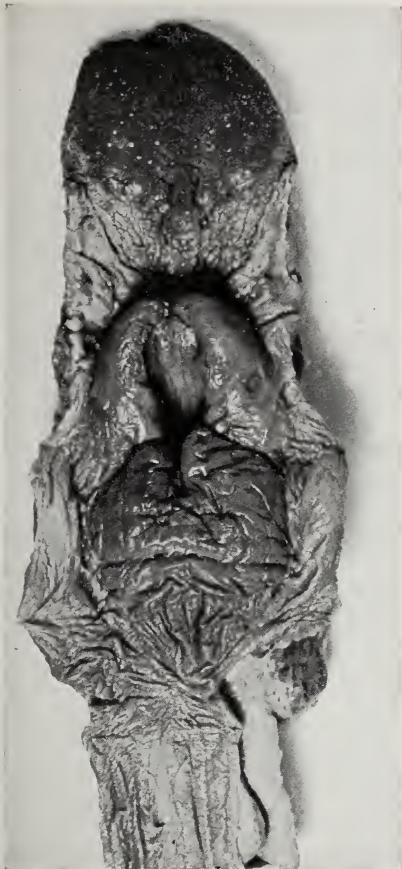


Fig. 220.—Œdema of the glottis.

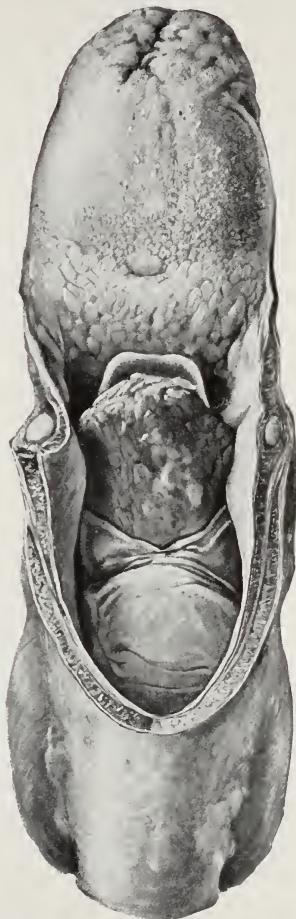


Fig. 221.—Meat impacted in the glottis.
Sudden death from asphyxia.

sons who have died with symptoms of choking, such masses so firmly wedged into the glottis as to be removed with difficulty.

From without, the *trachea* may be compressed by the growth of goitres, aneurysms, and tumors of the neck. In the case of goitres, it is not unusual to find the lumen of the tube flattened into a slit from the pressure exerted on each side. Dyspnoea increases in intensity with the narrowing of the passage. Syphilitic ulceration of the tracheal wall,

with scarring, is no uncommon cause of stricture. The narrowing is generally ring-shaped, and may occur just above the bifurcation, or sometimes even in one of the main bronchi.

It will be seen that, while some of these conditions can last only a short time, others are of long standing and are gradually produced. The latter can in time produce anatomical changes in the lung which are perhaps less striking, though analogous with those produced by similar narrowing of the bronchi.

OBSTRUCTION OF THE BRONCHI

The bronchi, like the trachea, may be completely or only partly occluded in any part of their course by *foreign bodies* of all sorts accidentally drawn into the larynx. Seeds, fruit-stones, teeth, pieces of bone, nails, buttons, pieces of tracheotomy tubes, etc., are the common objects found there. In the case illustrated in Fig. 222 a fragment of bone, together with a tangle of string, partially occluded the large bronchus, supplying air to the middle and lower lobes, leaving the bronchus to the upper lobe quite open. Tumors, *caseous lymph nodes*, and aneurysms may also gradually close the bronchus by pressure, or by actually growing into the lumen of the tube.

The result, when the occlusion is complete, is the collapse of the corresponding part of the lung (*atelectasis*), because the air which remains in the alveoli when the closure is completed is soon absorbed by the circulating blood.

Atelectasis.—The foetal state of the lungs is comparable to the condition of collapse seen in later life, except in that, until the first breath is taken, the alveoli have never been expanded. Since, in the adult, the thorax has grown to a size greater than could be filled by the collapsed lungs, there is even in the position of forced expiration a disproportion which keeps the lungs partly distended with air. In the infant, for a time, so nearly does the lung tissue fill the thorax, that the air which is found in the lung is quite proportional to the respiratory movements. Atelectasis is, therefore, more easily produced or maintained in the infant than in the adult. Indeed, areas of lung tissue often remain undistended with air, and if the condition persists, become obliterated and reduced to scar tissue. In the adult, when the lung has been expanded, the condition of collapse may be produced by: (1) Complete occlusion of the bronchi, or (2) by pressure from without. Only exceptionally is collapse produced in another way, as in those cases in which, while the bronchus is widely open to the trachea, it communicates also through a hole in the lung with the pleural cavity. When air can thus enter the pleura without the necessity of expanding the lung, that tissue gradually collapses. This requires some time, so that if, instead, a hole is made in the chest-wall, complete collapse of the lung does not occur at once.

The first mode of production of atelectasis by complete occlusion of a bronchus depends upon the fact that the air in the corresponding alveoli after the obstruction is complete, is soon dissolved in the circulating blood, so that the alveolar walls fall together. The area appears sunken and of a translucent, bluish-purple color. On section it is pasty

and often congested, the congestion being due to the kinking of the veins, which prevents the blood from escaping. Such airless patches are found about the regions of consolidation in lobular pneumonia, where they represent the parts of the lung supplied with air by branches of bronchi which, at a higher point, are obstructed by the inflammatory exudate. Precisely the same result is found if a foreign body completely closes the bronchus and far more frequently when a tumor growing into the bronchus completes its occlusion.

Pressure from without, the second cause referred to, is most effective when applied gradually and slowly, for the most forcible attempts to press air out of the lungs rapidly, fails unless the alveoli are ruptured, because the smaller bronchioles bend sharply on themselves and prevent the escape of the air. The growth of a tumor, however, or the gradual accumulation of fluid in the pleural cavity, may render airless the part of the lung pressed upon (*cf.* Fig. 102). A whole lobe or part of it, usually the lower and posterior part, may thus collapse into a soft, pasty, bluish, airless tissue, which sinks in water and gives no crepitation between the fingers. When cut into, it may be dry and inelastic, thus differing from an oedematous lung in which the air has been replaced by fluid. By stretching a little of the tissue, first in one direction and then in another, the movements of the alveolar walls can be seen so plainly that the condition of collapse is easily distinguished from that of inflammatory consolidation. Adhesions between the alveolar walls and the growth of fibrous tissue through them sometimes indurate and solidify the lung permanently, so that it cannot expand again.

Bronchiectasis.—When the obstruction is incomplete the bronchi distal to it become dilated (Fig. 222). This is because both inspiration and expiration become difficult in that portion of the lung on account of the partial blocking of the bronchus, although they go on easily enough in the rest of the lung. Quiet expiration is a more or less passive process, due to the elastic recoil of the distended lung, the sinking of the ribs from their actively elevated position, and the relaxation of the diaphragm and of the distended abdomen, although, of course, violent muscular contraction of the chest is available in forced expiration.

Thus the force available to carry air into the lung when the chest is expanded is the whole atmospheric pressure, part of which is used in stretching the elastic lung.* The force which drives the air out in quiet respiration is only the elastic contraction of the lung, aided by gravity and a relatively slight muscular action.

Consequently, if there arises a partial obstruction of a bronchus, offering constant resistance to the passage of air, inspiration will fairly readily overcome the resistance, drawing air into the distal part, while expiration will prove too feeble to drive it out. Air in such a case accumulates behind the obstruction until it is under a pressure equal to that which overcame the resistance of the obstruction, and at this pressure it will remain as long as breathing continues, while other air passes in and

* Just what pressure relations will exist on each side of a complete obstruction of the main bronchus within the chest in inspiration will depend upon the amount of air already in the lung.

out, just as tide-water passes in and out over a dyke, leaving a great depth imprisoned behind, up to the level of the top. It is this continuous distention of the obstructed bronchus which finally widens it and is a prominent cause of the condition known as bronchiectasis, although Dr. Crowe tells me that in dogs in which he has produced stricture of a

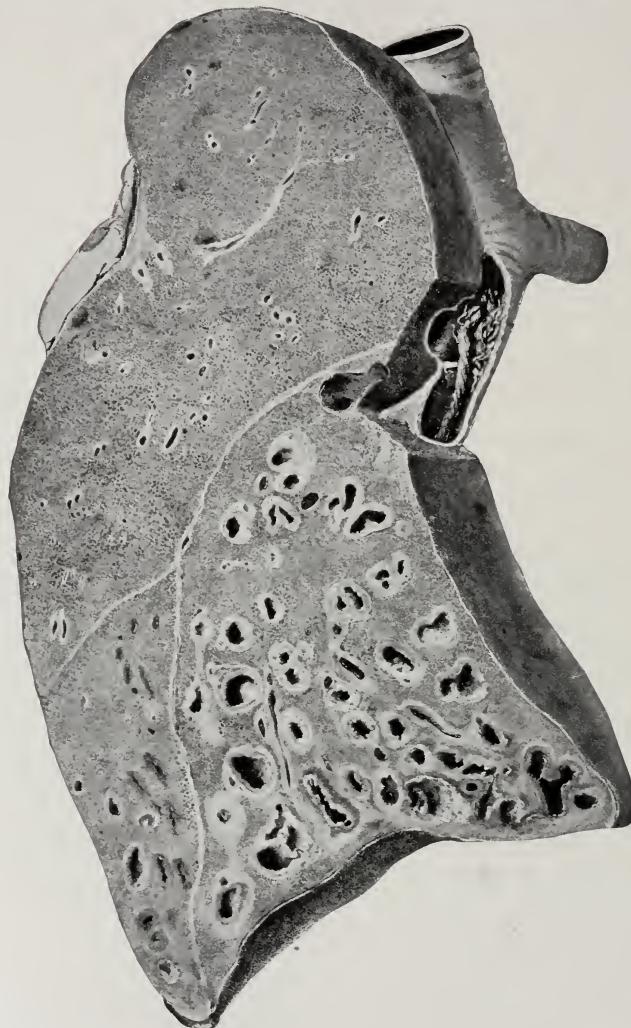


Fig. 222.—Partial obstruction of a bronchus by foreign bodies. Bronchiectasis involving the corresponding branches.

bronchus, easily seen through the bronchoscope as an extreme narrowing of the lumen, there is no dilatation of the distal part as long as the bronchus remains uninfected.

Most instances of bronchiectasis seem, however, to be due to infection of the bronchial wall which renders it inelastic, obliterates its

normal peristaltic muscular contractility and by actual destructive and inflammatory changes weakens and erodes it and causes the outpouring of exudate into its lumen. Even the reflex mechanism which ordinarily empties the bronchus by coughing, is inactive.

Anatomically, they vary greatly in appearance. In those acutely produced, the bronchi are deeply congested, thin-walled and soft, and filled with a purulent secretion. They are usually associated with lobular pneumonic patches of consolidation. In the more chronic cases the same cylindrical dilatation may appear, but it is perhaps more common to find the widening excessive at the ends of the bronchi, so that they become club shaped. Occasionally they are beaded with separate dilatations, or they may be blown out into wide sacs which can rupture into one another or into the pleura. In all these cases the bronchial wall is intensely inflamed and thickened by the accumulation of inflammatory exudate in its substance. The mucosa is thick and ragged, the musculature and elastic tissue spread apart, torn, and weakened, and the connective tissue as well, infiltrated with fluid and wandering cells. The cartilaginous plates tend to disappear, and a newly formed connective tissue occupies the bulk of the wall. All this tends to diminish greatly the strength and elasticity of the wall.

The lung tissue in these protracted cases is sometimes very emphysematous, but in others it is converted into a dense fibroid substance partly by the organization of inflammatory exudate within the alveoli, partly by the growth of fibrous scar tissue in the walls of the alveoli and the other tissues of the lung.

It is not well known what changes occur in the channels of communication between these widened bronchi and their alveolar tissue, but it is probable that, according as there is narrowing or complete obstruction of the tiny bronchioles at their entrance into the dilated bronchus, there will be emphysema or atelectasis in the corresponding alveoli.

Many theories have been formulated to explain the distention of the bronchi, but in these all are agreed upon one point only, that the infection and inflammation which weakens the bronchial wall and destroys its elasticity is a necessary factor. Not all cases of bronchitis are followed by bronchiectasis, and it may be that special bacteria, such as the influenza bacillus, which has often been found in bronchiectasis, are particularly able to cause the weakening of the wall. In the course of the recent epidemic, in which the bacillus of Pfeiffer was frequently found, bronchiectatic dilatation was described by many writers.

Pleural adhesions generally accompany chronic bronchiectasis, and Corrigan and Biermer express the idea that in indurated and adherent lungs the contraction of the scar tissue between the bronchi pulls upon them from all sides and thus dilates them. Possibly this is true in some cases, but it cannot be a general explanation.

Others declare that the accumulation of secretion in the bronchi is sufficient to distend them to the degree found, but it seems that this can at best be only an accessory influence, because by itself the secretion can never exert any great pressure. Most writers, too, lay stress upon

the effects of the violent expiratory effort with closure of the glottis in coughing, as capable of distending the bronchi. Reflection will show, however, that although under those circumstances the trachea might be distended, the pressure on the walls of the bronchi within the chest is from outside, so that it cannot distend them, as a rubber and glass model of the respiratory organs will demonstrate to perfection. Indeed, bronchiectasis may be experimentally produced in animals in the complete absence of cough. On the other hand, the violent inspiratory distension of the lung preparatory to coughing may be able to widen the bronchi if they are weak and it is constantly repeated.

This leaves the idea of the inspiratory dilatation, whether exerted directly or through the imprisonment of inspired air behind some obstruction, as the most plausible explanation. It was, indeed, the explanation given by Laënnec in his first work on bronchiectasis in 1819, and it has been recalled by Aron, and by Thornton and Pratt in their experimental work. When we attempt to apply this explanation of the cases of bronchiectasis as they occur, we find that it is completely satisfactory in those in which there is an obvious partial obstruction. But there are many others where obstruction is not so obvious, and these offer difficulties. It is true that we may say that thick, sticky, mucoid secretion may exert a valvular action in the bronchi, preventing the easy exit of air; or we may assume, with Hoffmann, that the weakened bronchus may kink during expiration like an old rubber tube, while stretching open on inspiration, in this way fulfilling the theoretical conditions.

But these things are hardly definitely demonstrated as yet, and the question needs further study.

LITERATURE

Œdema of Larynx: Peltesohn: Berl. klin. Woch., 1889, xxvi, 931.

Bronchiectasis: Bendove and Gershwin: Arch. Int. Med., 1934, liv, 131.

— Erb: Arch. Pathol., 1933, xv, 357.

— Thornton and Pratt: Johns Hopkins Hosp. Bull., 1908, xix, 230.

Open Pneumothorax: Graham and Bell: Amer. Jour. Med. Sci., 1918, clvi, 839.

The effect of partial or intermittent obstruction of the air-passages upon the alveolar structure of the lungs may next be examined. It has been said that complete obstruction of a bronchus quickly results in atelectasis or collapse of the corresponding part of the lung, but it is also true that partial or intermittent obstruction causes an overdistention of the alveoli with air. There are many other causes assigned for the overdistention, but the importance of this one will become evident in studying the type condition, emphysema.

Emphysema.—Excessive distention of the alveoli may be produced rapidly in the lung, when the tissue of the alveolar walls is quite normal, so that if the air be allowed to escape, the alveoli at once return to their normal size, and their stretched walls to their normal thickness. If this overdistention be maintained at not too great a degree, the capillaries are, as Tendeloo has shown, widened so that nutrition of the alveolar wall may be well kept up. A still greater distention narrows

and compresses the capillaries, so that the blood passes with difficulty or not at all. Nutritive changes possibly dependent on this great stretching and the impaired blood supply weaken the elastic alveolar wall after a time, so that it may remain permanently stretched, or, after the breaking of its elastic fibres, give way at one or more points. Then the margins about the hole retract, and two alveoli are thrown into one.* At times great sacs are formed on the surface and along the edges of the lung by this process, while the remainder of the organ is softened and assumes a very coarse texture, from the wide-spread loss of alveolar walls. Such a lung is very voluminous, but feels peculiarly soft and non-resilient. The characteristic crepitation or crackling felt on pinching the lung tissue is altered, and one has the sensation of bursting large bubbles under the finger instead of the fine crackling produced in the normal tissue. There is also a peculiar pallor, which is due to the obliteration of so much of the capillary bed and to the absence of coal-pigment.

Microscopically, the most striking feature is the large size of the alveolar spaces and the extreme thinness of the alveolar walls. With suitable stains one may observe the fracture of the strands of elastic tissue and the formation of holes in the walls, as well as the narrowing, obliteration, and rupture of the capillaries.

This is the chronic substantive emphysema in which one may sometimes discern evidences of attempts at repair in the new formation of elastic tissue and the growth of new blood-vessels and connective tissue. Atrophy of the lung tissue is perhaps the most characteristic feature of a subtype, the so-called senile emphysema. In old people the lungs are sometimes found to collapse into a very small bulk on opening the chest. They may contain much coal-pigment, but the tissue is extremely soft and wide meshed. In such cases it is customary to ascribe much of the thinning out and disappearance of the alveolar walls to senile atrophy, but it may be questioned whether it is not sometimes the end-result of a very protracted process of the kind described above.

The causes of emphysema are somewhat different in the various forms, although only a few principles can be concerned. When, through lobar pneumonia, tuberculosis, tumor formation, etc., a large portion of the lung is rendered solid, so that it cannot expand with the enlargement of the thorax, the whole inspiratory effort is expended upon the remaining open lung tissue, which thus becomes overdistended (vicarious emphysema). So, too, in drowning, water is drawn in to fill part of the lung, while further violent inspiratory efforts above water overdilate the rest of the alveoli with air.

In many conditions in which the trachea or bronchi are partly ob-

* The alveolar walls contain a rich network of capillaries, abundant elastic tissue, and some wavy fibrils of connective tissue, and are covered on each side by the respiratory epithelium. The elastic tissue stretches across in coarse bands, frayed out here and there into fibres which join again in other directions to form new bands. Another set of fine fibrils arises from the elastica of the vessels and accompanies the capillaries (Orsos). Pores in the alveolar walls (pores of Kohn) are frequently seen, but there is much evidence that they are present only in diseased lungs.

structed, continued distention of the alveoli occurs by the imprisonment of air introduced in inspiration over the obstacle in the way described in connection with the formation of bronchiectasis. This is especially clear in the case of valvular obstructions which allow inspiration only, as in the case of a stalked polyp in one of these air-passages, or a flapping film of diphtherial false membrane. It is true also of the thick, sticky, mucous exudate which may collect in the inflamed bronchioles in chronic bronchitis, and is particularly shown in the areas of emphysema which occur side by side with areas of atelectasis in the neighborhood of patches of bronchopneumonic consolidation. Asthma, in which the bronchioles are narrowed partly by muscular contraction, partly by swelling of their mucosa and by exudate, presents the conditions mentioned. Inspiration is violent, and expiration prolonged and labored, and emphysema is the regular accompaniment. In all these cases it seems to be the inspiratory effort which is active in dilating the alveoli. Generally this is effective in producing a permanent anatomical change only when aided by a partial obstruction, and when kept up through a long time. Whether it itself can thus produce the nutritive disturbances which lead to rupture of the alveolar wall is not perfectly certain. Doubtless other injurious agencies may also play a part, because it is known that the lungs of certain people exposed to mechanical conditions of this sort develop emphysema, while others do not.

Nearly every writer on the subject ascribes the widening of the alveoli to the increased intrathoracic pressure produced by cough, which is a forced expiration during closure of the glottis, suddenly relieved by its opening. It must, however, be clear that, as in the case of bronchiectasis, the increased intra-alveolar pressure is produced only by their compression, with decrease in their size. Only in such an unprotected place as the suprathoracic apex of the lung could one imagine this pressure capable of blowing out the alveoli. In the sternal margins it is still more doubtful. But cough is preceded each time by an extreme inspiratory distention of the lung, which, incessantly repeated, might lead to changes in the size of the alveoli. Tendeloo presents some interesting arguments with regard to the predominantly marginal and apical distribution of emphysema, based on his ideas as to the unequal expansion of the alveoli in different parts of the thorax. His laws seem, however, to depend upon doubtful evidence, and must be read in the original. When there are no adhesions in the pleural cavity, nor consolidated areas in the lung, the expansion of all alveoli would appear to us to be uniform.

In wide-spread emphysema of long standing, such as often accompanies chronic bronchitis or asthma, the capillary bed in the lungs is so much narrowed by the obliteration of many channels that the blood passes with difficulty, and hypertrophy of the right side of the heart is a consequence.

Such persons usually present a peculiar thoracic deformity—the chest is enlarged, with the ribs constantly in the position of inspiration, so that further respiratory movements are shallow. The costal cartilages often become calcified and rigid, and Freund has suggested that this condition

may be primary and constitute the real cause of the emphysematous enlargement of the lungs. The evidence is not clear, however, in favor of this idea.

LITERATURE

- Eppinger: Ergeb. d. allg. Path., 1904, viii, 267.
Tendeloo: Ursachen d. Lungenkrankheiten, 1902. Ergebni. d. inn. Med., 1910, vi, 1.
Freund: Lungenkrankheiten u. Rippenknorpel-Anomalien, Erlangen, 1859.
Kountz and Alexander: Medicine, 1934, xiii, 251 (Review).
Marchand: Asthma, Ziegler's Beiträge, 1915, lxi, 251.
Orth: Berl. klin. Woch., 1905, xlii, 1.
Orsós: Ziegler's Beiträge, 1907, xli, 95.

CHAPTER XXII

TYPES OF INJURY—OBSTRUCTION (Continued).—OBSTRUCTION OF THE URINARY TRACT

Urethral stricture. prostatic obstruction. Hypertrophy of prostate. Cystitis. Urinary calculi. Hydronephrosis. Renal calculi. Ascending renal infection; pyelonephritis.

THE course of the urinary tract in the male is beset with so many more difficulties in the form of narrow places than in the female that the greater proportion of obstructions may naturally be expected in that sex.

URETHRAL STRICTURE

In the female the bladder opens by a canal so short and wide that obstruction to the flow of urine is seldom observed below the ureters. In the male it may occur at the prepuce, at the meatus, in the urethra, and especially in its prostatic portion, and at the vesical orifice. *Phimosis*, which is a congenital or acquired narrowing of the prepuce, may sometimes be sufficient to offer a considerable obstacle, and even give rise to fatal complications. A similar effect is produced by those constrictions of the meatus by scar tissue which occasionally follow the healing of an ulcer of the glans or a syphilitic chancre. It is, however, much more common to find the narrowing of the urethral canal higher up, and there it is due sometimes to mechanical *trauma*, but far more often to *gonorrhœa*. When the urethra is torn across, as in those cases in which a man falls from a height astride a beam, it is difficult for the surgeon to secure such perfect healing that there is not some narrowing at the place. Nevertheless, such cases are very amenable to treatment. Far different are those in which, in the course of a protracted gonorrhœal infection, the wall of the urethra becomes ulcerated and infiltrated with inflammatory exudate. This usually produces its most profound effects in the bulbous portion, although other places may be involved instead. The organisms penetrate deep into the mucosa, and lodge in the lacunæ and crypts, where they keep up the injury in the most persistent way. Healing with scarring of the ulcerated tissue results in the narrowing of the canal, and such *strictures* (Fig. 223) frequently make it impossible for the bladder to empty itself. To this are often added the injuries caused by forcible attempts to pass catheters which, in inexperienced hands, pierce the urethral wall and wound the surrounding tissue. The healing of these false passages, added to the mass of scar tissue around the urethra which constricts and deforms it, is the cause of ever-impending occlusion.

PROSTATIC OBSTRUCTION

Complex conditions exist about the region of the prostate, so that a variety of alterations may take part in producing obstructions there. Among these abscesses of the prostate and cancerous tumors springing

from the gland are important, but by far the most common is the so-called hypertrophy of the prostate of old men. The obstruction caused by an abscess is transient, and depends upon the bulging of the prostate until the urethra is pressed flat, while that caused by the cancer is quite irregular, because the tumor may encroach on the urethra in any way. But the hypertrophy of the prostate follows roughly certain general rules, and the type of obstruction is for that reason fairly constant.



Fig. 223.—Gonorrhœal stricture of the urethra. At A the urethral canal is surrounded by scar tissue and greatly narrowed. There is hypertrophy of the bladder.

Hypertrophy of the Prostate.—Despite the most lengthy discussions, our ideas are still quite hazy as to the reasons for the enlargement of the prostate which is so frequent in men over sixty years of age, and even as to its anatomical characters the most diverse statements are made. It is evidently desirable that more accurate observations in this regard should be made and analyzed.

The prostate is a sexual gland derived from the Wolffian body, just as are the

seminal vesicles, and its function is not to control the flow of urine, but to furnish its secretion in jets at the moment of ejaculation, in such a way as to mix it with the sperm in the urethra. In accord with this requirement we find that its abundant smooth muscle is arranged around the glands, so that it can suddenly exert pressure upon them. The internal sphincter of the bladder controls the discharge of urine, and is practically independent of the musculature of the prostate. So, too, the external sphincter of Henle, which consists largely of voluntary muscle, is independent, although its fibres extend in some cases into the prostate.

The bulk of the gland tissue in the prostate is collected in the lateral lobes, where it forms pyramidal radiating masses opening through 40 or 50 ducts into the urethra. The glands are acinar, lined with cubical or cylindrical epithelium, and often contain yellow, horn-like, concentrically laminated concretions (corpora amylacea). The posterior commissure is chiefly muscular, and contains few glands. There are a few, however, which extend upward toward the bladder inside the sphincter. There are also urethral glands there, such as are to be found throughout the course of the urethra. The anterior commissure is tightly connected with the symphysis pubis.

Enlargement of the prostate is due in most cases, as we see it at autopsy, to the formation of a rather sharply outlined mass on each side of the prostatic urethra.



Fig. 224.—Hypertrophy of lateral lobes of prostate. Cross-section showing lateral compression of urethra. Prostatic concretions.

These push outward and stretch into a flattened layer the original tissue of the gland and compress the urethra into a narrow slit elongated anteroposteriorly. These masses may become very large and irregular in outline so that the compression and consequent obstruction of the urethra is extreme and discharge of urine is impossible without catheterization. Associated with these nodules there is very often a pear-shaped mass which springs up inside the sphincter and lifts up the floor of the trigonum, projecting upward and forward into the bladder. Such a hypertrophied midlobe which springs from the urethral glands in the midline may attain a great size and is especially sure to obstruct the outflow of urine because with the contraction of the bladder it acts as a plug to close the urethral orifice. Besides, the stretching of the sphincter from its presence may produce incontinence of urine which is a familiar clinical indication of beginning prostatic hypertrophy.

Opinions differ as to the exact nature of these masses which grow in the prostate. In section those lateral to the urethra seem to be composed of glands which are much more tortuous and septate than normal and lined with columnar epithelium. The mass is sharply outlined against the compressed original prostatic tissue but it retains not only a connective tissue framework but the smooth muscle which is characteristic of the normal gland. From the cylindrical epithelium and the extraordinary ramification and papillary ingrowth of the glands, it seems clear that they

are newly formed and greatly multiplied. They often, indeed generally, show some evidence of cell infiltration which has stirred the suggestion of their origin on the basis of a long continued infection. The glands which make up the overhanging mid-lobe are perhaps somewhat different in form and have always been regarded as urethral glands.

Many ideas have been put forward as to the exact course of the growth of such masses and their histological relations. Reischauer, who has written extensively, feels that they begin as tumor-like growths of muscle and connective tissue in the mantle of the prostatic urethra and that any participation of glands in the formation of such a fibromyomatous nodule results from their contact and inclusion in its growth. If this mixture occurs early enough it produces a fibro-adenoma but on the whole he regards it as very similar to the formation of myomata in the



Fig. 224A.—Hypertrophy of the prostate with enlargement of the midlobe. Hypertrophy of the bladder with diverticula.

uterus. Grassmann also finds that the localized tumor arises from the peritubular framework of lateral urethral glands and similar accessory glands in the floor of the bladder whose active sprouting mingles them with the fibrous and muscular tissue to produce a fibromyoadenoma. In old men, he, like Runge, Tietze, Netter and Newburger and recently Rich, has observed a beginning cancerous change in these glands. All authors tend to emphasize the periurethral or pre-spermatic glands in the origin of these masses, although they recognize also a participation of the main glandular structure of the prostate. In monkeys where there are no submucosal urethral glands, prostatic hypertrophy has never been recorded, but in rats where such glands are present, a typical example was found in an old rat.

For a long time there has been discussion as to whether in such prostatic hypertrophy we are dealing with a tumor growth or perhaps with the effect of a chronic infection—not necessarily gonococcal, since, as Pomeroy points out, mixed infection

is present in a great proportion of men. It is argued that if they were adenomata they would not have smooth muscle in the stroma, as these masses have.

But recently attention has been especially turned to the possible rôle of the endocrine system. For a time castration was the accepted surgical treatment of prostatic hypertrophy but that gave place to the modern prostatectomy. Lower and Johnston found that in the early stages of glandular hypertrophy the suppression of the male hormone, or of the anterior pituitary gonad-stimulating hormone which regulates the production of the male hormone, slowed down or stopped the hypertrophy. This could be done by removal of the testes which then prevents further glandular proliferation but does not affect the late stage when scarring has occurred. Martins and Rocha found through parabiosis of a castrated male with a female rat that because of their common circulation the excess hypophyseal function in the castrated rat, from loss of the regulating testicular hormone, provoked precocious sex maturity in the female. They found that this testicular hormone, which is from germinal epithelium, could prevent the alterations in the hypophysis but not the atrophy of accessory genital organs. Witschi and Levine also found that castrates



Fig. 225.—Hypertrophy of lateral and midlobes of the prostate, showing antero-posterior widening of the urethra, distention of the bladder, and cystitis.

produce an excess of follicle growth stimulating hormone which in parabiotics will produce continuous oestrus. McCullagh finds that in rats castration causes atrophy of the prostate and hypertrophy of the hypophysis and adrenals. An extract of the testis made with fat solvents (and perhaps derived from the Leydig cells) is called *androtin*, while an aqueous extract of the germinal epithelium is called *inhibin*. Androtin prevents the atrophy of the accessory sex glands or regenerates them, while inhibin prevents the characteristic changes in the hypophysis which consist in its enlargement from increase and vacuolization of the basophile cells. It is possible that with the advance of age, the disappearance of the germinal epithelium of the tubules diminishes the inhibin, allowing the hypophysis to stir the remaining tissue—the Leydig cells—to an excess production of androtin which is comparable with theelin and can cause prostatic hypertrophy.

Indeed, it seems that the discovery of the exact cause and nature of prostatic hypertrophy is imminent. Its analogy with myomatosis uteri seems an interesting suggestion but not yet clear. Certainly the ideas of its dependence upon infection, sexual excess or tumor formation seem to be overshadowed by these more recent ideas of its endocrine relations.

LITERATURE

- Grassman: Virch. Arch., 1928, cclxx, 514.
Jenkins and others: New England Jour. Med., 1934, ccxi, 569.
Lower and Johnston: Jour. Urol., 1931, xxvi, 599.
Martins and Rocha: Endocrinology, 1931, xv, 421.
McCullagh: Science, 1932, lxxvi, 19. Endocrinology, 1935, xix, 466.
Pomeroy: Urol. and Cutan. Review, 1935, xxxix, 163.
Randall: Surgical Pathology of Prostatic Obstructions, 1931.
Reischauer: Virch. Arch., 1925, celvi, 357; Bruns Beiträge, 1934, clx, 460.
Witschi and Levine: Proc. Soc. Exp. Biol. and Med., 1934, xxxii, 101.

OTHER FORMS OF OBSTRUCTION

It is not only in the urethra that obstruction to the emptying of the bladder appear, for plugs may be formed in the bladder itself. These are often loose in the cavity of the bladder, in the form of urinary stones, or foreign bodies which have been pushed into the bladder through the urethra. Then there are the stalked, papillary, tassel-like tumors, which very commonly reveal themselves later as carcinomata, and which can drift into the urethral orifice and cause a temporary obstruction. Tumors invading from the uterus or rectum through the bladder-wall may block the urethra, just as the tumors of the bladder-wall itself, but their usual fate is to break down into a canal into the rectum or vagina, which allows the escape of urine but renders infection of the bladder inevitable.

Very important in connection with mechanical obstruction of the flow of urine is the presence of solid calculi composed of materials derived from the urine. These are found not only in the bladder, but in the pelvis of the kidney, and, indeed, it seems that the renal pelvis is the seat of original formation of many of them. It is not clear that obstruction has anything to do with their primary formation, although the growth of some of them at least seems to be greatly favored by such changes in the urine as follow obstruction. But they themselves are effective, just as in the case of gall-stones, in acting as plugs which retard the flow of urine either intermittently or continuously.

Urinary Calculi.—Concretions of crystalline material, mixed usually with some organic substance, and found at any point from the renal papillæ and renal pelvis to the urethra, constitute the group of urinary calculi. According to their position, they have the opportunity to assume one form or other, and an irregular mass from the pelvis of the kidney, if it be swept into the bladder, is likely to become round by the continuous application of new layers of crystals. These calculi vary in their chemical composition, and accordingly in their appearance, depending partly upon the position in which they are formed, but chiefly and almost entirely upon the chemical character of the urine in which they form. Since the urine may frequently change its character during the months or years which go by in the growth of the stone, the end result is apt to be made up of layers of laminæ of quite different color, consistency, and chemical composition (Fig. 226).

Ebstein thought that the organic or albuminous supporting framework which one can find in every calculus was the necessary skeleton upon which the deposit of crystals took place, and that without such a nucleus of organic material no crystallization in this form would occur. Aschoff, Moritz, Kleinschmidt, and others dispute this, and think this organic meshwork which is present in crystals, even when they are made to form in urine *in vitro*, is an accidental accompaniment of the crystals, probably formed through their own power of absorption. Still, they admit that it

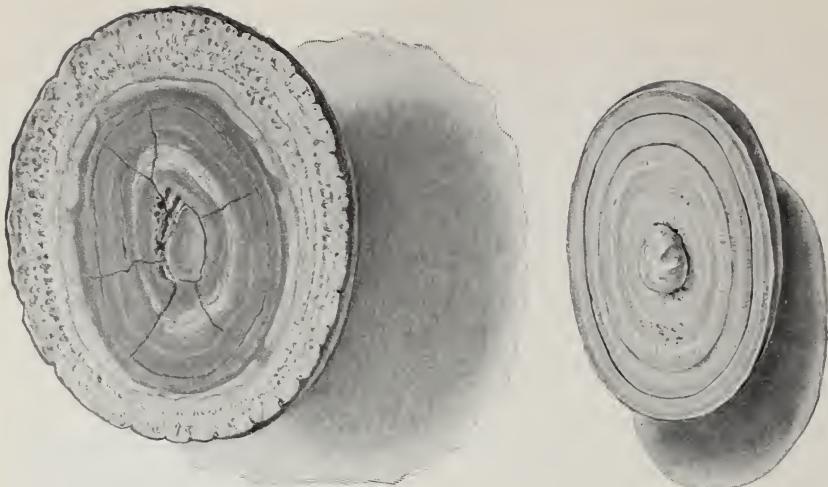


Fig. 226.—Laminated vesical calculus. Central mass of uric acid with peripheral zones of carbonates and phosphates.

Fig. 227.—Urinary calculus of uric acid in laminæ about a central quartz pebble.



Fig. 228.—Uric-acid calculi with fine lamination.

is of some help in holding the forming stone together. The application of new layers of crystals to a concretion already formed is thought to occur, just as rock candy crystallizes on the string. But it involves the idea of an oversaturation of

the urine with crystallizable substances, or else such changes in the urine that it becomes less able to hold those substances in solution. Thus if the urine is acid, uric acid may crystallize out, while if it is alkaline, phosphates, ammonio-magnesium phosphates, and ammonium urates may appear. Or something may cause the precipitation of those colloid materials in the urine which tend to hold the uric acid in solution, after which it quickly appears in crystalline form. Bacterial infection, especially when it produces ammoniacal decomposition of the urine, is favorable to the formation of phosphatic concretions.

Thus there is no insurmountable difficulty in explaining the growth of such stones once started, but it is more difficult to explain their origin. Of course some are formed around foreign bodies—hair-pins, pieces of catheters, etc., which have been introduced into the bladder, but these incrustations are relatively rare (Fig. 227). Ebstein and others, including Kleinschmidt, are reduced to the explanation that most calculi, whether found in the renal pelvis or in the bladder, are formed originally in the tubules of the kidney. This idea has been elaborated especially for the uric-acid stones, because they are the commonest and because the conditions found in the so-called *uric-acid infarcts* of the kidney do explain their origin fairly



Fig. 229.—Vesical calculi formed of calcium oxalate. One in section shows laminæ of phosphates and carbonates.

well. These are frequent, especially in the kidneys of children and infants, and produce a curious yellow streaking of the papilla of the pyramid, sometimes with actual stony concretions embedded in ragged cavities near its tip. Microscopically, it is found that this is due to the abundant excretion of uric acid by the cells of the tubules. Sometimes (Aschoff) these are uninjured and secrete the uric acid in minute crystals on their surface. Other cells may be destroyed in the process. The uric acid appears in minute, round "sphæroliths," which become massed together with an albuminous material, secondarily gluing them together. This forms the primary concretion, which may pass quite out through the urethra, or may form the nucleus for a urinary calculus.

Calculi may form in normal non-albuminous urine, and may grow to a considerable size without causing any symptoms—usually from their angular form they wound the wall of the renal pelvis or of the bladder, and then cause bleeding and inflammation, which in turn are likely to change the reaction of the urine and initiate the deposition of layers of material of a different character from that which composed the stone. When the stone causes obstruction and bacteria are introduced, this change in reaction and the deposit of phosphates are inevitable.

Kleinschmidt classifies all these calculi as non-inflammatory and inflammatory, in each of which groups there are primary and secondary formations which represent stages in the history of the stone, just as do successive strata in a geological formation. Several of the crystalline substances in the urine may form concretions without any appreciable admixture of other things, so that in these calculi the chemical composition is the same from the centre to the surface. Such practically pure concretions are those composed of uric acid, calcium oxalate, xanthin, cystin, or calcium phosphate. Some of them grow in the same way as mixed stones to a large size. In other cases they form the nucleus upon which, with a change in the character of the urine, layer after layer of other substances are deposited. When there is no inflammatory process, such secondary stones may be formed upon a uric-acid concretion as nucleus with layers of uric acid and urates, or layers of oxalates and calcium phosphate. So, too, a calcium oxalate nucleus may be turned



Fig. 230.—Mixed oxalate and urate calculus coated with phosphates.

into a secondary calculus by being enveloped in layers of uric acid or calcium phosphate.

When bacterial infection and an inflammatory process supervene, phosphates, especially the ammonio-magnesium phosphate, sometimes with calcium carbonate, etc., make their appearance as strata of white, rather crumbly crystals, on the surface of one of these nuclei, just as they form an incrustation over any foreign body in the bladder. Indeed, they may form the whole calculus by themselves, without any obvious non-inflammatory stone or foreign body as a nucleus.

Uric-acid calculi (Fig. 228) are hard, smooth, oval or rounded stones when formed in the bladder, or moulded to the cavity when in the renal pelvis. There is often a central granule of ammonium urate about which fine, delicate yellow or yellow-brown laminae of very compact appearance and great regularity are laid down. In other cases the consistence is more like that of pumice-stone, especially when there is much admixture of urates and the lamination is correspondingly indistinct.

Pure calcium oxalate stones are rare, but mixed stones, in which it forms a considerable part, are common. They are often formed about a nucleus of uric acid or urates, and the oxalate covers this in layers of varying thickness, distinguished by their dark brown color and by the extremely rough, jagged external surface which they present (Fig. 229). The irritation caused by this usually leads to the deposition of carbonates and phosphates, which fill up the depressions and smooth off the surface (Fig. 230). Urates may also alternate with layers of oxalates. Such stones are extremely hard, usually fairly round, and occur especially in the bladder.

Phosphatic Calculi.—In other cases, especially when the bladder is inflamed, ammonio-magnesium phosphate and calcium phosphates and carbonate predominate, usually on a nucleus of uric acid. These stones may or may not be laminated (Fig. 231). They are nearly pure white, with occasional yellow or brownish layers, and the surface is rough. Rarely, instead of being chalk-like, these phosphate stones are

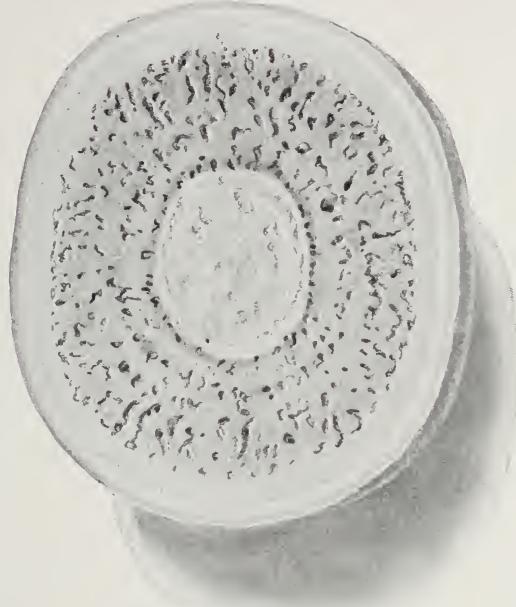


Fig. 231.—Phosphate calculus with a layer of oxalates.

radially crystalline. The non-laminated type are usually round and rough, loosely built, pumice-like concretions of a yellowish-white color, but material of this sort is often deposited irregularly on other stones, especially when they are cracked or irregular and lodged in a bladder where there is ammoniacal decomposition of the urine.

The obstruction produced by calculi is dependent, as long as they are loose in the bladder, upon the posture of the patient and upon the size and shape of the stone, so that unless it is impacted in the urethra, the obstruction is intermittent.

LITERATURE

- Ebstein, W.: Natur u. Behandlung der Harnsteine, Wiesbaden, 1884.
- Fowler, H. A.: Johns Hopkins Hosp. Rep., 1908, xiii, 507.
- Kleinschmidt, D.: Die Harnsteine, Berlin, 1911.

Paralytic Dilatation of the Bladder.—Normally, when the bladder is filled to a certain degree it tends to contract and empty itself, the act of

micturition being under the voluntary control of a sphincter, and being in itself the effect of nervous reflexes by way of nerves which run to and from the lumbar and sacral cord. When injury of the spinal cord results in complete paralysis of the lower extremities and of the lower part of the body, as is so frequently the case in fractures of the spine, etc., neither afferent nor efferent impulses are effective. There is no sense of overfilling of the bladder, no desire to micturate, and often no power, even by the aid of the abdominal muscles, to empty the bladder. Hence it gradually becomes distended to an enormous size, and must be emptied by the introduction of a catheter.

LITERATURE

Langworthy and others: Bull. Johns Hopkins Hosp., 1935, lvi, 37, 211.

CYSTITIS

These various conditions offer a more or less insuperable obstacle to the discharge of urine from the bladder, and the immediate result is its incomplete instead of complete evacuation. Ordinarily the residual urine does no harm, except in that it occupies space in the bladder which thereupon fills more quickly, so that micturition becomes abnormally frequent. That is true so long as the urine remains sterile, but with increased difficulty in urination it may become necessary to pass a catheter into the bladder, and sometimes this operation falls to the hands of the patient himself. Naturally, in such conditions, it is not long before bacteria are carried into the residual urine and find there an excellent culture-medium. As soon as this happens, the urine, which may have been clear before, becomes turbid and alkaline, full of bacteria, desquamated epithelial cells, and leucocytes, showing that the response to infection in the form of an acute cystitis has appeared.

Naturally, a great variety of bacteria may be concerned in this process, and in such cases there is commonly a mixture of several forms, sometimes even with yeasts and fungi in addition. The inflammation (cystitis) which they set up will vary in its intensity according to the type of infection, but more especially according to the degree of obstruction and the resistance of the individual.

Forms of Cystitis.—We may distinguish catarrhal, purulent, and diphtheritic forms, and there are others that almost merit the name gangrenous.

In the mildest infections the bladder-wall becomes swollen and reddened, and a few leucocytes pass through. The urine is acid when *Bacillus coli* is the infecting agent, but otherwise it is often alkaline, with a small amount of ammonia and a sediment of phosphates, desquamated cells, and mucus. The purulent form follows upon more intense infections, and is characterized by haemorrhages in the mucosa and pus-containing urine. These haemorrhages may be mere petechiae.

In the diphtheritic form much more extensive haemorrhages appear, surrounding the patches of most intense inflammation. In these areas the bacteria are found to have caused a superficial necrosis, with the coagulation of a layer of yellowish or greenish fibrin upon the surface and into the depth of the necrotic mucosa. The loosening of such a false membrane leaves an ulcer with hemorrhagic base, and surrounded by a deep-red halo. Such ulcers are usually found at first upon the more prominent parts of the wall, where the muscular trabeculae project, and upon

the smoother trigonum. In advanced, long-standing cases, though, the ulcers become deeper and may cover much of the bladder-wall, some of them are scarred, while others are newly formed; discoloration occurs; there arises much blackish-green staining, probably largely from sulphides, which blacken the haemosiderin formed in the hemorrhagic areas, and the bladder-wall presents an extremely foul, ragged, and deeply stained surface. In a bladder of this type the urine contains all the materials which could be shed from such a wall.

Usually a great dilatation of the bladder follows upon such long-continued obstruction to the outflow of urine. Its walls become stretched, and particularly those portions which lie between the main muscular trabeculae may be bulged out into diverticula. At the same time there is a distinct hypertrophy of the muscle bundles—a work hypertrophy which arises in the oft-repeated attempt of the bladder to discharge its contents (Figs. 224A, 225). Whether the dilatation or the hypertrophy will predominate depends upon the age and general condition of the patient. There are old men without much obstruction in whom atrophy of the muscle of the bladder allows it to become distended and to retain residual urine.

The entrance of the ureters into the bladder is oblique, through the muscular wall, so that the more tensely the bladder is distended, the greater is the pressure tending to flatten and close the end of the ureter as it slants through the bladder-wall. In addition to this the actual orifice is guarded internally by valve-like folds of mucosa which readily allow the urine to pass downward only. Therefore the entrance of fluid from the bladder into the ureter is normally excluded, and it is impossible, even with great force, to inject colored fluids into the ureter by distending the bladder with them. It requires some destructive change in the intravesical part of the ureter to make this influx possible—either the erosion of all these guarding tissues or something which will render the ureter so rigid that it will not collapse when the bladder is distended. Nevertheless, it is evident that if it becomes difficult for the urine to escape from the bladder, it becomes equally difficult for it to leave the ureter and enter the bladder, so that an obstruction which ends in distention of the bladder is equally an obstruction to the escape of urine from the kidneys and ureters.

EFFECTS OF OBSTRUCTION ON THE KIDNEYS

We have now to consider the effects upon the kidney with its pelvis and ureter of—(a) Obstruction without infection; (b) obstruction with infection; and (c) the rare infection by way of the urinary tract without obstruction.

Hydronephrosis, by which is meant a dilatation of the pelvis of the kidney, often accompanied by hydro-ureter and practically invariably by a distention and thinning of the renal substance itself through the accumulation of fluid in that cavity, may result from various causes. All those types of obstruction which lead to distention of the bladder may be accompanied by hydro-ureter and by hydronephrosis, but, in addition, there are those in which the ureters are blocked in some way. Therefore in the latter group the hydronephrosis may be unilateral.

The pressure of tumors from the outside, such as those which arise from the uterus and ovaries, even if they do not invade the substance of the ureters, often sets up such a blocking of their lumen. The same effect may be produced by an inflammatory process in the ureteral wall which leads to stricture formation, and Sampson has diagrammatically figured the effect in this direction of those operations for the removal of pelvic tumors in which the blood-supply of a portion of the ureter has been

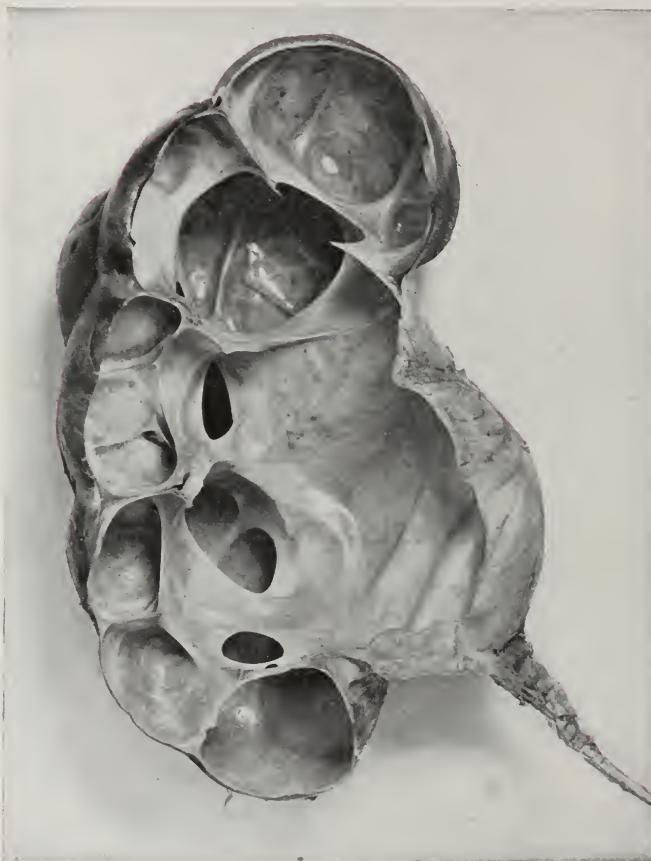


Fig. 232.—Hydronephrosis resulting from stricture at the uretero-pelvic junction. Extreme dilatation of the calyces.

disturbed. Necrosis with scarring, and even rupture of the ureteral wall after the distention has begun, may follow.

Renal calculi formed in the pelvis of the kidney, when small enough, pass through the ureter, causing intense pain, but, as is well known, there are normally several constrictions in the course of this tube, and the calculus may stick at one of these so as to cause complete or partial plugging. Higher in the neck of the ureter or in the pelvis itself the same thing may happen.

Renal calculi, formed as has been described above, present themselves in various forms and sizes, the larger ones being moulded into the calyces and about the papillæ so as to present a complete cast of the pelvis of the kidney, branching into each recess and extending in a pointed, curved projection down into the ureter (Fig. 233). Sometimes they are in several pieces, and the fragments may be fitted to one another as though articulated. At the other extreme we find small, loose, irregular calculi, sometimes no more bulky than coarse sand. It seems that unless they become impacted in the ureter these calculi cause no great distention of the pelvis. In children the common uric-acid infarcts already mentioned are often associated with concretions which may be partly embedded in the renal substance itself.

Finally there are some deformities of the pelvis, especially with relation to the insertion of the ureter, which can give rise to hydronephrosis, and which in turn are emphasized by it. These are especially the instances in which the ureter springs from a point high up in the pelvis



Fig. 233.—Renal calculus in pelvis forming a complete mould of all the calyces, and extending into the ureter.

and leaves it at an acute angle. There is then a valve-like arrangement, which is brought into play by any disarrangement of the kidney and completed by the distention of the pelvis. Sometimes the ureter divides before it reaches the hilum of the kidney, so that the pelvis is in several compartments with their corresponding calyces and papillæ. Then it is possible to have a partial hydronephrosis if only one of these branches is obstructed.

Geraghty and Frontz mention also a form of hydronephrosis which depends on the constriction of the ureter by an inflammatory process with scarring, which is likely to occur near the transition of the pelvis into the ureter. Hunner has also made a careful study of the various types of ureteritis with stricture and hydronephrosis, and finds them far commoner than was formerly suspected. We have recently met with such a case at autopsy which is illustrated in Fig. 232.

The fluid which accumulates is generally clear, and contains urea and other urinary constituents, although in unusual proportions. It has generally been looked upon as urine, but except perhaps in those cases in which the obstruction is intermittent, it will be seen, from the mode of development, that it must differ a good deal from normal urine. It often contains casts of the renal tubules and desquamated epithelium.

Cohnheim made the statement that only partial or intermittent obstruction is followed by great distention of the pelvis, while complete obstruction results in cessation of the flow of urine and atrophy of the kidney. In human beings this has the appearance of being true, for in cases of complete obstruction of the ureter one finds the kidney reduced to an insignificant, flattened, fibrous mass, in which hardly any well-ordered renal substance can be found (*cf.* Fig. 81). On the other hand, an intermittent or partial obstruction can cause the distention of the ureter and pelvis until a sac is formed which may occupy a great portion of the abdominal cavity. It has been shown recently by Ponfick and others that the absolute closure of the ureter is followed by such distention of the pelvis and the kidney as to reduce the kidney to a thin layer of firm fibroid tissue, although many recent investigators combat this idea vigorously. In the earlier stages the bulk and weight of the kidney substance, exclusive of the accumulated fluid, actually increase up to about thirty-six days after the ureteral ligation, after which they decrease steadily. In view of this we may easily conclude that the atrophic remnant which we find in human beings after the ureter has been plugged by a stone are the final results of a much longer period of obstruction than even the seven months through which Ponfick watched his experiments.

With the distention of the pelvis the calyces become widened and the papillæ flattened until in time they come to form only circular portions of the wall of the hemispherical calyces, the orifice being located only as a slight central elevation with radiating blood-vessels and tubular markings. Even more complete distortion occurs, and hardly any trace of the papilla is left—the whole kidney is reduced to a multilocular sac in which the partitions, as Ponfick points out, are held in place by the blood-vessels, whose course they indicate. The section shows that the pyramids lose their radiate appearance because the tubules come to lie parallel with the surface of the kidney (Fig. 234). The cortex becomes very thin, and loses its striations, which are obscured in the gray, scar-like tissue which takes their place. It is strange that sometimes this effect is very irregular, so that one finds patches of relatively thick renal cortex scattered in the otherwise thin wall of the sac. Possibly this is due to the unequal diminution in the blood-supply of various areas of the cortex, which comes through vessels which run in the partitions of the sac and may be exposed to different degrees of pressure.

Most observers agree that the secretory process ceases at a point before the fluid attains a pressure higher than that of blood. Ponfick describes the appearance of hyaline casts, of leucocytes, and especially of red blood-corpuscles, together with a coagulable fluid in the tubules and glomerular capsules. The epithelial cells, at first swollen, later become

flattened, and even the glomerular tufts may disappear, leaving spaces that look like tubules. There is apparently the formation of an actual exudate of inflammatory character in response to the destructive effect upon the cells. Associated with it comes a diffuse formation of abundant new connective tissue everywhere between the tubules and about the glomeruli. The end-result is that we have in an advanced case an extraordinary thinning out of the renal substance, which assumes a gray, uniform, translucent appearance, and an almost leathery consistence. In this the tubules are found lined by a uniform, flattened epithelium, and often interrupted by the collapse of their walls, so that spindle-shaped or even rounded portions remain, filled with hyaline casts. The glomeruli are obliterated and converted into fibrous nodules, or else surrounded by

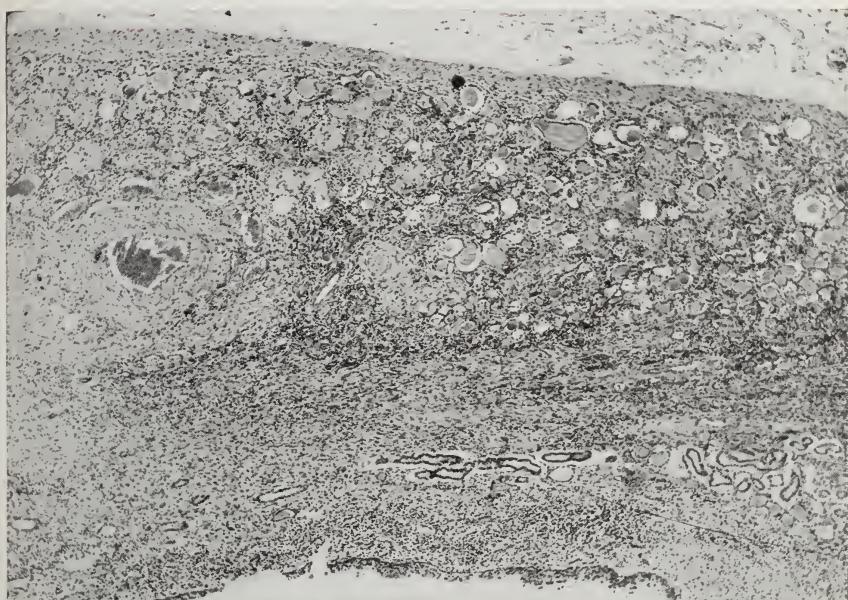


Fig. 234.—Hydronephrosis. Section shows the thinning and flattening of cortex and pyramid, with obliteration of glomeruli and tubules.

a thickened fibrous capsule, and everywhere the interstitial connective tissue is prominent not only through its actual increase, but because of the disappearance of many tubules. It will be seen that this process is, in nearly every respect, analogous to that which follows the ligation of the duct of such a gland as the pancreas.

Ascending Renal Infection.—In all forms of obstruction to the outflow of a secretion we have traced the liability of the tissues to infection, and the kidney is no exception to this rule. With the advent of virulent bacteria in an already formed hydronephrotic sac there arises an inflammation which is of a far more intense character than any which may have been associated with the mere mechanical obstruction, and when the sac is filled with a purulent fluid, we speak of the condition as *pyo-*

nephrosis. A similar condition, naturally with somewhat different course and clinical symptoms, may arise when the distending fluid is from the first infected and the inflammatory process is intense throughout. Thus, when there appears an infection about impacted renal calculi which may not in themselves have caused an effective obstruction, or when an ob-



Fig. 235.



Fig. 236.

Figs. 235 and 236.—Pyelonephritis—cases of prostatic obstruction with cystitis.

struction lower in the ureter or in the bladder or urethra causes the damming-up of urine which quickly becomes infected, we have a distension which is by no means so great, but in which the pelvic walls are injured by the bacteria and present a haemorrhagic, ulcerated, and purulent surface.

It is hard to draw a line between the cases in which the distention is predominant and those in which the inflammatory processes are more imposing. These latter, which are known under the name *pyelitis*, or more usually *pyelonephritis*, constitute a form of ascending suppurative nephritis which is most commonly associated with obstruction and stagnation of urine. But it must be borne in mind that, with very slight differences an inflammatory process in the kidney with suppuration and

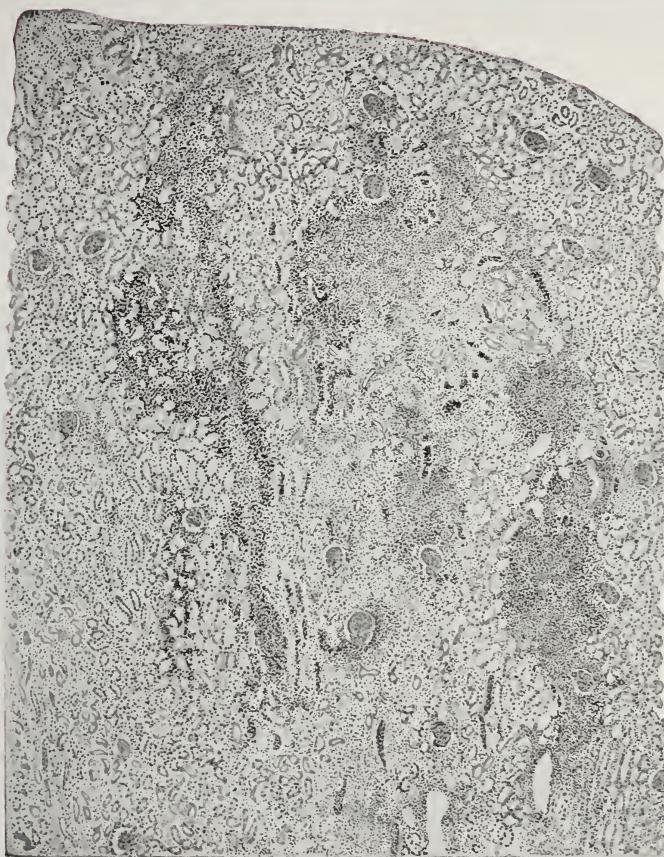


Fig. 237.—Pyelonephritis. There are beginning abscesses in the cortex, shown as areas of necrotic tubules with purulent exudate about them. Many of the tubules contained bacteria.

secondary inflammation of the pelvis may be caused by bacteria brought to the kidney through the blood-stream when there is no disease of the lower urinary tract at all. This can often be easily distinguished, and we shall speak of it elsewhere.

In all these cases in which infection of the kidney is associated with obstruction and infection of the urinary passages, there appear abscesses in the substance of the kidney itself, in addition to the acute, oftentimes very intense, inflammation of the mucosa of the pelvis. These are usu-

ally situated chiefly in the cortex, and are sometimes very small, but generally conglomerated, so that they reach the size of a pea and bulge on the surface. If one tears off the capsule of the kidney, many of them are broken open and exude a greenish-yellow pus. On section, the tissue around them is grayish red and swollen, and has lost the distinctness of its markings. Often, but not always, there are grayish-yellow, opaque streaks running down through the pyramid toward the papilla, which are produced by extensions of the abscesses along the conducting tubules (Figs. 235, 236, 237).

Active discussion has raged for a long time as to the paths followed by bacteria, which, from an infected bladder, arrive at the production of more or less isolated abscesses in the cortex of the kidney, and many views have been proposed. It has been stated that the organisms get into the blood-stream from the bladder, and lodge finally in the kidney, which is rendered susceptible by the obstruction. Others think they pass along the lymphatics of the ureter or by the venous anastomoses between the vessels of the pelvic organs, ureter, and kidney. Neither

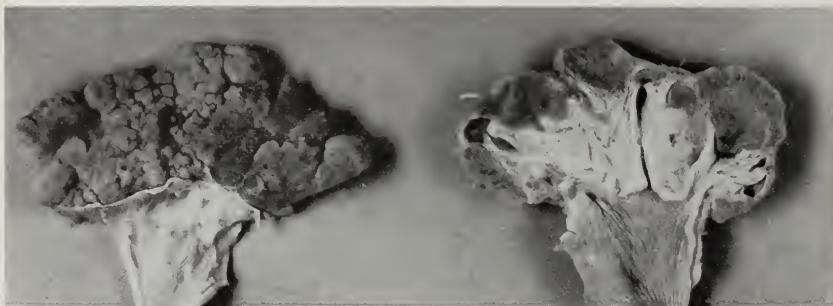


Fig. 238.—Chronic pyelonephritis in a child with extreme scarring.

of these last views seems to me based on probability, because they involve retrograde embolism, which is not to be lightly called to our aid.

The more common view is that the bacteria pass up the lumen of the ureter to the pelvis, and thence into the kidney. They cannot easily ascend the ureter when it is open and flushed by the normal stream of urine, but if it is obstructed and occupied by a nearly stagnant column of urine, it is easy to believe that bacteria may spread to the kidney. This is especially true if any inflammation of the ureteral wall in its intravesical part has rendered it rigid, and thus made useless the guard at the ureteral opening. Having attained the pelvis and produced a pyelitis, it remains to explain their entrance into the kidney. Orth looks askance at the glibly expressed belief that they wander up the tubules, but Schmidt and Aschoff have found bacteria in the tubules in animals in which they have experimentally obstructed and infected the ureters, and adopt this idea. Without it we must have recourse to the blood-vessels, of which, of course, only the arteries are available, or to the lymphatics. Muller thinks he can prove the lymphatic transmission by finding the tubules attacked and perforated on one side by exudate, which

also fills the lymphatics. It is difficult, however, when the inflammation has proceeded to such a degree, to say which way it is working, and the findings of Schmidt and Aschoff, which show that the bacteria can enter the tubules, seem, after all, most convincing.

Chronic forms of renal infection occur especially in children and young people and lead to extreme destruction and scarring of the kidney with thickening of the walls of the pelvis (Fig. 238). Such cases have been studied by Longeope and others and it is obvious that such reduction of the kidney substance must cause great disturbances in metabolism.

LITERATURE

- David, Vernon: Surg., Gyn., and Obst., 1918, xxvi, 159.
Geraghty and Frontz: Jour. Urology, 1918, ii, 161.
Hunner: Johns Hopkins Hosp. Bull., 1918, xxix, 1.
Jores: Ergeb. d. allg. Path., 1907, xi₂, 146.
Longcope and Winkenwerder: Johns Hopkins Hosp. Bull., 1933, liii, 255.
Orth: Lehrb. d. spez. Path., 1893, ii, 59.
Ponfick: Ziegler's Beiträge, 1910, xlix, 127; 1911, I, 1.
Sampson: Johns Hopkins Hosp. Bull., 1903, xiv, 334.
Schmidt and Aschoff: Pyelonephritis, Jena, 1893.

CHAPTER XXIII

TYPES OF INJURY—OBSTRUCTION (Continued).—GENERAL DISTURBANCES OF CIRCULATION

Mechanism of circulatory organs, arteries, capillaries, arterial hypertension. Pathological obstructions. Pericardial and pleural effusions. Emphysema. Chemical influences. Arterial and myocardial disease. Coronary obstruction. Valvular lesions and their effects. Cardiac hypertrophy and dilatation. Decompensation. Disturbances in conduction of impulses in the heart. Chronic passive congestion.

Mechanism of Circulatory Organs.—Reflection upon the general mechanism of the circulation of the blood will give one an idea of the extraordinary number of things that can fail in playing their proper part and upset the smooth working of the whole. Incidentally, it gives, too, a sense of wonder that a machine of such marvelous complexity should work at all, and not be constantly interrupted or overtaxed by the variable tasks laid upon it and the difficulties thrown in its way. It is found, however, that not only does it keep up a definite standard output of work day and night, but it will do this in spite of the most unreasonable obstacles.

The Heart.—The heart, as a bulbous muscular pump, must keep the blood moving in two circles, one through the lungs, the other through the rest of the body, for which reason it is in two halves; and it must do this promptly, having a new supply of blood ready when it has discharged one, wherefore it has its auricles. There are wonderfully perfect valves to maintain the direction, and the left side of the heart is more powerful than the right, because it drives the blood into a larger field and against greater resistance. Still, with these unequal tasks, which may vary between two beats, one side of the heart may not eject more or less blood than the other. If the right ventricle throws out so much as one drop more than the left in each beat, the lungs would be overdistended and burst within a few minutes. This perfect coördination between the two sides is even more remarkable when we think that the ventricles are formed essentially from two coils of one long muscle band, the tendinous ends of which are attached to the valves as the chordæ tendineæ, and that the tasks of the two sides are not only different, but vary differently. To be effective, the auricle must empty itself into the ventricle at the precise moment required, and the ventricle must be ready for its new load; to expel the blood with adequate force, the walls of these chambers must contract not only rhythmically, but uniformly, and to insure this rhythmic and perfect contraction there are special telegraphic connections with central stations at at least two places, from which controlling impulses are sent out—one sets the pace, the other relays the message.

These are the constituents of the remarkable conduction system discovered by His, Keith and Flack, and Tawara, which consists essentially in the sino-auricular node found by Keith and Flack in the angle between the entrance of superior and inferior vena cava into the auricle, and the node of Tawara which lies at the lower margin of the auricle near the septum membranaceum, and gives off the branching bundle of His which spreads to the Purkinje cells in the inner layers of both ventricles. From the sino-auricular node delicate fibres spread toward the Tawara node in the auricle wall but the connection is not so obvious as it might be. The sympathetic and parasympathetic system influence this mechanism from without and can modify the rate. Still, an isolated heart will beat with normal rhythm but may, on the other hand, be affected by the chemical composition of the circulating fluid.

LITERATURE

His, W., Jr.: Arbeiten aus der Med. Klinik zu Leipzig, 1893, 14-49.

Keith and Flack: Jour. Anat. and Physiol., 1907, xli, 172.

Lewis, Oppenheimer and Oppenheimer: Heart, 1910, ii, 147.

Tawara: Reizleitungssystem des Saugetierherzens, Jena, 1906.

The Blood-vessels.—The heart is aided in its work by the arteries, and to a less extent by the veins. They are not merely elastic tubes, in places, in the veins at least, furnished with valves, but active contractile organs, which not only drive on the blood by a sort of peristaltic contraction, but control the head of pressure with which the heart works, by narrowing or widening their own calibre. Were it not for this healthy opposition to the push of the heart, there would arise one of the vicious circles that may prove disastrous to the whole circulation; not only would the arterial blood escape into the distensible veins through the capillaries, but the back pressure into the coronaries, upon which the nutrition of the heart depends, being gone, the heart would fail at once. The fact that this controlling contraction and relaxation of the arterioles occurs locally in different regions of very different extent explains the possibility of rapid variations in pressure, which must be compensated either by extra effort of the heart or by other changes in calibre in the vessels.

Recent work of Krogh, with his students, Vimtrup, Carrier, and many others, and of Hooker and others in this country, has shed much light upon the activities of the capillaries which now assume an unsuspected importance. These channels vary greatly in number and form in different tissues, and their walls are not simply endothelial, but are given an effective contractility by the so-called Rouget's cells which clasp about them. Their contraction and expansion is independent of that of the arterioles and exhibited locally, so that some are open while others are closed. The amount of blood in such a tissue as the skin depends largely upon the content of its capillaries, while its temperature depends upon the rate of circulation through the arterioles. If the capillaries in a large region of muscle were dilated to their maximum capacity they could receive an enormously increased amount of blood—so great an amount as to leave the heart and large arteries without sufficient fluid to keep up the normal circulation—and this is the current explanation of shock. On the other hand, it seems evident that they may be so narrowed as to offer serious resistance to the flow of blood—a resistance which has usually been ascribed to the

contracted arterioles alone. The capillaries are made to contract or dilate by direct stimuli or through their sympathetic innervation, sometimes by reflexes from the spinal cord, at other times by axone reflexes which are those transferred from a sensory to vasomotor fibre without passing up to the central nervous system. But there is also the possibility of a chemical control by such substances as the products of the adrenal and pituitary glands, and it is well known from the researches of Dale that histamine causes their dilatation while it affects the arterioles in the opposite way.

Control of Blood-vessels.—The heart and blood-vessels then work in coöperation almost as intimate as that of the two sides of the heart; but it is agreed that the maintenance of the normal height of the blood pressure is not dependent upon the rate of the heart beat nor on the volume of its output except, of course, when there are very gross disturbances in its action, such as would result from its rupture or occlusion of the coronaries or extreme disablement through narrowing of its valves. Instead, the pressure is maintained as in the case of a fire engine by the appropriate narrowing of the outlet, that is the peripheral channels through which the blood is poured into the capillaries and thus into the veins. The contraction and dilatation of the arterioles is under the influence of a part of the nervous system, but even yet the entire mechanism is not perfectly understood. It is generally agreed that the impulse to contraction comes by way of the sympathetic system. This has been traced to its origin in the paraventricular nuclei in the posterior and lateral walls of the third ventricle from which connections extend to other centres in the medulla and in the spinal cord, especially from the eighth cervical to the sacral region. From these the connections to the paravertebral chains of ganglia, the splanchnic nerves, etc., are well known. It is true that the paraventricular nuclei receive afferent fibres from the supra-optic and tuberal nuclei and from the thalamus but direct stimulation causes great rise in blood-pressure, while destruction of these nuclei produces low blood-pressure and inactivity. They, therefore, are known to act powerfully on the sympathetic and also stir the outpouring of adrenalin from the medulla of the adrenals.

On the other hand, the supra-optic and especially the tuberal nuclei more anteriorly placed in the third ventricle are connected with the parasympathetic system and send out such impulses as are carried by the vagus to the heart and intestinal tract. Direct stimulation of the tuberal nuclei has been shown by Beattie to cause currents in the vagus which slow the heart rate, dilate the vessels of the skin with sweating, and increase the peristalsis of the intestinal tract with hyperæmia and increased acid gastric secretion.

Beside these mechanisms there are, in the wall of the aortic arch and especially in the dilatation of the carotid known as the carotid sinus, peculiar nervous mechanisms discovered by Hering and studied minutely since by Heymans and de Castro which exert a strong influence upon the calibre of the arterioles and hence upon the blood-pressure through impulses sent to the vasomotor centres in the brain by way of nerves which accompany the glossopharyngeal nerve. The action of the carotid sinus is that of a depressor so that it appears that excessive pressure within the sinus is responded to by such impulses as will reduce that

pressure. This nervous mechanism is regarded as a sort of rein on the vasopressor activities.

In attempting to explain variations in blood pressure, then, many things must be kept in mind. The activity of the nervous system must be in response to physiological or pathological processes and it is clear that it is essentially reflex and primarily adapted to the needs of the body—thus a widening of the vascular bed and increased blood flow to the alimentary tract during digestion must be such a reflex, although perhaps local influences can overcome the central reflexes. There seems to be relatively slight tonus in the cerebral vessels but it has been shown that cerebral activity involves very little metabolic change. Chemical substances in the circulation have hardly been shown to influence the blood-pressure except in the case of such secretions as adrenalin and pitressin. Cushing showed that intraventricular injection of pitressin from the posterior hypophysis stirs a high blood pressure at once, and there is much evidence of the part played by the neurogenic outpouring of adrenalin. Since hypertension or high blood pressure has long been associated with chronic nephritis, a pressor substance has been sought in the blood of such patients but although a few have obtained positive results, others have shown that normal blood contains quite as powerful pressor principles.

The mechanism of the hypertension associated with kidney disease is not yet known. Of course, there has been prolonged argument as to whether the destruction of renal tissue is the cause of the hypertension or actually the result of hypertension produced in some other way. Since the hypertension is due to the narrowing of the arterioles throughout the body, much attention has been devoted to the arteriolosclerotic narrowing of the vessels of the kidney. Again, the question arises whether this is cause or result of the kidney's disease and, therefore, whether possibly the effect of the arteriolosclerosis is to produce the hypertension.

Our own feeling is that since, in spite of the conspicuous changes in the hyaline arteriolar walls in the kidney and in the spleen, margins of the adrenals and pancreas, it is hard to find any other arterioles anywhere in the body showing these changes, it is difficult to believe that these local narrowings cause the general hypertension when there is such abundant opportunity for collateral circulation. It would seem preferable to believe that some cause—as yet unknown—operates to produce hypertension, that the violent contraction of the arterioles underlies, in places, the hyaline changes which render the narrowing permanent and that this is associated with the alterations in the kidney. This is suggested by the cases of so-called essential or idiopathic hypertension in which no such anatomical changes are found but only a greatly hypertrophied heart from the effort necessary to drive the blood through such contracted arterioles. At this point it seems most important to call attention to the fact that under ether anesthesia such high blood pressure falls to normal and even in sleep it is lowered.

Other factors such as excess of carbon dioxide in the blood, especially with lack of oxygen, causes heightening of blood pressure. The carotid sinuses are sensitive also to such effects.

Much attention has been devoted recently to endocrine effects and perhaps especially to the action of adrenalin. The efferent influences from the central nervous system are partly neurovascular, partly indirect by stirring the adrenals. Kylin is especially interested in this possible explanation and directs attention to the effect of the hypophysis contrasting the condition in Simmond's disease where there is atrophy of the hypophysis, low pressure, hypoglycaemia, etc., with that in cases of so-called essential hypertension. He refers to the Cushing syndrome in which with hypophyseal tumor there is hypertension. Orias, in experiments on toads, finds that this is produced by an extract of the intermediate lobe of the hypophysis.

On the whole it appears that there is yet much to be learned about this complex situation but at least the governing influences of certain nervous mechanisms seem well established, although the influences that bear upon them are not so clear.

LITERATURE

- Beattie: Science, 1932, lxxv.
Fishberg: Hypertension and Nephritis. Phila., 1931.
Hering: Pflüger's Arch., 1924, ccvi, 721; Dtsch. Med. Woch., 1931, lvii, 528.
Heymans: Bull. acad. roy. de med. de Belgique, 1934, xiv, 594. Le Sinus Carotidien. Univ. de Gand, 1929.
Kahler: Ergebni. d. inn. Med. u. Kinderheilk., 1924, xxv, 265.
Kylin: Ztschr. f. Kreislaufforsch., 1935, xxviii, 1.
Orias: Compt. rendu Soc. biol., 1934, cxvi, 894.
Raab: Ergebni. d. inn. Med. u. Kinderheilk., 1934, xlvi, 452.
Rathery: Bul. et mém. Soc. méd. d. hôp. de Paris, 1934, I, 1510.
Weiss, Soma: Ann. Int. Med., 1934, viii, 296.

Other Influences.—There are other factors of a more mechanical nature which have a very great influence upon the circulation, namely, respiration, the condition of the abdominal contents, posture and muscular activity, and many others. Respiration aids the flow of venous blood to the heart by producing a partial vacuum in the thorax during inspiration, and at the same moment increasing the intra-abdominal pressure. Most of this is done by the diaphragm, which both sucks and presses the blood out of the abdominal veins. Enteroptosis or sagging of the abdominal viscera, which pulls down the diaphragm and diminishes its excursion, annuls to a great extent this beneficial action. Great accumulations of fluid or large tumors in the abdomen bring about the same result in a different way by pressing the diaphragm up and immobilizing it. The circulation is made easier by the recumbent posture —more difficult by the erect, but, of course, this is not felt much by the normal heart. Violent muscular exercise elicits greater activity of the heart, both to aérate the blood more rapidly and to bring it in increased quantity to the active muscles. The heart may be overtaxed by too great and prolonged effort, so that it dilates and the man falls in a faint or dies. This is really an example of the response of the heart to demands which arise from an enormously accelerated metabolism.

From all this it is seen that in the circle through which the blood is forced the conditions in each part are influenced by those in the pre-

ceding and succeeding parts. Each portion of the circle is governed by regulating mechanisms, and instantly adapts itself to new conditions, whether these are produced by changes within the stream-bed or by influences from outside, and this very adaptation, like the original change, is felt not only just in front of or just behind that point, but all around the circle. All these regulatory mechanisms act together to maintain the arterial blood-pressure at a fairly definite standard, which reaches 110 to 150 mm. of mercury during systole in the larger arteries, falling with each pulsation to 60 to 80 mm. in diastole. As the blood advances into the arterioles and capillaries, the pressure sinks and the differences between systolic and diastolic pressure disappear, so that in the veins the stream is constant, and at a pressure which still decreases toward the heart. In the pulmonary circulation its pressure is very much lower and the pulsatory variations less, but it passes with greater velocity through those capillaries than through the capillaries of the systemic organs. The importance of the maintenance of this pressure and the corresponding rapid exchange of blood are most evident in the coronary circulation of the heart and in the brain. The nice balance of this mechanism is maintained with great tenacity.

LITERATURE

- Bayliss: Vasomotor System, Longmans, Green, 1923.
Evans, C. Lovatt: Recent Advances in Physiology, Churchill, London, 1926.
Hooker: Physiological Reviews, 1921, i, 112.
Krogh: Anatomy and Physiology of Capillaries, Yale Press, 1922.
Vimtrup: Ztschr. f. Anat. u. Entwickl., 1922, lxv, 150; 1923, lxviii, 469.

PATHOLOGICAL OBSTRUCTIONS

Pericardial Effusion.—Mechanical influences quite outside the circulation itself can have such effects. The accumulation of fluid in the pericardial cavity may go on gradually until the sac is enormously distended, but if it comes suddenly, as in the case of a haemorrhage from the heart, or when one injects it experimentally in an animal, the pericardium has no time to stretch. Then the heart is greatly embarrassed because it cannot expand to allow the entrance of blood from the veins. Great distention of the veins occurs, with heightening of the blood-pressure there, while the amount of blood thrown into the aorta becomes so small that even the action of the vasoconstrictors fails to keep up the blood-pressure, little blood goes into the coronary arteries, and the heart gives up its beating. Quick removal of the fluid from the pericardium may restore the normal conditions in time to start the heart once more. Moderate collections of fluid (hydropericardium or pericarditis) may cause only a tolerable overfilling of the veins and decrease in the arterial blood flow.

Intrapleural and Pulmonary Obstruction.—Effusions of fluid into the pleura compressing the lung (*cf.* Fig. 102), tumors in the pleura, narrowing and distortion of the thorax by deformities, such as curvature of the spine (skoliosis, kyphosis, etc.), and destructive changes in the lungs themselves have a similar effect in obstructing the circulation, but act at a different point. Now the difficulty which still affects the

whole blood-stream lies in forcing the blood through the compressed or reduced pulmonary stream-bed, and the burden is put upon the right ventricle. It rises at once to its increased task, and may be able to perform it by drawing on its reserve power. Often it can go on like this, forcing the obstacle and maintaining the normal circulation, in time growing in thickness and strength of wall through the increased exercise. But if it fails only partially, the blood accumulates in the veins and in the auricle, and reaches the aorta in diminished amount.

Emphysema.—One of the common obstructions acting at this point is emphysema of the lungs (see p. 420), in which the rarefaction of the lung tissue obliterates much of the stream-bed in the lung. Other changes, which, by cramping the thoracic organs or obstructing the pulmonary blood-flow, produce the same effect, will be referred to later and easily understood. This is the narrow pass for the whole circulation. Afterward in the systemic circle nothing can so readily obstruct the whole blood-flow, since there are always roundabout ways, and the closure even of large arterial trunks has practically no effect upon the blood-pressure. Even the whole aorta below the renal arteries may be ligated, with only a trifling rise in blood-pressure. Ligation of the renal arteries adds little to this; that of the splanchnic arteries has much more effect, but even this (Longeope and McClintock) is a matter of only a few millimetres of mercury. Such extreme obstructions are, of course, rare and of little importance, as far as the circulatory apparatus goes; their importance relates rather to the nutrition of the tissues which those vessels should supply.

Toxic Influences.—Chemical influences have great importance also, in so far as they affect the nervous control of the heart or arteries (atropine, adrenaline, etc.), or the muscular walls of these structures (barium, ergot, etc.), but their effects are transient and need not be considered further here. The poisons at work in many infections act upon the heart to injure its muscle and weaken its power, or, as in the case of diphtheria, affect also the vasomotors, paralyzing their control over the vessels and thus allowing a fall in blood-pressure which may be fatal in withdrawing blood from the coronary circulation. This constitutes the underlying principle of the shock in which patients die in such intoxications.

Anatomical Changes in the Blood-vascular Apparatus.—Changes in the circulatory apparatus itself are productive of great changes in the blood-flow, nearly always in the sense of an obstruction, or diminution in the efficiency of its propulsive power. These commonly affect the elasticity and contractility of the arterial walls, the muscular power of the heart-walls, the efficiency of the valves, and the mechanism which maintains the rhythm of the heart, and may be considered in this order.

THE EFFECT OF ARTERIAL DISEASE

Disease of the walls of the larger arteries resulting in their loss of elasticity and partial rigidity is extremely common, especially in older people but since these larger arteries serve chiefly as the broad channels for the passage of blood and in this diseased condition lose only their

elasticity and muscular contractility, it seems that the heart is not much burdened by their failure in the slight aid they ordinarily give. This opinion is not based on any exact estimation of the difference between the normal and sclerotic aorta, carotids, femorals, etc., but rather upon the fact that the heart seems unchanged in spite of extreme sclerosis of these larger trunks. Hasenfeld, Longcope, and others feel that rigidity and narrowing of the splanchnic vessels has more effect than that of other regions.

But when we approach the smaller, more muscular, branches and especially the minute arterioles, the anatomical changes in the walls, as well as the extreme contractility, play the really important part in the alterations in blood-pressure. Whether the arterioles, and capillaries, too, for that matter, are kept in a state of contraction by nervous impulses, or are actually narrowed by the changes in their walls, described on page 337, the effect is to offer resistance to the passage of the blood and to require a higher blood-pressure. This extremely common condition, so often associated with advanced changes in the kidneys, results in great hypertrophy of the heart which is especially striking in the left ventricle. Such hypertension may last for months or years and ends in such accidents as cerebral hemorrhage or the final failure of the heart.

THE EFFECT OF MYOCARDIAL DISEASE

The arrangement of the musculature of the heart-walls (J. B. MacCallum, Mall) is such as to control with the greatest completeness the propulsion of the blood—not only does it obliterate the cavity of the ventricles, but by the contraction of the papillary muscles it insures the proper tension and perfect closure of the auriculoventricular valves. Further, special subdivisions of the muscle support the semilunar valves, and maintain their closure in such a way that even with slight imperfections of the valves leakage is much diminished by this muscular action. The heart muscle has always been regarded as a network of cells attached to one another along transverse cement lines, but in recent years there has been a tendency to look upon it as a sort of syncytium without cellular limits, the cement lines being thought to be the product of physical influences which act more intensely with the advance of age (Cohn, Aschoff, and Tawara). The muscle fibrils, with their sarcoplasmic discs, are arranged in each fibre around a central space, in which lies the nucleus surrounded by undifferentiated protoplasm. It is in this space at the poles of the nucleus that a yellowish pigment begins to accumulate in early years of life, and increases with the advance of age. With great wasting of the heart muscle this pigment may become so abundant as to give a chestnut-brown color to the whole heart (brown atrophy). As indicated elsewhere, it is one of the lipochrome pigments and takes a reddish stain with Sudan. The specific stimulus-conducting system of fibres will be described later.

Myocardial Injuries.—Myocarditis.—Degenerative and destructive changes occur in the heart muscle in the course of various infections, intoxications, and nutritive disturbances, but are not specially characteristic of any. Fat accumulates in the form of fine droplets arranged in

the sarcoplasmic discs, and therefore often in longitudinal lines. This fat is, as a rule, not uniformly distributed, but is very abundant in certain little groups of fibres, while almost absent in the neighboring ones. On the whole, it is far more abundant in the inner layers of the heart-wall than the outer. This results in the peculiar mottling with minute, opaque, yellow patches, most commonly seen in the wall of the right ventricle below the orifice of the pulmonary artery, and in the papillary muscles of the left ventricle, although it may be spread all over the interior and deep in the substance of both ventricles. This is the so-called tigering or faded-leaf appearance (*cf.* Figs. 39 and 40). Ribbert thinks that this peculiar distribution is due to unequal nutrition in the regions of different minute branches of the coronary arteries. It is found most often in extreme and long-standing anaemias, protracted febrile states, and in chronic diseases, such as nephritis, associated with anaemia. The presence of the fat seems to have very little detrimental effect upon the function of the heart, or perhaps it should be said that the diseased condition of the muscle which leads to the retention of the fat does not greatly impair its activity. Dr. Welch, in studying animals kept for a long time at a fever heat, found abundant deposition of fat in their hearts, but no special functional alteration. In the same way we find a certain cloudiness of the heart muscle in such infections as typhoid, but although we may name this parenchymatous degeneration, we cannot find that it indicates much harm to the heart.

On the other hand, in a few very acute and intense infections or toxic processes, such as diphtheria and scarlet fever, there may be actual necrosis or hyaline degeneration of fibres here and there, much like that seen in the rectus abdominis in typhoid fever, and these or even slighter lesions, not easily seen as changes in the muscle, may in these diseases give rise to a wide-spread acute inflammatory reaction with focal accumulations of leucocytes, oedema, and fibrinous coagula. It is impossible that these things, involving as they do the loss of many of the muscle-fibres, should not weaken the heart. Such is its reserve power, however, that it generally continues to beat well enough in spite of them. They have been regarded by many authors (Stejskal and others) as the cause of the sudden collapse and death at the height of diphtheria (and also in peritonitis and other septic infections), but Pässler and Romberg, MacCallum, and others have shown that deaths of this sort are due rather to failure of the vasomotor control of the arteries (or possibly to the effect of Dale's capillary poisons), which allows the blood-pressure to fall and the whole heart to suffer acutely from lack of nutrition. Abscesses in the myocardium in the course of general septic infections or resulting from embolism of the coronary branches by infected fragments of endocardial vegetations (septic infarcts), and extensions into the myocardium from endocardial vegetations, produce similar effects, but they will be considered elsewhere.

Calcified foci are sometimes found which may be the outcome of the healing of such necroses. So, too, it must be admitted that scar tissue of no specific character may remain as the result of their healing, and that, therefore, these lesions may give one explanation of the origin of the so-

called fibrous myocarditis. That there are other changes potent in bringing about this scarring of the heart muscle we shall see.

Tubercles such as to cause destruction of the myocardium occur rarely, although they are sometimes found in the endocardium (Baker). So, too, syphilitic lesions of caseous or gummatous character are very rare but may cause great disturbance, especially by involving the conduction bundles. On the other hand, the occurrence of a widespread lymphocytic infiltration later with scarring in patients with known syphilis, accounts for the failure of the myocardium with decompensation and death. This has been recognized as syphilitic by several authors, although no spirochaetes have been found, and it seems entirely probable that it is so. After acute articular rheumatism, the aetiology of which is still uncertain, there appear, as Aschoff and others have shown, many minute nodules scattered through the heart wall, especially in relation with small branches of the coronary artery. These are accumulations of wandering cells evidently in response to the invasion of the infective agent (Fig. 445), and there is associated with them, as a rule, an intense inflammation of the tissues of the auricular wall, the valves, and of the pericardium. Such hearts are nearly always hypertrophied and finally show evidence of decompensation and failure.

Affections of the coronary arteries are particularly important in producing changes in the heart muscle. In some cases fragments of the thrombotic vegetations upon the heart valves may be thrown as emboli into these vessels, suddenly obstructing a branch of the whole artery. In others arteriosclerotic thickening of the vessel walls gradually leads to narrowing of the lumen, which may be extreme, or which may be quickly completed by the formation of a thrombus upon the degenerated plaque, obstructing the flow of blood altogether. Any of these modes of obstruction is effective in shutting off the blood-supply from a certain part of the heart wall because, although Spalteholz has shown clearly by injections that there are rather numerous anastomoses between the coronary arteries, these are insufficient to maintain the enormous supply of rapidly moving blood which the heart muscle needs. A less active organ might find it sufficient, but in the case of the heart wall a part rather less in extent than the region supplied by the obstructed artery dies. The dead area promptly assumes the character of an anaemic infarction, and may at times occupy large parts of the walls of both ventricles, together with part of the interventricular septum. Experimental occlusion of various branches of the coronary arteries shows a variable result; often the heart stops beating at once, especially in the case of the anterior descending branch of the left artery, but in other cases, or in an animal of another kind, it may not. That human beings can often withstand extensive occlusion of the coronary arteries is familiar to every one from autopsy experience, for it is not uncommon to find large infarctions, revealed only by death from their rupture or from some other cause. Indeed, many of these heal completely into a rather thin fibrous scar, which replaces the heart wall and is lined with thrombi (Figs. 239, 240). Frequently the scarred area is bulged out into an aneurysmal sac..

The extent and position of such scars corresponds naturally with the distribution of the obstructed coronary artery. Occlusion of the anterior descending branch of the left coronary produces a scar in the anterior half of the septum and in the wall of the anterior part of the left ventricle extending toward the apex. This scar may even be exposed in the anterior part of the right ventricle. Occlusion of the right coronary produces a scar, hollowed out and depressed, in the posterior half of the interventricular septum behind the papillary muscles of the mitral, which are themselves generally involved; the scar also occupies



Fig. 239.—Occlusion of left coronary artery producing necrosis and scarring in a characteristic position.

the posterior portion of the wall of the left ventricle. The position of other scars can be calculated from the distribution of the occluded coronary branches, but these are the most common (Figs. 239, 240).

The effect of such obstructions when they concern the smaller branches is to produce little infarcts, which can be seen and felt upon the surface or in the interior of the heart as inelastic, hard, yellow, opaque masses with a halo of deep red. More common still is the discovery of various stages in the healing and scarring of such infarcts. But from finding scars in the heart wall one cannot be sure that in-

farests preëxisted—indeed, many of these scars seem to have been gradually formed by the wasting away of undernourished heart muscle-fibres and their replacement by fibrous tissue, especially in cases where no obvious obstruction or extreme narrowing of the vessels can be found. And, after all, in that stage one cannot feel sure that they have not arisen through the healing of focal areas of toxic or infectious injury, which, after passing through a stage of inflammatory reaction, have ended in scars. / Indeed, it has been suggested by R. Keith that the extensive scars and aneurysmal dilatations of the ventricular walls are the end-results of a tertiary syphilitic process with gumma formation.



Fig. 240.—Occlusion of right coronary, scarring of heart wall and papillary muscles in its area of distribution. Thrombus formation.

and he was able to collect a very complete series of hearts showing the most gradual transitions from fresh gummata through all stages of healing to the well-developed aneurysmal sac. While this is not proof, the lack of marked sclerotic changes in the coronaries in some of these cases and the frequency of syphilitic lesions in other parts of the circulatory apparatus make the idea seem very plausible. Warthin has ascribed much myocardial scarring to syphilis, but it seems to us that a better explanation rests on the sclerosis of the coronary arteries. It is true that in syphilitic aortitis the orifices of the coronaries are often greatly narrowed, but the effect of this is doubtful.

Thus, although from the presence of fresher stages in the form of

infarcts it is sometimes possible to feel certain that the scars are due to embolic or arteriosclerotic and thrombotic occlusion of the coronary vessels, it is by no means always so. The fresher of these scars can often be felt on the surface of the heart as soft, depressed areas, which on section look gelatinous or spongy, and are grayish red and semi-translucent (Fig. 241). They are composed of a loose, soft granulation tissue, very rich in small blood-vessels, which have doubtless grown in from neighboring vascular areas. The older ones are dense, shining,

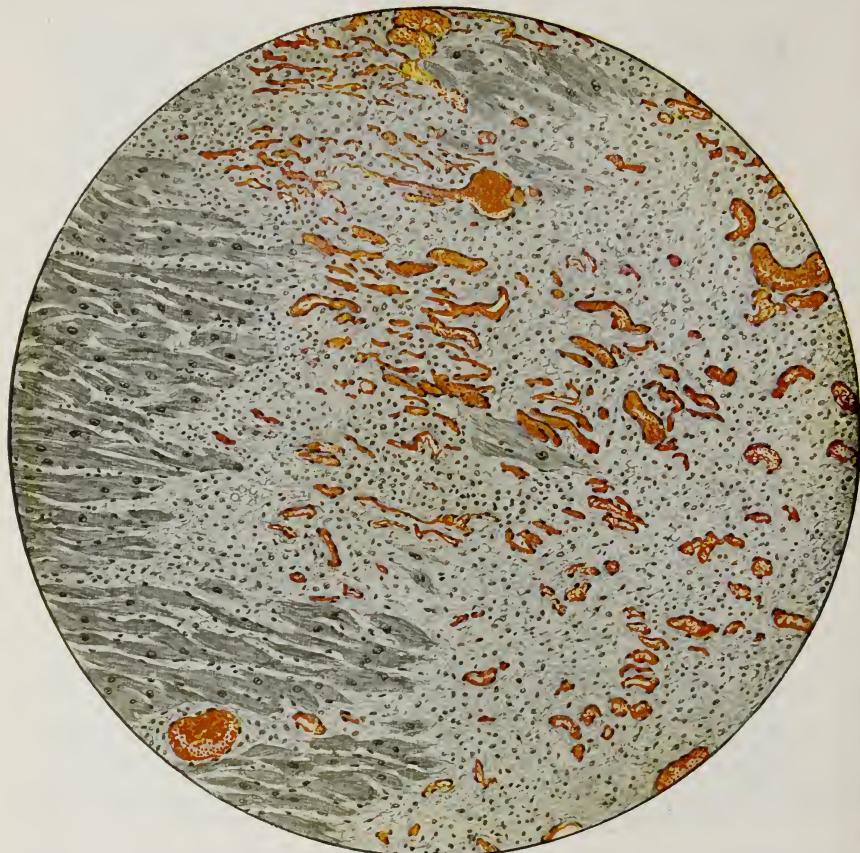


Fig. 241.—Vascular soft scar in the heart wall. This is an early stage in the replacement of dead heart muscle by scar tissue.

tendon-like, pearly white patches, sometimes very small and finely distributed, sometimes so large as to occupy much of the thickness of the wall (Fig. 242). They are often indefinite in outline and radiate into the neighboring tissue. Under the microscope they are formed of compact fibrous tissue poor in blood-vessels, but sometimes pigmented. Around their margins the muscle-fibres are frayed out, often reduced to pigmented strands (J. B. MacCallum), or swollen, with very much enlarged and deeply staining nuclei. Whenever any of these scars

reaches the endocardial lining of the heart, it is covered by thrombi which doubtless began to be formed in earlier stages, when injured heart tissue was exposed to the passing blood. One may not say that all thrombi formed on the lining of the heart overlie such definite areas of destruction of the heart wall, but nearly always, on cutting through the base of a globular intertrabecular thrombus, there is found a superficial scar. As mentioned above, it is at the apex of the heart that the conversion of the whole wall into scar tissue, thickly lined with thrombus material, is most common.



Fig. 242.—Old scars in the heart wall (chronic fibrous myocarditis).

There is much dispute as to the effect of these scars, or rather of the injuries which give them origin, upon the muscular power of the heart. Unquestionably the destruction of heart muscle and its replacement by rigid scar tissue must deprive the heart of some of its strength, but such is the phenomenal reserve power of this organ that a great deal may be destroyed before the circulation is impaired. In a dog one may inject strong alcohol with a hypodermic syringe into the muscle of the heart wall, so as to coagulate instantly a patch of the muscle; the slight fall of pressure is almost instantly made up, and this may be repeated a dozen times until almost all the wall of the ventricle is turned

into a hard, dead white mass before the circulation finally begins to fail. Aschoff and Tawara lay little stress on such scarring of the heart as a cause of the final breakdown of the circulation, and most clinical writers also agree that even extreme degrees of fibrous alteration may exist for a long time without giving rise to any symptoms. Irregular, feeble, slow pulse and dyspnoea are generally given as the symptoms, but these are not particularly distinctive. Whether the conversion of a part of the heart muscle into scar tissue is followed by hypertrophy of the rest of the muscle, so as to enlarge the whole heart, is a question difficult to answer because the condition seldom occurs without other

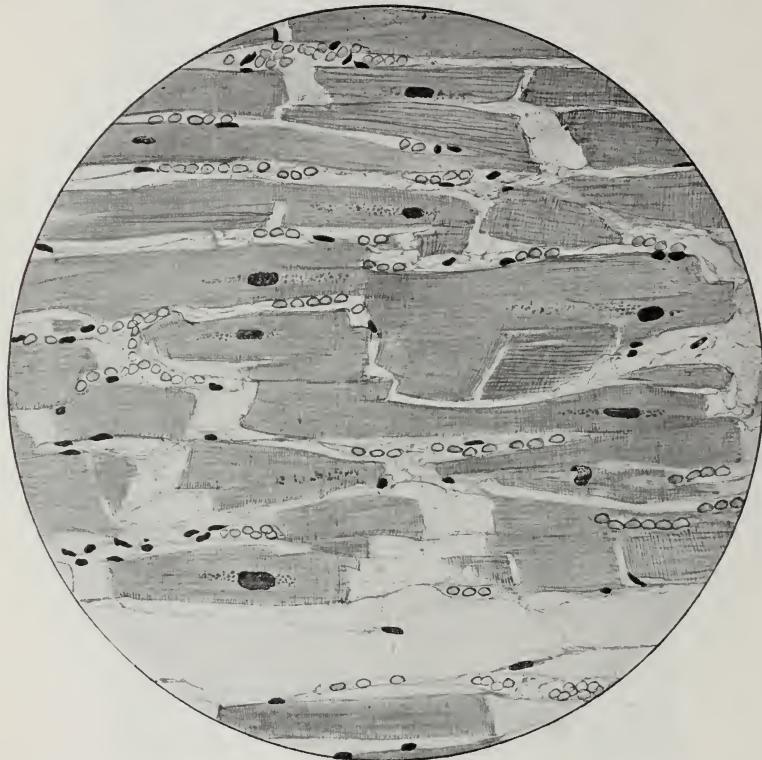


Fig. 243.—Fragmentation of the myocardium, showing simple transverse fractures.

changes within or outside of the heart, which could also be concerned in causing cardiac hypertrophy. Exact experimental study seems not to have been carried out with reference to this point, except that Stewart has found that when myocarditis is produced by injections of adrenaline the scarred hearts are distinctly hypertrophied and weigh more than the normal in proportion to the body weight. He thinks the action of the adrenaline, which causes the formation of scar tissue and enlargement of the muscle-fibers, results in an enlarged organ whose functional capacity is below normal. Naturally, although the scars probably occupy less space than the muscle which they replace, the increase of

the remaining muscle, in its attempt to carry on the work of the heart, might more than compensate for this, and result in an enlargement of the whole heart. Clawson points out the pretty obvious probability that myocardial failure is rarely due to any anatomical changes in the heart muscle, but rather to fatigue and exhaustion, and further shows that myocardial strain is not a cause of scarring.

Fragmentation of the Heart Muscle.—In many hearts, especially those of old people, and perhaps also those of persons who have long suffered from chronic infections or from advanced circulatory decompensation, there is found wide-spread



Fig. 244.—Fragmentation of the myocardium with disintegration of the fibrils (degenerative fragmentation).

disintegration of the heart muscle, nearly every fibre being fractured transversely once or twice. These uneven or step-like breaks seem to cross the muscle-fibre at any point, and are not essentially separations of the fibres at the so-called cement line. J. B. MacCallum distinguished simple fragmentation (Fig. 243) from a degenerative form (Fig. 244), in which the fibre breaks across a place where it was evidently in extreme extension, and where the fibrils break at different levels, so as to produce an area made up of many short lengths of individual fibrils. It seems possible to recognize the existence of this condition in many cases from the softness and flabbiness of the heart. There has been much dispute as to its significance, and since it seems incompatible with the continued activity of the heart, and yet is surrounded by no evidence of any reaction on the part of the tissues, it is gen-

erally thought to occur during the death agony, and to be produced by the final irregular contractions. Such evidence is not conclusive, however, and we must await further information.

LITERATURE

- Aschoff: Verh. Dtsch. Path. Gesellsch., 1904, viii, 46.
Aschoff and Tawara: Path. Anat. Grundlagen der Herzschwäche, Jena, 1906.
Clawson: Amer. Jour. Med. Sci., 1924, clxviii, 648.
Cohn, A.: Verh. Dtsch. path. Gesellsch., 1909, xiii, 182.
Hasenfeld: Dtsch. Arch. f. klin. Med., 1897, lix, 193.
Levy, Bruenn and Kurtz: Amer. Jour. Med. Sci., 1934, clxxxvii, 376.
Longcope and McClintock: Johns Hopkins Hosp. Bull., 1910, xxi, 270.
MacCallum: Amer. Jour. Med. Sci., 1914, cxlvii, 37.
MacCallum, J. B.: Johns Hopkins Hosp. Rep., 1900, ix, 307. Jour. Exp. Med., 1899, iv, 409.
MacCallum and Taylor: Johns Hopkins Hosp. Bull., 1931, xl ix, 356.
Passler and Romberg: Dtsch. Arch. f. klin. Med., 1899, lxiv.
Stejskal: Ztschr. f. klin. Med., 1902, xliv, 367.
Stewart, H. A.: Jour. Exp. Med., 1911, xiii, 187; Jour. Path. and Bact., 1912, xvii, 64.
Warthin: Amer. Jour. Syph., 1918, ii, 425.

CARDIAC VALVULAR DISEASE AND ITS CONSEQUENCES

Mechanism of the Obstruction.—In another place (page 240) the nature of infectious endocarditis was discussed, and it was found that thrombotic vegetations on the valves might impair the accuracy of their closure; further, that the erosion and destruction of the valves would produce extreme incompetency to close the orifice. It was emphasized there that persons in whom bacterial endocarditis has caused havoc in the valves seldom recover, and that the scarring, calcification, thickening, and distortion of the valves so commonly found at autopsy must be thought of as the result of other diseases. Of these, first in importance is rheumatism, which in each of the recurrent attacks throughout years, injures the valves and leaves a thickened scar. Second only to this is syphilis, which produces changes in the aortic semilunar valves which render them incompetent. Secondary bacterial infection is common on rheumatic valves, not on the syphilitic. Whether arteriosclerosis plays any part in the distortion of the heart valves seems extremely doubtful although a short time ago we confidently referred many of them to an extension of arteriosclerosis. Of course, congenital malformations must be kept in mind when considering the mechanical effects of valvular deformities. Since the circulation depends so largely upon the perfect action of the valvular mechanism, it is important to study, in cases where it is defective, the changes in the rate and volume of the moving blood and the consequent changes in blood-pressure. In a mechanical model, such as that of v. Basch, these relations are complicated, but they become much more so in the living circulatory apparatus, where many compensatory mechanisms are at work. *Every valvular lesion produces an obstruction to the circulation*, either by opposing a barrier to the flow or by failing to maintain the advance effected by the contraction of the heart. Accumulation of blood, therefore, occurs behind each diseased valve, and unless exceptional compensation is available, the amount of blood actually propeled into the circulation beyond it, is reduced by the amount of that accumulation.

It is not meant that any particular corpuscles or cubic centimetres of the blood remain stagnant behind the injured valve, but that, while there may be constant mixing in this region, it is as though a stream ran in and out of a lake. The vessels in that area are overfilled and distended, and the exchange of blood is slow—not like the torrent which normally sweeps the stream-bed clean at each beat.

When an obstruction or regurgitation occurs at any valve, say the aortic, the amount of blood thrown into the aorta must be constantly less than normal as long as the cavity of the ventricle retains its normal dimensions, and the wall its normal force of contraction. This may be modified by the power which the ventricle possesses of dilating to receive more blood, and expelling it with greater force, but in order to throw the normal quantity of blood into the arteries the left ventricle must receive that amount plus the amount regurgitated. This is possible only if there is an actual addition to the amount of the blood, although constriction of the arterioles may keep up the normal blood-pressure. If for a time a diminished amount, less than the normal by the quantity held back or regurgitated, circulates in narrowed vessels, there would be a rapid addition of fluid from the tissues and water taken into the stomach until the circulating amount was again normal. Indeed, one receives the impression from observing the amount of blood in the vessels at autopsy in cases of long-standing chronic passive congestion from cardiac lesions, that there is a great increase in its quantity.

The changes in the distribution of the blood may be thought of perhaps in terms of numbers, quite arbitrarily selected, to represent the amounts of blood concerned. This is, of course, entirely schematic, but it serves as a concise way of describing the probable changes.

Thus if the amount handled by any one part of the heart in one systole, say the right ventricle, be represented by 10, the left auricle will receive 10 and the left ventricle also 10. If, now, insufficiency of the mitral valve arises, a portion, say 4, is driven back from the left ventricle into the left auricle, and 6 goes on into the aorta. With the same systole 10 again reaches the left auricle and meets the 4 regurgitated from the ventricle, so that the left auricle now contains 14. That which follows will depend upon the activity of the left ventricle. If it will not receive more than the usual 10, 4 remains stagnant in the auricle, 6 is thrown into the aorta, and 4 more regurgitated. By this time 6 is thrown into the auricle from the right ventricle instead of 10, and meets with 8 of regurgitated blood, making up 14, of which 10 goes again into the ventricle. Thus the circulating blood amounts to 6, while the stagnant blood in the pulmonary circulation amounts to 4. The right ventricle forces 6 into the pulmonary circulation, already containing 4, and into which the left ventricle simultaneously forces 4.

It is usual, however, for the left ventricle under such circumstances to dilate and to exert greater force in the expulsion of the greater amount of blood received. This may be represented as follows:

When the left ventricle has thrown 6 into the aorta and there is 14 in the left auricle, the ventricle dilates at the next diastole—perhaps not enough to receive the whole 14, but enough to receive 12. Of this, it expels 8 into the aorta, while 4 is again regurgitated. The regurgitated 4 meets now with 6 driven in by the right ventricle, and 2 left behind from the 14, making in all 12. With the next diastole the ventricle receives the whole 12, regurgitates 4, and throws 8 into the aorta. By this time the amount 8 thrown out by the ventricle into the aorta reaches the auricle and meets the 4 regurgitated. The whole 12 passes into the ventricle, and thus a circulation is established in which 8 circulates while 4 is regurgitated with each systole.

These examples assume the ability of the ventricle to empty itself completely, but if, finally, it does not, a new set of conditions arises in which the ventricle itself forms part of the reservoir for stagnant blood. Many other conditions which commonly occur may be represented and discussed in this numerical way.

What has been said shows clearly enough that an increased strain is put upon the chamber of the heart behind the defect, because it is made to handle an increased amount of blood, and often, though not always, to propel it against an increased resistance.

As explained, the heart is particularly remarkable in being able to rise instantly to the emergency if an excess of work is suddenly demanded of it, and this adaptation takes place so smoothly that not a single beat is lost or disturbed. This is an evidence of its great reserve power, which is ordinarily not drawn upon, but which permits it to perform greatly increased work for a limited time, as one sees in the case of any violent muscular exertion during which the heart pumps with increased force and rapidity. But if the excessive work must be kept up for a long time, the heart-wall thickens like the muscle of a blacksmith's arm, to enable it the more easily to bear its burden. Such hypertrophied hearts and even normal hearts, when the muscle is injured or badly nourished or finally exposed to entirely excessive strain, may give way and dilate to a degree which makes their proper pumping impossible.

While these are, in outline, some of the principles concerned in the effects of valvular lesions, they come into play differently with lesions of different valves.

Aortic Insufficiency.—Regurgitation through the aortic valves may follow destruction of the valves by fresh or repeated bacterial infection, or their thickening and shortening caused by rheumatism, but it is most commonly the result of syphilitic infection which produces a specific type of arteriosclerosis of the aorta, and analogous scarring and retraction of the aortic valves (Fig. 245). Generally they are thickened into a cord-like roll at the margin, with loss of the filmy border which would complete the closure, and they are shortened laterally and pulled apart so that a space remains between the valves at their insertion. At times the diseased valves rupture or tear, the fragments flapping in the stream. Experimentally one may imitate this disease by cutting through a valve with a hook, which can be pushed down the carotid artery, after which the effects are quite like those observed clinically. There need be no great disturbance of the circulation or of the blood-pressure. The pulse is changed to a bounding, collapsing type, with a dicrotic wave low on the descending limb. This character is due to the lowering of the diastolic pressure after each beat by the rapid regurgitation of the blood, so that the aortic wall is not kept at its usual high tension. The pulse pressure is high, because the systolic pressure remains nearly normal, while the diastolic pressure cannot be kept up. With such a condition the pulse is felt in the most distal vessels like a water-hammer, and can be seen as alternate flushing and paling in the capillaries of the fingers and toes (Corrigan pulse).

During diastole the regurgitant blood returns to the ventricle, making a loud diastolic murmur, and the ventricle dilates to receive it as well as the auricular blood. So perfect is the left ventricle in its power of response to the increased demand that ordinarily it succeeds in ejecting an amount into the aorta sufficient to allow of regurgitation and still maintain the normal filling of the vessels. This requires the ability to dilate and to handle the excess of blood, and generally the left ventricle is found enlarged and its wall thickened, but without necessarily producing any change in the pulmonary circulation or the right

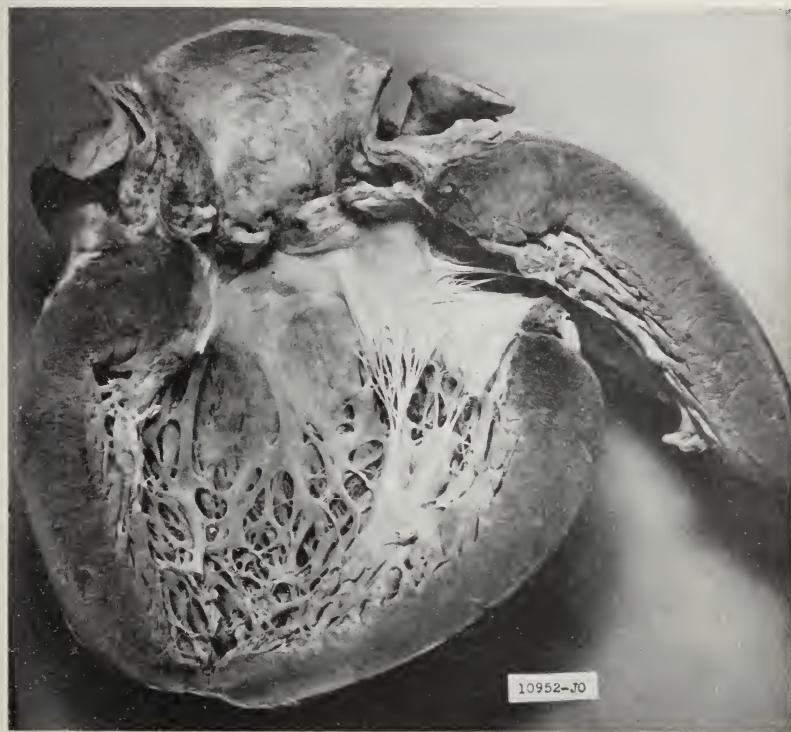


Fig. 245.—Aortic insufficiency (syphilitic). There is great thickening with shortening of the aortic valves, which are thereby rendered incompetent. The left ventricle is hypertrophied and dilated.

heart. Extreme defects of the valves, especially when the ring of muscle in the conus arteriosus which supports them fails, may be followed by failure on the part of the left ventricle to carry on the great excess of work without leaving a great deal of residual blood in its cavity. Then it becomes difficult for the auricle to empty itself, the pulmonary vessels remain partly filled, and the right ventricle hypertrophies in the attempt to drive its blood through them. Compensation is, however, maintained in aortic insufficiency much better than in other lesions, and death often comes unexpectedly from a final sudden failure.

Stewart has claimed that the collapsing character of the pulse is due to the rapid escape of blood, not by regurgitation, but through widened peripheral capillaries, and that in view of the very slight regurgitation the hypertrophy of the left ventricle is due to its exposure to the diastolic pressure of the aorta. These results I have not been able to accept, although the last statement implies a regurgitation during diastole.

Aortic Stenosis.—Aortic stenosis (Fig. 246), produced by thickening and fusion of the aortic valves, narrows the aortic orifice so as to offer a mechanical obstruction to the expulsion of blood; usually since the



Fig. 246.—Aortic and mitral stenosis. The heart is cut vertically in such a plane as to pass through both narrowed orifices.

valves are incapable of closing accurately there is some regurgitation too. The blood is forced out slowly with a rasping systolic murmur, producing a pulse which, in contrast to that of aortic regurgitation, is small and rather slow. Again, the increase in effort is felt and assumed by the left ventricle, which hypertrophies in response, but for a long time does not dilate. It is not until it finally fails to accomplish its momentary task of expelling the blood that residual blood plus that from the auricle overdistends it, and it becomes difficult for the auricle to empty itself. In both aortic insufficiency and stenosis it seems in-

evitable that the coronary circulation should be impaired in the extreme degrees of the disease, thereby weakening the heart itself.

Mitral insufficiency (Fig. 247) gives rise to rather complicated and extensive disturbances of the circulation because the ventricles, the effective compensating mechanisms, are put at a disadvantage. Part of the blood received by the left ventricle rushes back into the auricle during systole, producing, as usual, an audible murmur. This diminishes the amount available for the aorta and distends the auricle and pulmonary veins. The right ventricle drives its blood into this partly filled pulmonary circulation with increased effort, and in time hypertrophies. The pulmonary circulation remains overdistended, and the left auricle, laboring with blood under high pressure and in increased amount, dilates and hypertrophies.

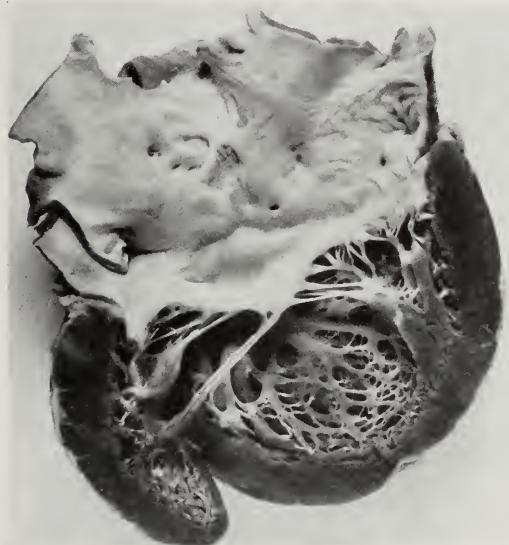


Fig. 247.—Mitral insufficiency of rheumatic origin. It is almost impossible to find a heart with uncomplicated mitral insufficiency and this shows some stenosis.

The left ventricle, too, takes part in the compensatory process, and dilates to receive an excess of blood until it can, in addition to the regurgitant amount, throw out a nearly normal quantity into the aorta. Consequently the left ventricle dilates and hypertrophies. The pulsation produced by the systolic regurgitation is felt through the pulmonary circuit, and the wave impinges upon the wall of the right ventricle before its valves are closed. In a sense the right ventricle is working against the left, which doubtless contributes to the need for hypertrophy. Compensation begins to fail through the final inability of the left ventricle to expel all the blood brought to it, and the emptying of the left auricle and the pulmonary veins is embarrassed. The same obstruction is felt by the right side of the heart, and with the dilatation of the right ventricle which may follow, a relative insufficiency of the

tricuspid valves can arise, that is, the tricuspid ring becomes so wide that the normal valves are too small to close it. Doubtless, however, here, as in the case of the mitral valve, the failure of the usual muscular support of the valves which helps to close the orifice contributes largely to the insufficiency. Such relative insufficiency or even the difficulty which the right ventricle finds in expelling all its contents into the over-distended pulmonary circulation will impede the outflow of the systemic venous blood, and a general chronic passive congestion ensues. The patient becomes cyanotic and very short of breath, with a cough which expels sputum tinged brown by the presence of pigmented cells. œdema of the extremities and the body and effusion into the serous sacs



Fig. 248.—Advanced mitral stenosis, the valves with roughened precipitous margins and extremely thick chordæ tendineæ.

follow. The end is usually brought about by continued dilatation of the heart and final failure, although temporary recovery with partial disappearance of the symptoms may take place over and over. Such decomposition or break in compensation is, however, more commonly found in other forms of valvular disease or in myocardial failure.

Mitral Stenosis.—The narrowing and rigidity of the mitral valves (Fig. 248) present an obstacle to the outflow of blood from the auricle into the left ventricle. Usually the change in the valves is such that the orifice is bounded by thick, precipitous edges, which may fit together fairly well if they can move into approximation; otherwise, if they are rigidly held apart, there is necessarily mitral insufficiency

combined with the stenosis. This is the usual condition, and is really avoided only in those rare cases in which a delicate film, capable of completing the closure, persists past the line of rigidity and calcification. The narrowing of the actual orifice through which all the blood must pass may be extreme, so that a mere crescentic slit is left with rigid margins only a few millimetres apart, and it is wonderful that life can be maintained until this is developed. Globular thrombi formed in the auricle may sometimes add to the obstruction, or even suddenly complete it by plugging the mitral orifice.

With such difficulty in expelling its blood the left auricle dilates and becomes hypertrophied (Fig. 250). The blood is driven through the



Fig. 249.—Mitral stenosis with great hypertrophy of the left auricle, which has been cut across. Stenosis of the tricuspid.

narrow hole and produces a thrill and a simultaneous presystolic rough murmur. But much of it fails to get through and accumulates in the pulmonary vessels, where the circulation is accordingly very slow and under a high pressure because of the compensatory activity of the right ventricle.

The effects of this upon the lung are described below, but the right ventricle must obviously hypertrophy. If it does so adequately, it may prevent the appearance of any symptoms except those from the lung if the stenosis is not extreme, and enough blood may be forced through to allow the left ventricle to propel a satisfactory quantity into the aorta.

If the orifice is so narrowed that the left ventricle receives much less than it should handle, its wall atrophies and it shrinks to a relatively small size as compared with the enlarged and thickened left auricle and right ventricle in the same case. As in mitral insufficiency, a final break in compensation produces cyanosis, serous effusions, cough, dyspnoea, and often the coughing up of blood from the lungs (haemoptysis).

Pulmonary stenosis is nearly always a congenital anomaly, and is one of the commonest and most important of those found in the heart. It is generally associated with other imperfections, such as an open foramen in the septum ventriculorum. *Pulmonary insufficiency* is rare and sometimes due to malignant endocarditis.

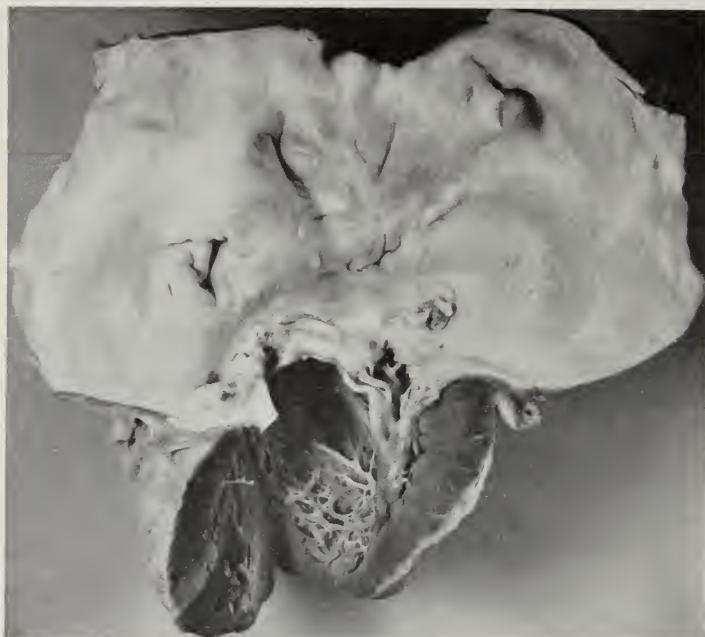


Fig. 250.—Extreme mitral stenosis with great enlargement of the left auricle.

Tricuspid regurgitation, generally due to a relative insufficiency (though sometimes caused by endocarditis), is often secondary to lesions on the left side or to obstruction in the pulmonary circulation—it causes a murmur and pulsation as well as great distension of the systemic veins. *Tricuspid stenosis* also occurs, and is accompanied by symptoms generally resembling those of mitral stenosis, *i. e.*, presystolic murmur, cyanosis, etc., but this is less significant, as it is usually associated with valvular lesions on the left side.

Indeed, valvular lesions affecting several valves at once, either to produce insufficiency or stenosis or both, are the rule rather than the exception, and hence in the calculation of the effects, complexities arise. It is possible that one lesion may partly compensate for another, al-

though such compensation is seldom an unmixed good. Mitral stenosis may diminish the regurgitation if added to mitral insufficiency. In all cases the outcome depends largely upon the extent of the defect, and persons with definite valvular lesions go on leading an active life for years without any symptoms because the strength of the compensating ventricles is not too greatly overtaxed.

Congenital Malformations of the Heart.—Some mention should be made at this point of the effect of malformations of the heart in producing disturbances in the proper flow of the blood. Such malformations are common in any hospital in which children are treated but because of their fatal effect the more serious forms are rarely seen in grown persons. There is a most extensive literature devoted to them and the student is especially referred to the work of Vierordt and of Schwalbe. In order to understand them it is necessary first to study the development of the heart which is well described by Tandler in Mall and Keibel's *Embryology*. No two cases are precisely alike, but there are certain commoner types which may serve as examples.

In general it seems that they depend upon imperfections or abnormalities in the final union of the septa which divide the original common cavities of the heart. A septum grows to separate the right from the left auricle, another grows up from the apex to separate right and left ventricles, while a third grows downward to divide the arterial trunk into aorta and pulmonary artery. These unite, the final stage being apparently completed by the formation of the septum membranaceum. It is important to remember that the foramen ovale is secondarily formed in the intra-auricular septum and that the ductus arteriosus remains as a communication between the pulmonary artery and the aorta. The exact relation of these to the branchial arches bears less on cardiac malformations.

As a makeshift explanation of the common malformations which at least allows us to enumerate them, we may say that they result from various inequalities or irregularities in the position of the three septa and in their final union. Thus, common forms are produced by unequal division of the truncus arteriosus. If the septum is displaced toward the right there is a narrowing of the pulmonary artery. When its valves appear they leave a very small orifice, the union of all the septa remains incomplete so that in place of the septum membranaceum there is an opening from right to left ventricle. Generally the foramen ovale and ductus arteriosus remain open. Again, the arterial septum may lie as far toward the other side so that the beginning of the aorta is extremely narrow while the pulmonary artery is wide. Then the essential compensation lies in the ductus arteriosus which is greatly widened so that the pulmonary artery seems to be continued as the aorta after giving off its branches to the lungs, and one must search for the cord-like proximal portion of the aorta. The returning blood from the lungs may pass into the right auricle through the wide foramen ovale and the left ventricle may be reduced to a very small size. In another form which the Germans call "Rechtslage," there is a wide gap in the place of the septum membranaceum and the relatively large aorta seems

to open equally out of right and left ventricles while the pulmonary is small. Such incompleteness in septum formation between the ventricles may allow a continuity of the tricuspid with the mitral valves. It may go further still and while two auricles are formed, there is no trace of ventricular septum.

Most interesting is the complete transposition of aorta and pulmonary so that the aorta arises from the right, the pulmonary from the left ventricle. It may be imagined that this could result from a twist of the descending septum of the truncus arteriosus, so that it unites in reversed position with the other septa. Except for the compensation of a very wide foramen ovale and ductus arteriosus it is difficult to see how such a circulation could go on.

There are many other forms, to appreciate which the student must consult the appropriate literature, or a museum. The early monograph of Rokitansky on the defects of the septa of the heart is beautifully illustrated but rather puzzling. It is evident that any of these deformities must offer great obstacles to the proper circulation and aëration of the blood and such infants are cyanotic (blue babies). Occasionally even with cyanosis and dyspnoea the person may reach adult life.

Compensation, Cardiac Hypertrophy, Dilatation, Decompensation.—It is clear, from the description of all these valvular lesions, that in each case extra work is demanded of the heart, and that while this task is sometimes assumed by the chamber directly behind the obstruction, the burden is in the end usually felt by the whole heart. When blood regurgitates into a chamber so that it must dilate to accept more than its usual quantity, it does so, and emptying itself with the next systole, it rises to the emergency by the use of its reserve power. When the systolic discharge is opposed by a stenosis, the chamber again uses its reserve power to drive out the blood, but does not necessarily dilate. Such work at high tension is possible for a time for the normal heart, as we see every day in people who make violent muscular efforts. When they are again at rest the heart subsides to its normal work and is itself unchanged. In its growth it probably merely maintains its proportion to the body musculature.

It is different with such an effort as is required of the heart by a valvular defect, because that is a constant, never-lifting burden which weighs on the ventricle wall with every beat night and day. After a time the heart-wall thickens and strengthens itself, probably chiefly by an enlargement of the muscle-fibres rather than an increase in their numbers. Its reserve force increases in proportion, and now what was an extreme effort near to the maximum limit for the normal heart is a moderate achievement for the hypertrophied one, to which still greater putting forth of strength is possible through its newly advanced reserve power.

This has not been agreed upon by all writers. Martius stated that while the absolute power of the hypertrophied heart was greater than that of the normal, nevertheless, in carrying on the increased work, it was nearer to its limit of endurance than the normal heart was with the lesser burden—in other words, its reserve power made up a relatively small part of the new strength. But Romberg and

Hasenfeld think that the hypertrophied heart is just as alert and capable as the normal in response to increased demands, although it must be remembered that the hypertrophied heart is commonly working at an increasing disadvantage.

Hypertrophy is usually thought of as the response to increased work, and it is often called a work hypertrophy. Although this does not explain it, unless perhaps we think that excessive work demands an increase in the metabolism of the cell and thus promotes growth, it is no better explained by Horvath's idea that growth depends on stretching, or by E. Albrecht's, that it is a sort of inflammatory process, or even by Loeb's theory of the imbibition of water with subsequent addition of new material. Stewart thought it due to injury of the heart muscle, followed by enlargement and scarring, in the hypertrophy produced by adrenaline injections.

The attempts at explanation of cardiac hypertrophy on other grounds than the response to increased work have been made chiefly because of the cases of so-called idiopathic hypertrophy, in which enormous enlargement of the heart appears without any valvular lesions or other evident obstruction to its work. Difficult as it is to explain these cases, the suggestion that they are of toxic or inflammatory origin seems quite unsatisfactory unless abundant scars are found in the heart muscle. Then, perhaps, the hypertrophy of the remaining muscle might effect a compensation for that which was lost. But still, and even in this case, the only acceptable explanation seems to be the increased demand upon the muscle.

Stewart has pointed out that even in experimental aortic insufficiency, where the left ventricle encompasses its new task without any increase in pressure in the auricles, the walls of the auricles hypertrophy. Whether this co-hypertrophy is quite independent of obstruction of the flow of blood or not in this particular case, the usual cause of the hypertrophy seems to be the extension of the influence of the obstruction from one chamber to another. It may be possible for the ventricle, in the case of aortic insufficiency of moderate degree, to assume all the new work, quickly expanding in each diastole to receive the original normal amount of blood from the auricle, as well as the amount regurgitated, and expelling it into the aorta, but even here, with an increase in the extent of the insufficiency of the valve, as well as the hypertrophy and power of dilatation, there might occur a disparity during which the auricle would have to make an effort, perhaps partly unsuccessful, to force all its blood into the ventricle. Then arises the need for auricular hypertrophy. But aortic insufficiency is well known to be the best compensated of valvular lesions. In mitral insufficiency the auricle must hypertrophy, the right ventricle must hypertrophy, and as soon as it fails, in the way just described, the right auricle feels the strain. Combined insufficiencies of the valves are even more certainly followed by a distribution of the excess of work all through the heart.

Thus no compensation restores the circulation to its original condition. In every case some part of the heart is working at a disadvantage, either against abnormal resistance or with an excessive proportion of the blood. Slowing of the pulse-rate may sometimes aid in compensating the first of these, while an addition to the amount of the blood in circulation may make up for the blood which lingers in the heart or in the pulmonary vessels, so that the aorta is once more normally filled. But such defects as mitral insufficiency or stenosis can

hardly be completely compensated, for in all cases there remains the overfilling of the vessels of the lungs.

At best all these compensations are subject to the probable increase in the severity of the valvular lesion itself, and to the fact that their deficiencies, such as the constant congestion of the lungs in mitral disease, may be aggravated to an intolerable degree by muscular effort or psychic disturbance which would be scarcely felt by a normal person.

Failure of compensation is, then, an impending danger in all these cases, and while, as we have seen, the hypertrophied heart is stronger both in its ordinary and its reserve power than the normal, there are many ways in which it can be overtaxed. Besides muscular exertion and psychic excitation, which have been mentioned and which in general the patient with a cardiac defect must sedulously avoid, there must be mentioned all the diseased conditions of the heart muscle which have been described above, and which are particularly common in hypertrophied hearts. Those which are acutely produced in such hearts must weaken the walls through destruction of muscle-fibres. Scars and old remains of such injuries indicate rather that that danger has been survived, and probably that part of the hypertrophy has arisen to make up for the fibres whose loss they signalize. Nevertheless, such a scarred heart is weakened and subject especially to the influences which conduce to failure. Sclerosis of the coronary arteries is particularly important in restricting the nutrition of the heart wall, and sudden complete failure of its activity may follow occlusion of these vessels by thrombi. Surprising degrees of sclerosis are survived, however, and even extensive infarctions of the wall.

Perhaps more important still in disturbing compensation in such an hypertrophied heart with valvular defects is the functional disturbance of the coronary circulation, either when, with extreme destruction of the aortic valves, the entrance of blood into the coronary arteries is deficient, or when great accumulation of blood under high pressure in the right heart and systemic veins impedes the return of the coronary blood into the right auricle. The wall of the heart suffers then a chronic passive congestion which involves malnutrition, and it fails through the action of this vicious circle.

Extraneous influences, such as chronic nephritis, extreme arteriosclerosis, pericardial effusions and adhesions, advancing pulmonary disease with obliteration of vessels, pleural adhesions, etc., may gradually heap more work on the heart until, in spite of its hypertrophy, it is unable to keep up its activity. Whether it can stop from sheer weariness and exhaustion one can hardly say, but it seems probable.

The first effect of failure of the heart-wall to meet the demand is the accumulation of blood in its cavities and its passive dilatation. Unlike the competent ventricle which expands and sucks in an excess of blood which it readily expels, the wall is overstretched and incapable of closing completely on the blood in its cavity. For some time it may continue to drive out part, dilating again to receive more, so that thus a feeble circulation is maintained. Sometimes, especially with the administration of drugs, it may recover and return to its former com-

petency, but often it only grows weaker and finally stops beating, hugely distended with the accumulated blood. It is in the course of such dilatation that the muscle of the auriculoventricular orifices fails to support the valves by narrowing those orifices, and relative insufficiencies with regurgitation occur. Extreme distention of the veins results, with cyanosis and often with dropsy. Profound dyspnoea attends the same condition in the lungs, and the patient lies helpless and gasping, propped up in bed until death or one of the temporary recoveries relieves him. Lewis and his colleagues have recently suggested that such dyspnoea is identical with renal dyspnoea, and due to the production of acids other than carbonic acid. Peabody, however, in his important discussion of cardiac dyspnoea, to which the reader is referred, states that acidosis plays no part in the dyspnoea of pure cardiac disease except in the extreme stages of decompensation, while in cases in which the cardiac disability is complicated by renal disease acidosis becomes more significant in that it renders the patients unusually susceptible to the production of dyspnoea by exertion. In general, the tendency to dyspnoea depends upon a diminution of the patient's pulmonary reserve, that is, a decrease in the maximum volume of air which he is capable of breathing in its relation to the volume of air which he breathes while at rest. The vital capacity or volume of air which can be expired after the greatest possible inspiration may be decreased during cardiac decompensation by many factors which limit the expansion of the lungs so that the margin of safety is narrowed. The question of dyspnoea in heart disease is shown to be much more complicated than we suspected, and our knowledge is still incomplete.

Disturbances in Conduction of Impulses in the Heart.—Since the remarkable discovery by His, Keith and Flack, Tawara, and others, of an unsuspected system of specialized fibres and nodes which serves to initiate and conduct impulses from the orifices of the great veins to the ultimate parts of the ventricles, a great deal of work has been carried out with interesting results concerning all the normal and abnormal features of the process.

Interruption of these communications or injury of the nodes by some gross lesion, such as a syphilitic gumma or other destructive process, might properly be considered here, and it is possible that before long we shall be able to recognize the less palpable injuries which give rise to the various disturbances of the cardiac rhythm. But at present in this book it seems better to omit the discussion of arrhythmias borrowed from the work of the clinicians and to refer the student to their special literature.

Chronic Passive Congestion.—From what has been said regarding the overdistention of the pulmonary and systemic veins and the consequent slowing of the circulation of at least part of that blood, one might expect to find changes in the tissues so supplied. With increasing failure of compensation the veins become more and more dilated by the increasing pressure of the blood, and less arterial blood is driven through the tissues into them. The capillaries are widened and pulsation passes into them—the tissues assume a deep bluish color and the

veins stand out tensely. In places, as in the subcutaneous tissues of the legs, they are irregularly dilated and tortuous. Everywhere there is malnutrition of the tissues, accompanied by certain pressure effects from the widening of the veins and capillaries. Neither nutritive nor gaseous exchange is carried on as it should be, and doubtless excretory products accumulate there. An almost universal result associated with the injurious effects upon the more sensitive tissues is the new formation of connective tissue in the congested and cyanotic organs.

The Lungs.—The lungs are most readily affected in mitral insufficiency and stenosis when compensation fails, and in myocardial disease, but local congestion may appear with the same results in collapsed areas of a lung on account of the kinking of the venules and obstruction of the return flow of blood. The capillaries in the alveolar walls become greatly dilated and tortuous, so that they project in loops into the alveolar cavities. Grossman and von Basch speak of a sort of

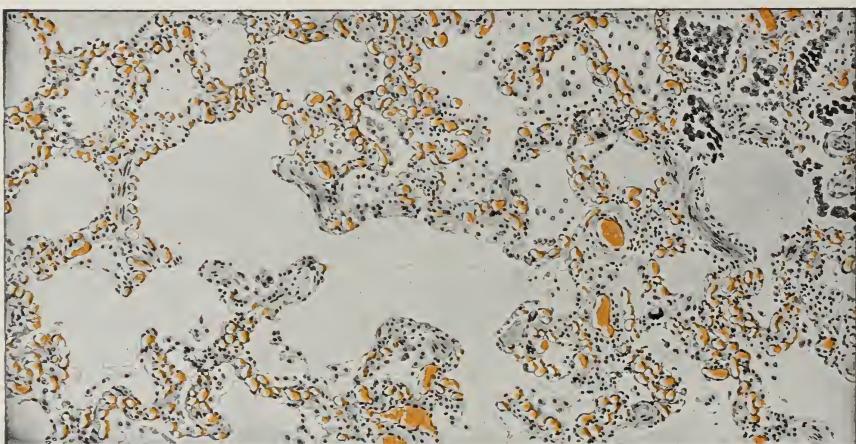


Fig. 251.—Chronic passive congestion of the lung with induration and muscular hypertrophy. Some alveoli contain the pigmented "heart-failure cells."

rigidity of the lung produced by this overfilling. The alveolar epithelium is ill nourished, and very many of the cells are desquamated into the air-cell; fluid exudes from the tense capillaries, often with red blood-corpuscles. These quickly disintegrate, and haemosiderin is formed from their haemoglobin and taken up by phagocytic cells which wander out from the alveolar walls and perivascular tissue. These are large mononuclear cells which for long have been regarded as desquamated epithelium. But the evidence seems to be entirely in favor of recognizing them as part of the great army of wandering mononuclear phagocytes, since they may actually re-enter the tissue with their load of pigment and since the epithelial cells which remain on the alveolar wall are not at all pigmented. They are coughed up in the sputum, and give a clinical indication of the existence of disease of the heart with pulmonary congestion, for which reason they are called heart-failure cells.

In the lungs they are generally sufficiently numerous to give a distinct rusty color to the cut surface.

The smooth muscle in the septa that form the vestibules in each lobule is greatly increased in bulk, and the alveolar walls in extreme cases become thickened and indurated by the appearance of new connective tissue (brown induration of the lung—Fig. 251).

The sluggishness of the circulation and the high venous pressure from obstruction makes it impossible for one arterial branch to supply,



Fig. 252.—Chronic passive congestion of the liver (nutmeg liver).

as in the normal, nutrition for the territory of another which may be plugged by an embolus. Hence it is that haemorrhagic infarctions are found in these congested lungs and practically only there.

Great dyspnœa usually accompanies such chronic passive congestion, and the explanation is not difficult in view of the inadequate aëration which the blood receives when it requires so long to send all of it through the lungs.

Such lungs at autopsy quickly lose any bluish color they may have had; instead, they are usually rather pale, sometimes dry, sometimes

œdematosus, and of a distinct rusty brown color, which, on the application of ferrocyanide of potassium and hydrochloric acid after fixation, turns to an intense Prussian blue (Perl's reaction for an iron-containing pigment). The consistence is altered, too, and the lung feels dense and elastic. In cases of long-standing congestion, especially in mitral stenosis, where the pressure in the pulmonary vessels has been high, arteriosclerotic patches in the pulmonary artery and its branches are common.



Fig. 253.—Chronic passive congestion of the liver. Necrosis of the cells about the efferent vein.

The Liver.—When the systemic veins are overdistended for a long time, the liver is among the first organs to exhibit the effects. It is enlarged so that it may be felt extending below the costal margin, and often it pulsates. At autopsy it projects as a tense bluish mass in which the impress of a finger remains for a little and is slowly filled up. On cutting the great veins the liver often visibly collapses and loses its uniform dark color, assuming a lobular mottling. On section this is extremely bright and distinct, the alternation of deep red and

yellow or gray markings giving rise to the name "nutmeg liver" (Fig. 252).

Close examination of the cut surface with a lens, if necessary, or of a thick frozen section without staining, shows that the ordinary lobular markings are much modified by the conversion of so much of the tissue into the deep red zones. Indeed, in places, quite extensive patches may be homogeneously red, spongy, and ooze blood. The grayish-yellow islands are found to surround in every case the minute

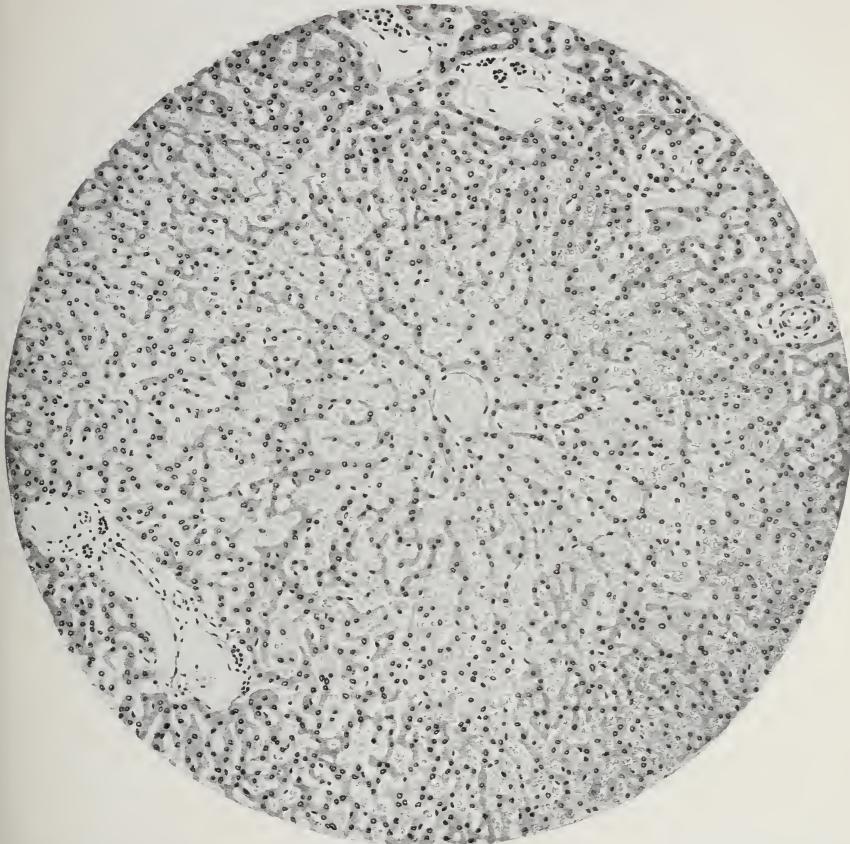


Fig. 254.—Chronic passive congestion of liver with dilatation of capillaries. Atrophy of liver-cells without necrosis. (Lambert and Allison.)

twigs of the portal vein and hepatic artery, a gray zone lying directly against the vein, and then a bright yellow zone which passes sharply into the crimson. Scattered in the anastomosing, irregular crimson bands there are often sharply outlined, opaque, orange-yellow flecks. Microscopical study explains all of this promptly. (See Fig. 154.) It is the lobule of Sabourin which is outlined and preserved in part as the pale islands—that is, for a certain distance around the afferent portal vein and hepatic artery the liver-cells are preserved. Those nearest

are well preserved and show gray; further out they are injured and loaded with refractive yellow fat-globules. Still further they are dead, and in so far as patches of dead cells sometimes remain, appear as opaque, orange-colored flecks (colored somewhat by blood-pigment). But in this region the overwhelming distention of the capillaries with venous blood and the escape of that blood into the intercapillary spaces

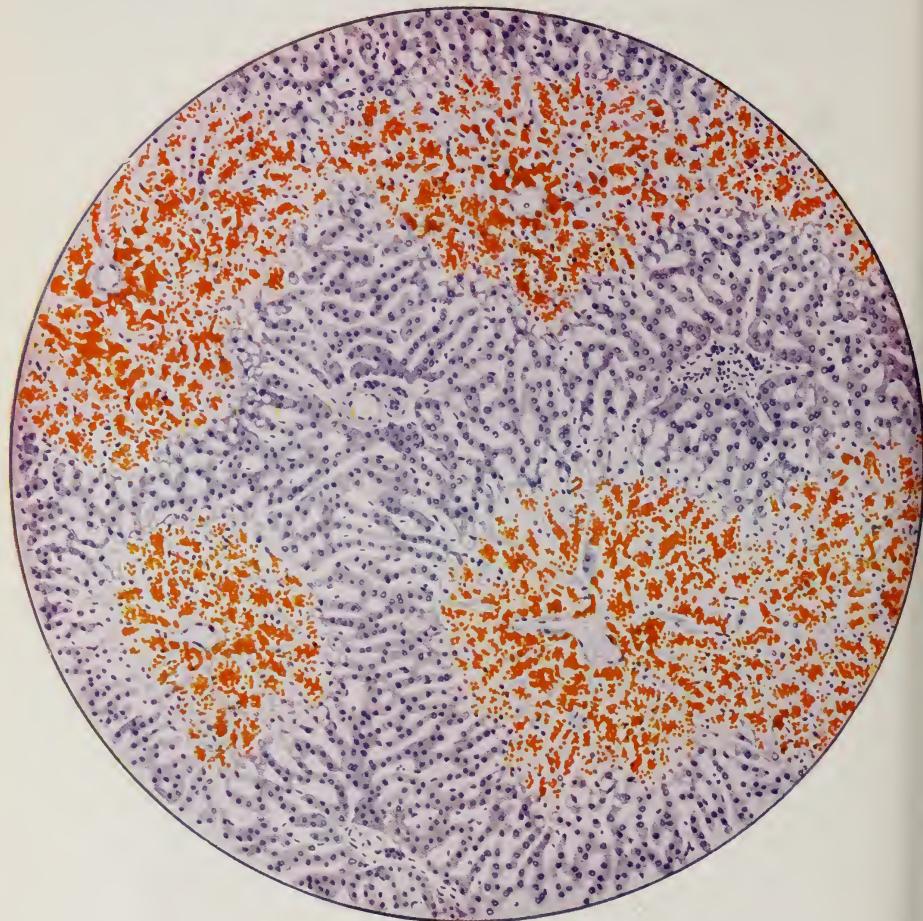


Fig. 255.—Chronic passive congestion of the liver, Type 4. Necrosis and haemorrhage about the efferent vein, with a narrow zone of fatty cells surrounding each necrotic area. (Lambert and Allison.)

formerly occupied by the liver-cells converts the whole tissue into a blood-filled sponge in which only the framework and capillary walls remain, with some débris of cells.

Referred to the old idea of the lobule, we must say that the blood-filled portion lies about the central or efferent vein, but that, owing to the course of the capillaries (*cf.* Fig. 154), it maintains a distribution equidistant from the portal vein, and hence extends from lobule to lobule.

Ordinarily all this is thought to be caused by the increased pressure of the venous blood in the capillaries, which is said to be felt with especial force in the liver because it is near the heart, but I think that these dying cells (Fig. 253) in no way resemble compressed cells, such as one sees about a tumor in the liver, nor does this seem a plausible explanation from a mechanical point of view, since if the pressure in the efferent vein were higher than that in the portal vein and hepatic



Fig. 256.—Chronic passive congestion of the spleen. Induration of the tissues between the venules renders them conspicuous.

artery, the blood must run the other way. Further, one may find well-nourished liver cells in contact with the walls of larger hepatic veins which seems inconsistent with their being injured by pressure. On the contrary, it is easier to believe that the sensitive liver-cells are badly nourished by the sluggish venous stream, and that oxygenation is especially interfered with, so that those which receive the blood-stream last suffer most severely and in time disappear, leaving a space which is then filled up with blood. On this ground the gradual transition from

practically normal cells near the source of nutritive supply through fatty to necrotic cells may be explained.

Mallory regards the necrosis of the cells as due to toxic influences usually of infectious origin and minimizes the effect of changes in blood-pressure. Lambert and Allison, who have gone over the literature and have studied 112 cases in which chronic passive congestion of the liver was well marked, divide the cases into five groups in which the lesions are as follows: (1) capillary dilatation with atrophy of the cells toward the centre of the lobule, (2) central degeneration with or without capillary dilatation, (3) marked fat accumulation in the cells about the hepatic veins, with midzonal hyperæmia, (4) central necrosis with haemorrhage, and (5) collapse fibrosis. The more extreme the stasis, the more certain is the central necrosis and haemorrhage, while the collapse fibrosis depends naturally upon a protracted course. They, too, think the necrosis to depend upon stasis alone which causes asphyxia in the most distal cells. Infection plays a minor part if any.

The Spleen.—The most striking features of the change in the spleen wrought by chronic passive congestion are its deep purple color and its extreme hardness (cyanotic induration). Enlargement is usually moderate, and the great increase in the size of the spleen in connection with cirrhosis of the liver is probably due to other causes than the mere congestion. The capsule is tense and smooth, and the cut surface stands firmly at right angles to it, neither bulging nor sinking into a concavity, as in so many enlargements from other causes. Malpighian bodies, trabeculae, and vessels stand out sharply in the background of the smooth, deep purple, splenic pulp. Microscopically (Fig. 256) one is impressed by the great clearness with which the splenic venules or sinuses are outlined. Their walls are thickened so as to present themselves as very definite membranes lined with endothelium, and every one is distended with blood. In the interstices there is a moderate increase in the connective-tissue framework, but no great accumulation of the cells of the pulp.

The *kidney* in such chronic congestion is sometimes little altered, since, as has been said, the effect of circulatory obstruction is often very unequally distributed. But the characteristic change is a notable swelling, with extreme rubbery hardness, such that the kidney tissue will snap away from between the fingers and almost rebound if dropped. The whole organ is deep purplish-gray in color, the surface smooth, the capsule not adherent, and on section, in the thick, grayish-purple cortex, one sees the striations with startling distinctness, the blood-vessels and glomeruli standing forth prominently in deep red, while the tubular portions are opaque and gray. The pyramids are also deeply reddened.

Microscopically little more is to be seen—the capillaries, especially of the glomeruli, are distended with blood, and there may be some coagulated fluid in Bowman's capsules or hyaline casts in the tubules. The tubular epithelium shows perhaps a moderate degree of cloudy swelling, but even this need not be marked. Interstitial connective-tissue increase may occur in extreme cases, but it is scarcely evident, as a rule, and it seems that the hardness is chiefly due to the distention with blood.

In contrast to this indefinite microscopical picture the functional changes are very marked. By itself chronic passive congestion can lead to the excretion of albumin and casts of various sorts in the urine, and also to distinct disturbances in the function of the kidney with regard to the excretion of water, salt, and other substances, for which, as is well known, the kidney has specific powers of secretion.

It is particularly important to estimate the part played by such congestion in producing the derangements found in cases of chronic



Fig. 257.—Hæmorrhoids. Vertical section showing distended vein near anus, partly occluded by a thrombus.

nephritis complicated by heart disease, for they can greatly aggravate the deficiencies of an already disabled renal function. If then, there is hope of relieving the factor of chronic passive congestion, the outlook for the patient is much improved.

Similar conditions of malnutrition with overdistention of the vessels are found in all other organs. In the stomach and intestine they lead to moderate digestive disturbances, often with excessive secretion of

mucus and with desquamation of many epithelial cells. In the rectum the enlargement of the veins produces the painful haemorrhoids, which often bleed and in time cause an extreme anaemia (Figs. 257, 258). They are, however, perhaps more often due to local conditions and especially to obstinate constipation. In the limbs we find the varicose



Fig. 258.—Haemorrhoids.

veins mentioned above, often associated with such derangements of the nutrition of the tissues that great ulcerations that refuse to heal appear over the shins.

LITERATURE

- Albrecht, E.: Die Herzmuskel, Berlin, 1903.
 Aschoff and Tawara: Grundlagen der Herzschwäche, Jena, 1906.
 v. Basch: Allg. Phys. u. Path. des Kreislaufes, Wien, 1892.
 Clawson, Bell, and Hartzell: Valvular Diseases, Amer. Jour. Pathol., 1926, ii, 193.
 Clendening: Corrigan's Description of Aortic Insufficiency, Arch. Int. Med., 1926, xxxvii, 780.
 Hasenfeld and Romberg: Arch. f. exp. Path., 1897, xxxix, 333.
 Krehl: Pathologische Physiologie, 1912, Nothnagel's Spec. Path. u. Therap., xv, Th. 1, Abth. 5.
 Lambert and Allison: Johns Hopkins Hosp. Bull., 1916, xxvii, 350.
 Lewis and others: Heart, 1913, v, 45; 1914, v, 367.
 MacCallum: Johns Hopkins Hosp. Bull., 1906, xvii, 251.
 MacCallum and McClure: *Ibid.*, 260 (mitral insufficiency).
 MacCallum: Johns Hopkins Hosp. Bull., 1911, xxii, 197 (aortic insufficiency).
 Martius: Erg. d. allg. Path., 1895, i, 38.
 Moritz and Tabora: Krehl and Marchand: Handb. d. allg. Path., 1913, ii.
 Peabody: Amer. Jour. Med. Sci., 1918, clv, 100.
 Stewart: Arch. Int. Med., 1908, i, 102 (aortic insufficiency).
 Stewart: Jour. Exp. Med., 1911, xiii, 187; Jour. Path. and Bact., 1912, xvii, 64 (hypertrophy).
 Thorel: Ergeb. d. allg. Path., 1903, ix₁, 559; 1907, xi₂, 694; 1911, xiv₂, 133; 1915, xvii₂, 90.

CHAPTER XXIV

TYPES OF INJURY (Continued).—OBSTRUCTION OF THE CEREBROSPINAL FLUID: HYDROCEPHALUS

The term *hydrocephalus* signifies that enlargement of the head which arises through the accumulation of large quantities of fluid within the cavities of the brain. Its cause has never been properly understood and even the anatomical studies of such brains have left much to be

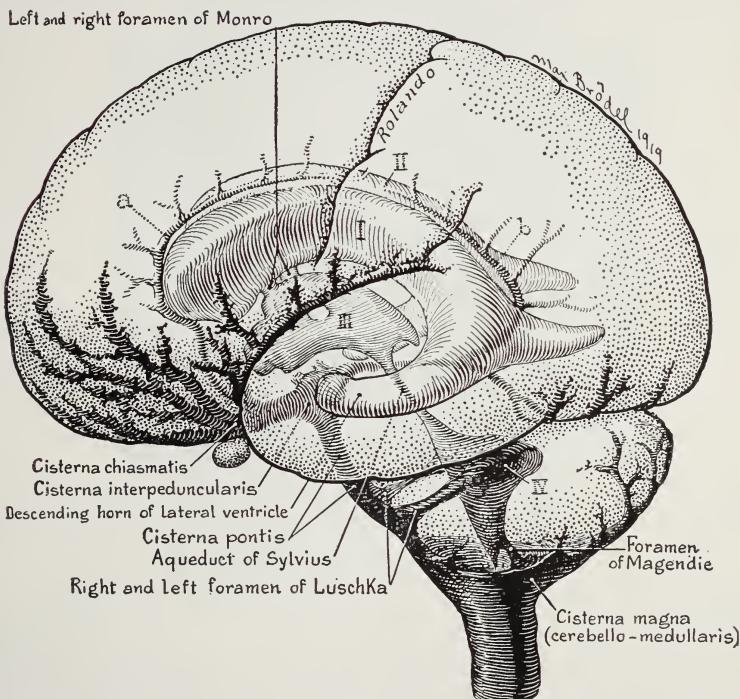


Fig. 259.—Diagram of ventricles of brain and subarachnoid cisternae (Dandy).

desired, since they failed to demonstrate the changes which led to the retention of the cerebrospinal fluid, and described only those which followed as secondary effects. Further, they were based on an imperfect or faulty conception of the paths of circulation of the fluid in the normal brain.

Hydrocephalus may be congenital and associated with malformation or prenatal inflammation in the brain; it may be the effect of pressure caused by tumor or cyst within the skull, or it may arise as the result of meningitis. Other causes more rarely give rise to it.

Advanced stages are easily recognized by the ungainly enlargement of the head, which becomes too large and heavy for the child to hold up. In the rather rare cases in which the patient survives to middle age, the head still rolls about on the shoulders. The skull becomes so thin as to form a very slight protection for the brain within; in places the bone is absent altogether, although new islands of bone may form in these spaces. The fontanelles remain widely open and the whole skull is so large with its overhanging forehead that the face seems to be an insignificant triangular appendage beneath. The orbits are stretched so that the eyes seem to be peering upward from the bottom of a space far too large for them. With such extreme distention the



Fig. 260.—Hydrocephalus in a child following cerebrospinal meningitis.

child, even if it survives for some time, usually becomes imbecile, but there are records of persons who retained an acute intelligence in spite of most advanced changes of this sort. Slight degrees of hydrocephalus are not so easily recognized except by Dandy's newly devised method of filling the ventricles with air, after which their dilatation is easily seen in a radiogram.

At autopsy the convolutions of the cerebrum are found flattened and smoothed out, although in most cases some areas show small convolutions in greatly increased numbers. The ventricles are dilated and filled with fluid, sometimes to so enormous a degree that the substance of the brain is reduced to a thin film of tissue which collapses like a wet cloth when the fluid is allowed to escape. This is true not only of the cerebral hemisphere but also of the tissues which form the walls of the

third and fourth ventricles. The corpus callosum, the septum lucidum, the commissures, and the fornix become extraordinarily attenuated, and even the corpora striata and optic thalami become flattened, although they resist the pressure longer than the rest. In some of the cases the spinal cord is also affected, the central canal being dilated (hydro-myelia). Atrophy of the ganglion cells of the cortex and of other parts of the brain and disappearance of the axones which belong to these cells is an inevitable consequence of this stretching of the tissue, and degenerations of the tracts in the cord result, although to an extent less than might be expected.

The mechanism of this retention of fluid has been clearly explained in the papers of Dandy and Blackfan, and more especially in Dandy's reports of his operative and experimental studies. The cerebrospinal fluid is secreted by the choroid plexuses in the cerebral, third, and

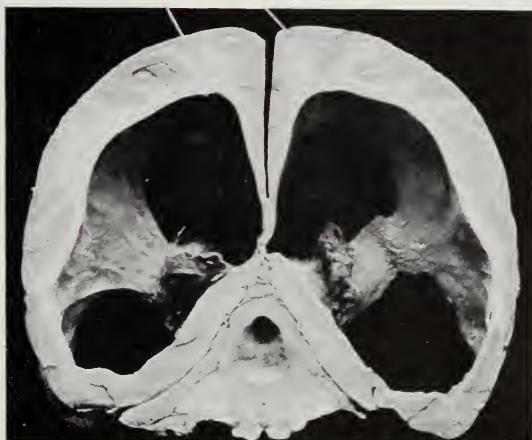


Fig. 261.—Hydrocephalus following cerebrospinal meningitis with old adhesions about the base of the brain. Transverse section looking forward, showing great dilatation of lateral and fourth ventricles, and of the aqueduct of Sylvius.

fourth ventricles. This is proven by the fact that if the foramen of Monro on one side be plugged, that ventricle becomes greatly dilated with fluid, but if afterward the choroid plexus be removed from that side, the ventricle collapses and no more fluid appears there, so that it soon becomes obliterated. In the normal brain the cerebrospinal fluid passes downward into the fourth ventricle from which it escapes into the meshes of the subarachnoid space through the foramina of Magendie and Luschka. Reaching the cisterna magna and the other spaces on the under surface of the brain it spreads upward and forward over the cerebellum and over the midbrain as it passes through the tentorium to the surface of the cerebral hemispheres, flowing always in the meshes of the subarachnoid space until it finally reaches the vertex and bathes the whole surface of the brain. Similarly, it flows downward into the spinal meningeal spaces. Various ideas have been formed as to the absorption of this fluid into the blood-stream, but it

seems that the explanation offered by Key and Retzius, in 1876, and strongly upheld by Weed in his studies of 1914, is undoubtedly the true one. The Pacchionian granules are really villus-like projections of the arachnoidal meshwork into the lumen of one or other of the venous sinuses of the dura. They are especially numerous along the longitudinal sinus where they hang in lateral pouches of the sinus and are covered by a rather thicker layer of cells which seem to allow the ready passage of the fluid. These granulations then form the specially designed pathway of the cerebrospinal fluid into the returning venous blood.

Dandy and Blackfan showed that cases of hydrocephalus fell into two groups according to their behavior when phenolsulphonephthalein

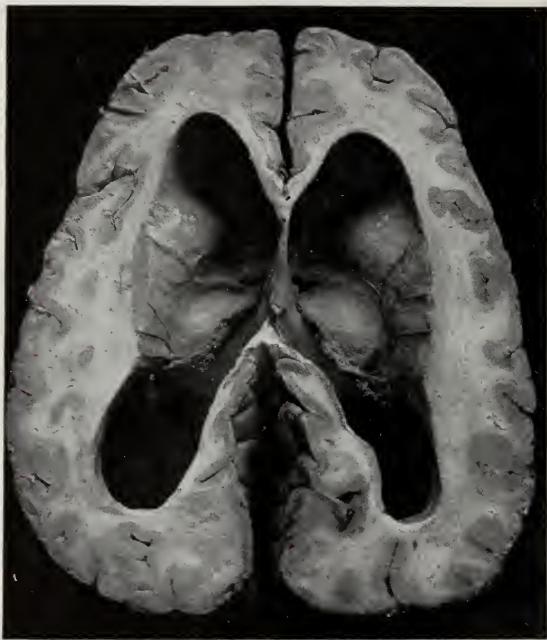


Fig. 262.—Hydrocephalus following obstruction of the aqueduct of Sylvius, showing dilatation of the lateral ventricles and of the foramina of Monro. The basal ganglia are less affected and become prominent.

was injected into the cerebral ventricle. In one group little or none of this colored material appeared in the spinal fluid, while in the other it appeared there at once. They designated these groups obstructive and communicating hydrocephalus respectively, and found it possible to explain them on anatomical grounds from what was discovered at autopsy. In the obstructive group the fluid cannot escape from the ventricles because there is an obstruction somewhere in its usual path. This may be in one or both foramina of Monro, or in the aqueduct of Sylvius, or there may be an occlusion of the foramina of Magendie and Luschka. Naturally, if the obstruction is in the foramen of Monro on one side,

the dilatation will be limited to that ventricle. An obstruction in the aqueduct of Sylvius will cause the distention of both cerebral and third ventricles. In the fourth ventricle the foramen of Magendie and both of the foramina of Luschka must be obstructed, else the obstructive type of hydrocephalus is incomplete. In all these cases the fluid is retained within the cavities of the brain, and never reaches the subarachnoid spaces at all. It is very different with the second group, the so-called communicating forms. In these, which are commonly the late results of meningitis with adhesions obliterating the meshes of the arachnoid and the cisternæ, the obstruction lies in the these adhesions which also bind the arachnoid to the dura about the midbrain, where it is closely surrounded by the tentorium and prevents the passage of the fluid into the subarachnoid spaces over the convexity of the cerebrum. Probably even more important is the obliteration by adhesions of the cisternæ from which this distribution normally occurs. Colored fluid injected into the ventricles can pass out through the foramina in the roof of the fourth ventricle and down into the spinal meninges, but cannot reach the cerebral subarachnoid spaces from which nearly all the absorption takes place. Therefore the ventricles become dilated, and in some cases there is also a distention of the spinal meninges. This is the type seen in meningococcus and tuberculous meningitis, but it must be remembered that in the presence of an inflammatory process there is another reason for the disproportion between the amount of fluid secreted and that absorbed.

LITERATURE

- Dandy: Johns Hopkins Hosp. Bull., 1919, xxx, 29. Ann. Surg., Dec., 1918; Aug., 1919.
Dandy and Blackfan: Amer. Jour. Dis. Child., 1914, viii, 406; 1917, xiv, 424.
Key and Retzius: Anatomie des Nervensystems und des Bindegewebes, Stockholm, 1876.
Weed: Jour. Med. Research, 1914, xxxi, 21, 51, 93; Amer. Jour. Anatomy, 1923, xxxi, 191; Brain, 1935, lviii, 383.

CHAPTER XXV

TYPES OF INJURY (Continued).—BACTERIAL DISEASE.— STREPTOCOCCAL INFECTIONS

General character of bacterial infection: Nature of bacterial action. *Pyogenic micrococci.* *Streptococcus infection*—of the throat, the middle ear, the digestive tract. *Wound infection:* *Erysipelas, pneumonia, endocarditis.* *General septicæmia; acute splenic tumor.*

GENERAL CHARACTER OF BACTERIAL INFECTIONS

As a type of injury, the harmful effects of bacteria play an exceedingly great part in the causation of disease, and must generally be reckoned with at some stage or other, even when they are not the primary cause of the ailment.

Of course, only a small number of the existing bacteria are harmful to man, and it seems that we must believe that these have gradually acquired, through long adaptation, their ability to thrive in contact with the living tissue. The rest live outside the body under all sorts of conditions, requiring in their struggle for existence heat, moisture, and nutriment. The latter they get partly from animal or vegetable matter, in which they hasten the process of decay, which depends largely upon their ferment activities. Such saprophytes may occasionally acquire the faculty of parasitic existence, and point the way followed by those which we now think of as obligate parasites.

Many of the disease-producing organisms scattered ordinarily in small numbers in the outside world may gain entrance into the body in overwhelmingly effective numbers, merely because they have had an opportunity to multiply in some culture-medium. A few typhoid bacilli which might readily be overcome in the intestine of any healthy man can, as in a recent case, cause a fatal epidemic if they are introduced into warm food and left to multiply until it is time for the crowd to partake of refreshments.

Bacteria live in great numbers on the body surface; they are taken into the digestive tract in great quantities in the food, and penetrate readily into all the external orifices of the body. At each point there is a mechanical or chemical guard of a sort, but nevertheless there is constantly an army of them besieging each portal. The impermeability of the horny layer of the skin, the constant irrigation of the conjunctival sac, the cilia of the respiratory tract, the acid gastric juice, the irrigation of the urinary tract, the acid vaginal secretion—all act as outpost guards. Nevertheless, in each of these positions it is known that bacteria are not entirely destroyed and that there is a characteristic flora, including pathogenic forms, waiting, as it were, to break through the second line of guards. The whole upper respiratory tract is smeared with bacteria; the mouth is a perfect incubator of dozens of forms, and

while the stomach and duodenum are relatively free, the lower intestine, and especially the colon, contains myriads.

Doubtless a few bacteria brought thus into the most intimate relations with the body surfaces pass into the real interior, that is, into the tissues themselves in healthy persons, but there is strong evidence to show they are rapidly overcome and destroyed by phagocytic cells and by the destructive action of the blood and tissue fluids. Were it not for these defences every one would quickly die from infection. Since infection does occur with fatal results, it is obvious that there must be failure of the defence or else the introduction of such overwhelming numbers of bacteria that defence is unsuccessful.

The chief portals of entry are, of course, the various mucosæ of the body, which are really as much exposed to bacteria as the outside skin, and the skin itself, which, through abrasions or wounds, can allow their entrance.

Having penetrated into direct relation with the tissues, most bacteria fail to multiply, but those which are adapted to such surroundings may do so, although constantly hampered by the antagonistic action of the body defences, especially such as are presented by the reaction of inflammation. Virulent bacteria in a person whose resistance is low may, however, grow rapidly and be quickly transported to other parts of the body by the lymphatic channels, or even in some cases by the blood-stream. If an infected appendix is ruptured, for example, some of the bacteria may be carried into the lymphatics of the diaphragm and thus into the general circulation, but usually the more obvious result is the production of generalized or even localized peritonitis.

Bacteria alone introduced into the tissues or body cavities are relatively easily killed. If, however, foreign bodies or dead tissue are present there, to afford a shelter against the disinfecting action of the tissue juices until multiplication to great numbers has occurred, the bacteria can more readily gain a dominating position. Bacteria in the uterine cavity in the puerperal state might be practically harmless were it not for the protected culture-medium offered by remains of detached and dead placenta, in which they reinforce themselves by growth until they can victoriously invade the uterine wall.

Changes in the virulence of bacteria, easily produced experimentally by repeated passage through the animal body, appear in the most striking fashion in the course of many epidemics, and the fading out of the epidemic seems to be due usually to the lack of any further susceptible material rather than to any decline in the virulence of the organism. In the great epidemics of streptococcus pneumonia this intensification of the activity of the streptococcus seems to have been exemplified.

It is not always easy to explain the very obvious changes in the power of resistance shown to bacteria. Many external conditions, such as chilling or starvation, may aid in this, but previous disease seems even more potent in this way.

This may explain the invasion of bacteria in a person already greatly weakened by some other disease and such secondary infections which show themselves perhaps most commonly in the form of lobular pneu-

monia are spoken of as terminal infections and constitute the very familiar cause of the death of old people who have long been ailing with some other disease.

The conditions are, however, rather more complex when a bacterial infection has been localized in some organ for a long time and then breaks out afresh in a wider distribution. For in that case the body has developed some immunity, especially in its power of agglutinating those particular bacteria and in the ability of its leucocytes to engulf them. But there is also the allergic reaction quite apart from these which seems to intensify the injury done by the bacteria so that the end-result will depend upon the quantity of the bacteria poured into the circulation, or into the bronchi or other tissue space at one time, and the balance of the defensive reactions.

Nature of Bacterial Action.—We are by no means clearly informed as to how bacteria produce their injurious effects. It is easy to say that they do so by elaborating poisons, but in reality, except in the case of a few, such as diphtheria and tetanus bacilli, which produce soluble toxins of great intensity, it is extremely difficult to demonstrate any poisons in the cultures of bacteria, even though they are known to be exceedingly virulent. It was thought that poison might be retained within their bodies (endotoxins), and liberated only upon their death and disintegration, so that the destructive effects would depend upon their death. It is true that when these bacteria are pulverized and extracted, poisonous substances are obtained with which the symptoms of the disease may be produced, but they scarcely compare in virulence with those formed by the diphtheria and tetanus bacilli; and it seems that perhaps the whole explanation is not yet before us. It is quite conceivable, however, that bacteria in the body may produce a more active poison than when grown in artificial culture-media.

The effects upon the tissues differ widely with the different bacteria, but in general they produce the death or profound injury of the adjacent cells, and quickly call forth an inflammatory reaction. A few, such as the typhoid bacillus, although causing necrosis of the neighboring cells, do not elicit the ordinary response of the neutrophile leucocytes, but rather produce a curious reaction, in which mononuclear phagocytic cells predominate. Others, such as the tubercle bacillus, may live a long time among cells which are not only alive, but actively multiplying, only to cause in time their complete destruction. While the effect of some bacteria such as the diphtheria and tetanus bacilli seems to depend therefore on their recognizable toxic products, the example of the tubercle bacillus shows us that some other factor is prominent in most instances in which no such pronounced toxin formation is found. This is doubtless the development of the allergic reaction which leads to the destruction of tissue upon the entrance of the protein of the bacterium into the body of an animal which has already experienced an infection with the same organism or even upon the extension of an infection which has been survived for a long time.

According to the character of the bacteria, their number, their concentration, and the resistance of the individual, infection may assume

various forms. Some organisms, notably those which produce soluble toxins (diphtheria and tetanus), appear to grow only at the point of inoculation or first infection, although they distribute themselves in small numbers in the blood-stream and tissues. From this local growth they diffuse their poisons. Others, having gained a foothold, tend to spread diffusely through the tissues, causing havoc wherever they go. Such are the streptococci, while the staphylococci are accustomed to concentrate themselves at various points in the tissues, and stir up an intense concentric inflammatory reaction around themselves (*abscess formation*). Either of these forms and many others may, however, in one way or another invade the blood-vessels and pour themselves into the flowing blood. When bacteria can be recognized in the circulating blood, we call the process *septicæmia*, and this term is being found to apply properly to more and more infectious diseases as careful blood cultures are made (pneumonia, typhoid fever, endocarditis, etc.). By *pyæmia* we mean that condition associated with septicæmia or bacteriæmia in which suppurative foci are formed here and there. The student should read in this connection the interesting works of Metchnikoff, Welch, and others upon these general topics of infection and immunity which can merely be outlined here. The remarkable progress in knowledge of this region of medicine in recent years has made the general and special consideration of infection and resistance the subject not only of many text-books, but of a literature so extensive as to be almost beyond the compass of one man's reading.

LITERATURE

- Metchnikoff: Immunité dans les maladies infectieuses, Paris, 1901.
Rich: Acta Pædiatrica, 1933, xvi.
Simon: Infection and Immunity, Philadelphia, 1912.
Welch: "Surgical Bacteriology," Dennis' System of Surgery, Philadelphia, 1895.
Zinsser: Infection and Resistance, New York, 1922.

The Pyogenic Micrococci.—While the bacteria belonging to this group unquestionably cause different diseases according to the special peculiarities of each, there is still a striking resemblance in their mode of action, and there are many things, such as endocarditis, lobular pneumonia, and meningitis, which may be caused by each of them in nearly the same fashion. We may, therefore, consider together in this chapter the effects produced by the *Staphylococcus pyogenes aureus*, the *Staphylococcus albus*, the *Streptococcus longus* or *hæmolyticus*, *Streptococcus mitior* or *viridans*, the *pneumococcus* or *Micrococcus lanceolatus* in its various types, the *gonococcus*, the *meningococcus* or *Micrococcus intracellularis meningitidis*, together with other forms and varieties. No attempt will be made to describe the organisms, nor to discuss their systematic relations, which are subjects for books on bacteriology.

STREPTOCOCCUS INFECTIONS

Since the time of Schottmüller, who first made use of the hæmolytic power of some streptococci for purposes of classification, many authors have been engaged in the attempt to put this upon a satisfactory basis,

but even yet without any very enduring result. The names of Gordon, Andrews and Horder, Holman, Smith and Brown, Blake, Smillie, Swift, and Kinsella are especially connected with this work, and certain things stand out clearly which were obscure before. It is agreed that the possession or lack of the power of haemolysis is of fundamental importance, so that streptococci are divided primarily into haemolytic and non-haemolytic forms. Attempts have been made by Holman to divide these groups further by studying the reactions of all the strains with various sugars, and while this gives reliable results, it is found that many of the subgroups are represented by rare examples because they are not the forms commonly concerned in the production of human disease, and we still find authors writing simply of haemolytic or non-haemolytic strains. Kinsella and Swift showed by the method of complement fixation that all the haemolytic strains are alike, while the non-haemolytic group is quite heterogeneous. Dochez has found, however, by testing the protection conferred by specific antisera that the haemolytic streptococci fall into four distinct groups which are not as yet to be distinguished in any other way. Haemolytic streptococci from human and bovine sources may appear much alike in the blood-agar plate. Brown utilized quantitative differences in the haemolytic titer in fluid media to differentiate them. Ayers and Avery and Cullen found that they could differentiate strains from these two sources by means of the final hydrogen-ion concentration produced in glucose broth. Ayers and Rupp found that the bovine strains hydrolyzed sodium hippurate, whereas those from human sources did not. These methods have been summarized and employed by Brown, Frost, and Shaw in a comparative study of haemolytic streptococci from human and bovine sources. Smith and Brown, and later Brown, in his monograph on the use of the blood-agar plate in the study of streptococci, describe as the α type of haemolysis the methaemoglobin formation and slight laking found round the colonies of the non-haemolytic form, *S. viridans*, while their β type of haemolysis is the complete ring of laking found about those of the haemolytic form, *S. haemolyticus*. The γ type is a non-haemolytic form which produces no methaemoglobin.

It must be evident from this that great difficulty is encountered in making any finer distinctions among these extremely common and widespread organisms. None of the old lines of classification based on the length of the chains, etc., are used any more, and *Streptococcus mucosus*, which formerly occupied a place here, is now recognized as *Pneumococcus Type III*.

While the two names, *Streptococcus haemolyticus* and *viridans*, are quite generally used in medical literature, it must be remembered that they are not specific, but indicate merely the beta and alpha types in blood-agar and that each of them includes a large number of species or varieties of streptococci. The haemolytic group includes very virulent strains, but also many harmless forms which are often found in milk. The same may be said of the *viridans* group, of which the pathogenic members usually produce less fulminant infections than the haemolytic streptococci.

It seems that we can separate rather sharply the pathological changes caused by the two main types of streptococcus, although it is possible that in some conditions either may be concerned. At least it is true that those lesions which are well known to be caused by either of them are perfectly characteristic, and it is probable that in time all will be found to have a specific peculiarity.

The Streptococcus Hæmolyticus.—While this organism is found in water, milk, etc., it seems probable that in most cases it is transmitted directly from another person to some portal of entry into the body. This is especially true in the respiratory infections, less so in the infections of the skin, digestive tract, etc.

Infections of the Respiratory Tract.—Abundant opportunity to observe such infections was afforded during the war in the bronchopneumonia which followed the epidemics of measles, influenza, and other diseases which occurred among the troops, but sporadic cases are not uncommon at any time. The invasion seems to take place in the mucosa of the nose, pharynx, and larynx, extending quickly to the accessory nasal sinuses, and later to the trachea and bronchi. Reddening of the mucosa, with a sensation of soreness of the throat, followed by swelling of the tonsils, the appearance of patches of whitish, necrotic material on the exposed surfaces, fever, and general illness are characteristics and last some days, but usually end in recovery. More severe effects of such angina are met with, and may be illustrated by the case of one of our colleagues who suffered from repeated attacks. In one of these the tonsils became greatly swollen and reddened, with thick patches of greenish, necrotic tissue and fibrin, which, on removal, left rather deep raw ulcerations. The whole pharynx was intensely inflamed, and firm lumps appeared beneath the angle of the jaw. He was profoundly ill, and the surgeons incised the swelling, which proved to be due to infection of the adjacent lymph-glands, from which a quantity of pus containing streptococci was drained. After that he recovered, but a year later the tonsillitis suddenly recurred, the surfaces of the tonsils, as well as the whole lining of the pharynx, became intensely inflamed and covered with a necrotic false membrane. There were tumefaction and induration of the glands and high fever. He rapidly became delirious, and then comatose. A rash, like that of scarlet fever, appeared over the whole body, with pin-point haemorrhages everywhere, and he died within seventy-two hours of the onset.

In other cases arising somewhat differently, from extension of the infection from a suppurating salivary gland, from a carious tooth, or from a peritonsillar abscess (quinsy), there may arise another form of angina, the so-called *Ludwig's angina*, in which all the loose tissues of the neck become densely infiltrated with inflammatory exudate in response to the dissemination of streptococci there. One case which we saw recently was thought to have started in an infected abrasion of the skin of the neck, but most of them arise from extension from the organs about the pharynx. The infiltration among the muscles and about the vessels and the pharynx is so dense as to be rigid and hard, so that these organs are solidly embedded. If death is postponed for a few

days, there may be liquefaction of some of the necrotic tissue and exudate.

Important are the numerous cases of *streptococcal sore throat* which occur in great epidemics with high mortality, and are generally traced to some dairy in which one or more cows with udders infected with the streptococcus give a milk which is thick, yellow, and stringy, and on examination proves to be really a mixture of milk and pus, with myriads of streptococci. Several epidemics of this kind have been reported recently in this country (Pearce, Capps, and others).

Smith and Brown and, more recently, Brown and Orcutt have studied some of these epidemics and have decided that the *streptococcus* concerned is a human parasite infecting the udder of the cow or introduced directly into the milk from an infected milker. It is not the bovine form which is so commonly present in dairy herds as the cause of the infectious mammitis or *garget*, but a human type which they have named *Streptococcus epidemicus*.

Severe streptococcal infections of the throat are well known to accompany scarlet fever, smallpox, diphtheria, and some other diseases, and, indeed, in the lack of all knowledge of the true cause of scarlet fever there are those who would ascribe it to the streptococcus.

In one great epidemic which we studied during the War, the primary disease was measles which affected those recruits from districts where they had not been previously exposed to the disease, as those from cities had. There was an overwhelming secondary infection with a haemolytic streptococcus and the combined effect was complicated. While those patients with measles who could be protected from any contact with the others infected with streptococci went through a relatively mild course, the streptococcus spread rapidly among the others and produced the most profound and generally fatal infection. There was rapid loss of voice and at autopsy the whole mucosa of the pharynx, larynx and trachea was found reddened and sprinkled with haemorrhage, or partly covered with greenish, pseudomembranous exudate, with ragged ulceration of the epiglottis, pyriform sinuses and vocal cords. There was sometimes a phlegmonous infiltration of the underlying tissue with enormous numbers of streptococci.

In the lungs which were often found collapsed by a great effusion of fluid in the pleura, the tissue was deep purple and throughout there could be felt hard nodules of varying size which on section projected as yellowish masses arranged in little groups about the terminal bronchioles and each showing in its centre the lumen of a tiny bronchiole exuding pus. About such groups was a broad zone of haemorrhage. The pleural fluid usually collected in great amounts was thin and watery with a massive sediment which seemed to be composed almost entirely of tangled chains of streptococci. Microscopic study of the sections from such a lung showed the terminal bronchioles filled with polymorphonuclear leucocytes with haemorrhage about them. Most striking, however, was the thickening and infiltration of their walls and of the walls of the adjacent alveoli with lymphoid cells or small mononuclears.

This interstitial infiltration, soon accompanied by the formation of

new connective tissue and by organization of the fibrinous exudate within the alveoli, gave the solidity to the areas about the bronchioles and these characters suggested the name interstitial bronchopneumonia which we have used for this type of lesion (Fig. 263). Hæmolytic streptococci were invariably found in predominant numbers and often in pure culture, but other organisms, especially the bacillus of Pfeiffer, were sometimes associated, and we have always felt that there might be some question as to the part it played, since it is known that a very



Fig. 263.—Interstitial bronchopneumonia.

similar nodular interstitial bronchopneumonia may be produced by the Pfeiffer bacillus alone. The characteristic form of interstitial bronchopneumonia is quite commonly found in children apart from any epidemic, but is nearly always a sequence of measles or pertussis, or perhaps some other of the infections of childhood in which as yet we are ignorant of the causative agent. In these cases which are currently discovered at autopsy (see Fig. 449) there is no abundant pleural exudate, but the

lungs on section are rather dry and suggest a wide-spread tuberculous infection. Doubtless the firm yellowish patches about the bronchioles have sometimes been mistaken for tuberculosis, but the microscopical study reveals the conditions described above. In these cases we have found various organisms, perhaps most commonly the Pfeiffer bacillus.

While the typical examples of interstitial bronchopneumonia (Figs. 264, 265) are made from photographs of cases in which measles was followed by a predominant streptococcal infection, it must be emphasized that this is a rather unusual sequence of events since all of our cases in recent years have shown other bacteria, most often the Pfeiffer bacillus, but always following a virus infection. It seems important to recognize the predisposing influence of the virus infection which makes

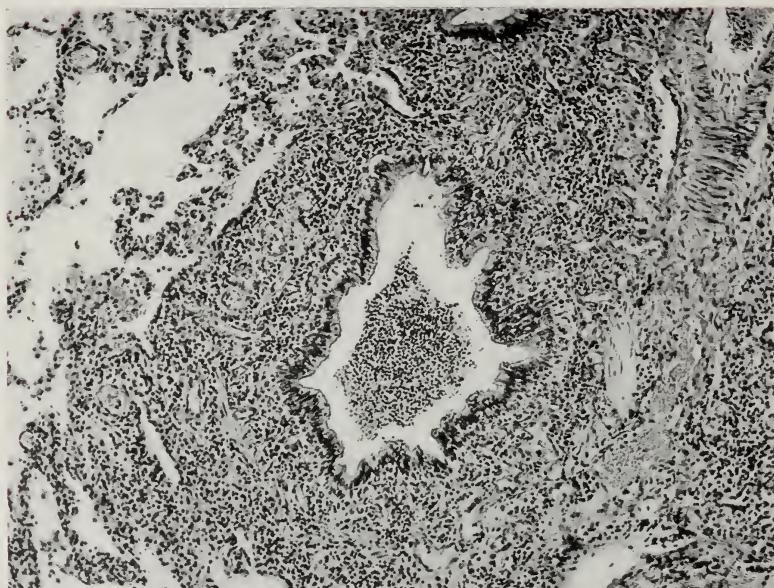


Fig. 264.—Interstitial bronchopneumonia with leucocytes in the lumen of the bronchiole, extreme infiltration of its wall with mononuclear cells.

possible the invasion of the bacteria and intensifies enormously their effects. Indeed, it is being realized that certain diseases can be produced only by such a combined effect and not by either organism separately.

There were other cases both after the measles and the influenza epidemic in which the haemolytic streptococci grew in extraordinary numbers through the substance of the lung in large areas. In these there was no interstitial infiltration, no nodule formation, and no restriction of the growth and spread of the bacteria. This type of acute pneumonia is usually patchy and without very definite outlines; the alveolar walls are not infiltrated with cells, but there may be extensive hyaline thrombosis of the capillaries. The number of bacteria found among the leuco-

cytes of the exudate is far beyond anything I have ever seen in other forms of pneumonia.

Infections of the Middle Ear.—The haemolytic streptococcus is a common cause of middle-ear inflammation or otitis media, but is by no means the only organism which can do this. Staphylococci and pneumococci may be concerned instead and, indeed, the Pneumococcus Type III, sometimes called Streptococcus mucosus, gives rise to the most severe, treacherous, and destructive form. Otitis media seems to be the result of the passage of bacteria from the infected and inflamed throat along the Eustachian tube to the middle ear. Of course, the opening of the tube is guarded, as Rich has shown, by folds of mucosa at its pharyngeal end, and is open only during certain movements of the muscles, especially the tensor palati. But when a sneeze is stifled by holding

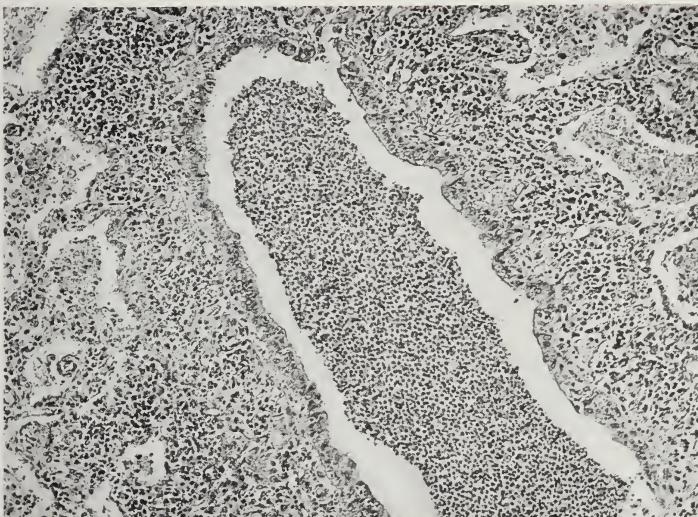


Fig. 265.—Interstitial bronchopneumonia. Leucocytes with bacteria in lumen of the bronchiole; extension of mononuclear infiltration into alveolar walls.

the nose, or when the nose is blown very hard, infected material may be driven up the tube. In a case which I followed, the attempt to smother a sneeze was followed by a sense of discomfort in one ear and next day by a sharp pain. The drum of the ear may be dulled a day or two later and bulge, or pus may be seen showing through it. If it is punctured the infection may clear up if the organism concerned is not a very tenacious one, but the outcome is very frequently not so happy. Instead the infection extends into the cavities of the mastoid process of the temporal bone, which fill with pus. Necrosis of the partitions of bone between these cavities takes place and may extend through other portions of the temporal bone until it reaches the dura mater with its lateral venous sinus. Libman finds that bacteriæmia may depend upon the thrombosis of the communicating jugular vein, and that it may be stopped by ligature below the thrombus. In this country and wherever

operative interference is reasonably prompt, thrombosis of the lateral sinus counts as a late complication, and any further extension through the dura to the meninges is rare. But in China and even in Austria and Germany the disease is often neglected until the infection has extended to produce not only local meningitis or meningeal adhesions, but an abscess in the temporal lobe of the brain. I have been especially impressed by the frequency of such abscesses in the German autopsy rooms as the cause of death, while they form the greatest rarity here. The exudate in the mastoid cells is purulent in the streptococcal and staphylococcal infections, but in the case of infection with the Pneumococcus Type III it appears as a pinkish gelatinous material which fills all the spaces and is loaded with the organisms.

Infections of the Digestive Tract.—Vague, and for the greater part unfounded, statements were formerly made about the part played by streptococci in the causation of dysenteries, but since the recent work of Shiga, Flexner, and others, it is clear that those affections are due to a totally different organism. Nevertheless, it still seems probable, although not proven, that some at least of the instances of terminal diphtheritic enteritis and colitis in persons dying after protracted illnesses may be due to streptococci.

Definitely of streptococcal origin are the *phlegmonous gastritis* and *phlegmonous enteritis*, in which the submucosa of the stomach or of the duodenum and jejunum is found to be enormously thickened by a tense inflammatory exudate loaded with streptococci. Invasion through some abrasion or ulceration of the mucosa, sometimes produced by a blow on the abdomen, gives origin to this condition. It is interesting from the fact that the walls of the digestive tract are rendered rigid and immovable by the exudate, and since this tract is unable to propel the intestinal contents, obstruction, with its characteristic symptoms, ensues, just as in paralytic ileus.

That the streptococcus may play an important part in appendicitis has already been mentioned.

Wound Infection.—Streptococcal infection through wounds or abrasions of the skin are perhaps not so common as those caused by the staphylococcus, but under certain circumstances, especially familiar to surgeons and pathologists, they occur and run a rapid course. A prick with a needle or a small unobserved cut during the performance of an autopsy in an infected case remains unnoticed for several hours, after which it shows a slight reaction and becomes painful: Little is to be observed at the point of the inoculation, but the whole arm aches, red lines, indicating an acute lymphangitis, run up the forearm, the epitrochlear and axillary glands swell and become very tender. A feeling of extreme illness with fever and perhaps a chill ensues. Infiltration of the loose tissue of the arm and axilla may take place and require surgical intervention, and although the body resistance is likely to overcome the bacteria, death from general septicaemia is not rare.

One instance of this sort in an artist colleague who was making a drawing at an autopsy had interesting complications. The swelling and tension in his arm were such that extensive incisions were made, in the midst of which the ulnar nerve was

injured with a clamp. On recovery it was found that half of his hand was paralyzed, and some months later a second operation was undertaken to find the point of injury. The nerve was found embedded in a dense scar, which was dissected away, after which, doubtless through allowing new nerve-fibres to grow down through this obstructed point, mobility and sensation gradually but completely returned.

More extensive wounds with laceration of tissue and soiling are prone to develop streptococcus infections. Fracture of the skull extending into the accessory nasal cavities may lead to a suppurative meningitis, while compound fractures of the other bones formed, in pre-antiseptic days, the most feared of traumatic injuries. Of course, since they often developed a pyæmic condition, it is likely that other organisms, including the staphylococci, were frequently concerned, but the diffuse inflammation and septicaemia caused by the streptococcus were not uncommon. Even now, with all our vaunted knowledge of bacteriology and antiseptics, the surgeons must be careful to treat soiled and lacerated wounds in such a way that the circulation is not interfered with by suture or bandages, lest streptococci multiply in the hampered tissues and finally invade the whole body. The conditions under which soldiers in the trenches in the Great War were exposed to lacerating wounds are familiar to every one, and although the tetanus bacillus and the gas bacillus added to the dangers, the most fearful streptococcus infections were described.

Erysipelas.—The haemolytic streptococcus responsible for puerperal sepsis, etc., is also the cause of the peculiar infection of the skin, which starts from some slight wound or abrasion and which has always been known as erysipelas. It is commonly seen on the face or head, but it is also frequent in other parts of the body. Erdmann, who studied 800 cases, found that 500 of them were uncomplicated cases of facial erysipelas, while far smaller numbers were affections of other parts of the body or migrating forms. It is a rapidly spreading inflammation of the skin, which becomes reddened and elevated into a dense, advancing, irregular margin, which pushes ahead, leaving the previously affected part pale again or somewhat pigmented. Where the skin is loose, it becomes oedematous and enormously swollen. Where it is stretched or tightly bound to the underlying tissues, the spread of the disease is likely to stop, and hence the treatment recommended by Wölfler, which consists in stretching the skin with strips of adhesive plaster. In the eyelids, scrotum, vulva, etc., the oedema may be such that the tense skin becomes necrotic. This is likely to occur, too, where erysipelas has started from old leg ulcers, or where it occurs in tuberculous or other wasted persons. Great blisters or bullæ are formed sometimes. The red, elevated, glistening, tense margin shows the characteristic anatomical lesion, which consists of a profuse infiltration of the crevices of the tissue and the lymph channels with streptococci. None seem to be found in the blood-vessels, but their presence in the lymphatic canals causes an inflammatory reaction which may be perivascular in its distribution. The corium is oedematous, and there are great quantities of wandering cells, largely of a mononuclear character. Occasionally the exudate is more nearly purulent, and abundant abscesses, loaded

with streptococci, may develop in the depths of the corium; but this is a rare consequence, and usually the process continues to spread without suppurating, by the advance of the streptococci, and fades in the region already traversed. It is rather remarkable that in a streptococcal infection, which elsewhere is met with an outpouring of neutrophile leucocytes, there should be found in the skin so many lymphoid or small mononuclear wandering cells. Compare the results of Rhoads and Goodner (Jour. Exp. Med., 1931, liv, 41) with dermal pneumococcus infection in which abundant mononuclear cells finally accompany the leucocytes.

The disease affects infants as well as adults, but is less common in older children. It is particularly likely to recur, and those persons who are predisposed may have a great many attacks, which in the end cause a great thickening and induration of the skin affected. It is not limited to the external skin, but may extend to the mucose, involving the pharynx, the larynx (often with fatal cedema of the glottis), the middle ear, the vagina, etc. Death occurs from general septicæmia, pneumonia, etc., but most often the cases recover. Erdmann has seen 93 deaths in 800 cases. Were it not for the fact that erysipelas commonly appears as a terminal infection in persons already weakened by alcohol or disease, the deaths ascribed to it might not reach so high a number. In a case which came to autopsy recently there was found a wide-spread tuberculosis of the lymph glands and spleen, but during the last two days of life erysipelas had set in and spread rapidly over the face and neck, causing such cedema of that side of the face that the eye was not only closed, but presented its lids as great bulging masses which projected out over the swollen cheek. The Streptococcus haemolyticus was recovered in the blood. In other fatal cases the cloudy swelling of the viscera, the acute splenic tumor, and other characteristic features of septicæmia were found. In women, attacks of erysipelas often appear with curious regularity with the periods of menstruation. Jordan, Jochmann, Reiche, and others have described cases of erysipelas caused by the staphylococcus, and Neufeld has found the pneumococcus responsible, but these are indeed rarely of aetiological importance.

Chr. Holmes discusses, in an interesting paper, the mystery which has long hung about the pathogenesis of erysipelas, and fairly demonstrates a plausible explanation of its mode of onset. Formerly a distinction was made between spontaneous and wound erysipelas, it being recognized that after operation or lacerated wounds an erysipelatous infection was likely to start from the edges of the wound. This distinction was given up because all erysipelas was later thought to begin in some abrasion, often very inconspicuous in nature. Holmes points out the great frequency of latent infection of the nose, nasal sinuses, etc., with streptococci and pneumococci, the overwhelming preponderance of facial erysipelas, and among these cases the very large proportion starting from the nose. Further, he collects many cases in which erysipelas followed operations which lay open infected nasal sinuses, infected middle ear and mastoid cells, etc., and quite logically draws the conclusion that in all probability facial erysipelas is most commonly the

result of the extension of infection from the nasal cavity. He further points out the frequency of extension of this inflammation to the eyelids, conjunctiva, and the various parts of the eye, where it may produce destructive effects.

Recently Amoss, Birkhaug, and others have been able to show that the streptococcus concerned in erysipelas is a peculiar one, immunologically different from others, as, for example, that commonly found in scarlet fever, and that its effects may be neutralized by the local injection of a specific antiserum, although unaffected by a serum prepared with other streptococci. This may go far to explain the peculiarities of infection with this organism.

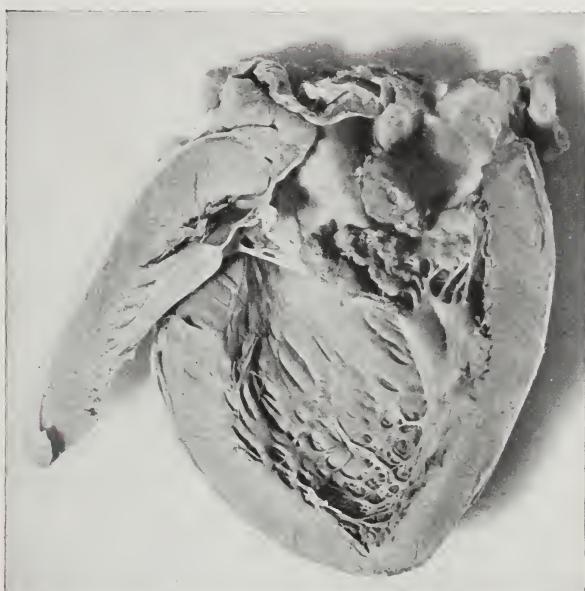


Fig. 266.—Endocarditis due to the *Streptococcus haemolyticus*. Great friable vegetations on the mitral valve.

Puerperal Endometritis.—The anatomical changes and mode of occurrence of infection of the puerperal uterus have been described in an earlier part of this book, and it need only be said here that while the non-hæmolytic forms of the streptococcus may be found in the normal puerperal uterus, the presence there of the hæmolytic form is of serious import and that the actual cases of puerperal endometritis are usually caused by this organism.

Endocarditis.—With regard to all the forms of bacterial endocarditis the student is referred to the admirable monograph of Dr. Thayer who has analyzed and studied all of our cases.

Streptococci are by far the commonest bacterial causes of endocarditis, outnumbering other bacteria that may be concerned by a great deal. They really fall once more into two groups, the beta-hæmolytic,

and the alpha-hæmolytic (*S. viridans*). Of these, the beta-hæmolytic streptococci are found in the relatively acute cases where infection of the heart valves is a mere incident in a general streptococcal septicæmia. The *Streptococcus viridans* is the cause of a subacute or slowly progressing destructive endocarditis in which, it is true, bacteria can be recog-



Fig. 267.—*Streptococcus* vegetation in mitral valve.

nized in the blood, but in which all the symptoms seem referable to the endocarditis and are the result of embolic processes from thrombi broken off the heart valves or evidences of disablement of the heart itself.

Endocarditis produced by the hæmolytic streptococcus is in our material, relatively rare. The vegetations are usually on mitral or

aortic valves and are small and friable at first, although they increase in size, and at autopsy may appear as large crumbling rounded masses of thrombus material (Fig. 266), sometimes large enough to obstruct much of the valvular orifice. They are often found on valves previously diseased and are not particularly characteristic in form or position. The vegetation may appear on both sides of the valve with perforation of the valve, and sometimes large holes so produced allow of regurgitation. Or the infection may extend into the muscular wall of the heart, as in one case in which in this way an abscess was formed in the septum in conti-

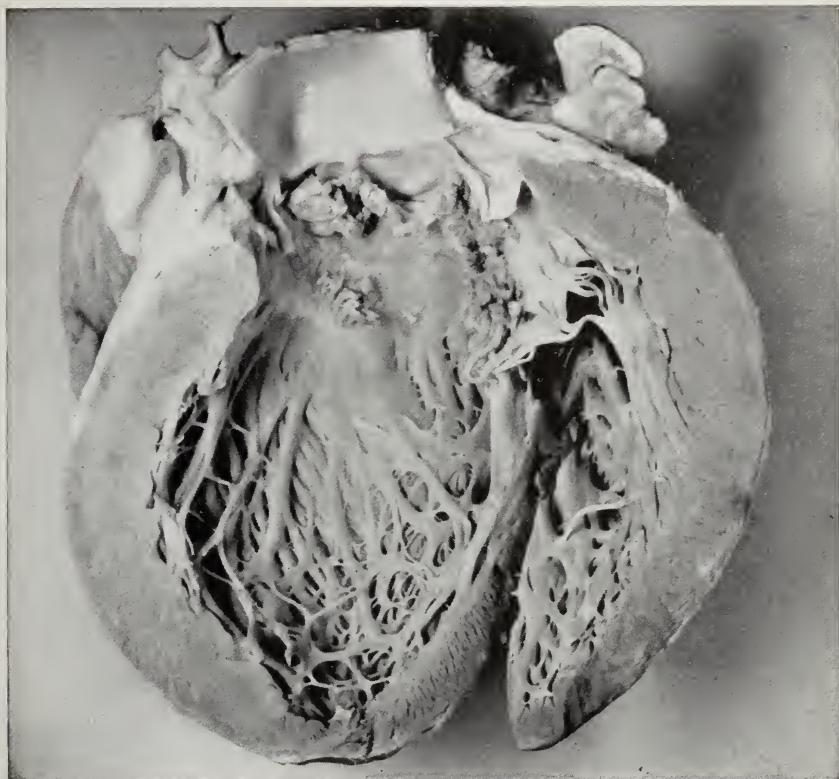


Fig. 268.—Endocarditis due to the *Streptococcus viridans*. Vegetations on septum and mitral valve produced by contact with a flapping fragment of the aortic valve.

nuity with a vegetation on the aortic valve. It projected beneath the pulmonary orifice and finally ruptured there, forming a communication between the ventricles.

Such endocarditis is associated with typical evidences of the existence of a generalized streptococcal septicæmia and is usually easily traceable to some very obvious portal of entry, such as a puerperal endometritis or extensive infection of the middle ear and mastoid with thrombosis of venous channels. Septic infarctions (Fig. 269) constitute a frequent accompaniment.

Subacute endocarditis (*endocarditis lenta*), caused by the *Streptococcus viridans*, is a far more characteristic phenomenon and can be recognized with almost complete certainty both clinically and by inspection of the lesions in the heart. The origin of the infection is usually obscure, but is often ascribed to abscess formation about the roots of a tooth. The infection begins gradually and goes on with increasing severity, but seldom with the fulminant violence of the haemolytic type, for months, usually ending fatally within a year. Such a patient shows increasing anaemia and is easily fatigued. Emboli are thrown into the tissues and produce in the skin minute, painful haemorrhages with pale

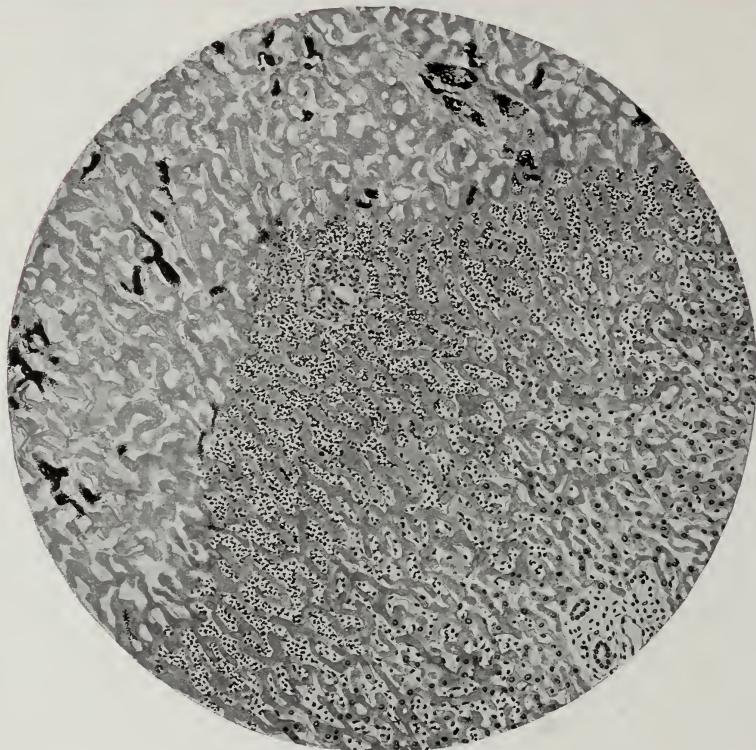


Fig. 269.—Margin of septic infarction in the liver. The capillaries in the necrotic region are crowded with streptococci.

or white centre. Larger emboli passing to the brain may cause a partial paralysis, and the effects of others are found at autopsy in the infarcts of spleen, kidneys, and other organs. Since these are infected emboli it is not surprising that their presence is still further injurious, and in the kidneys the acute and subacute glomerulonephritis which very frequently accompanies this type of endocarditis has been regarded as embolic by Löhlein and Baehr.

At autopsy the heart is generally enlarged, but without pericarditis. The lesions are found usually upon mitral or aortic valves, or both. It is evident in nearly every case that the vegetations are lodged upon

'valves which are much scarred and thickened. This may be due to the slow progress of the disease with constant efforts at healing, but it is generally suggested that a preceding rheumatic affection has prepared the way for the lodgment of these streptococci. We have observed in rheumatism a peculiar patch of thickening of the wall of the left auricle with Aschoff bodies and an inflammatory reaction which ends in the formation of a puckered scar there, and in the cases of *Streptococcus viridans* endocarditis this same place forms the site of vegetations in very many cases. Dr. Thayer feels that this is another example of the

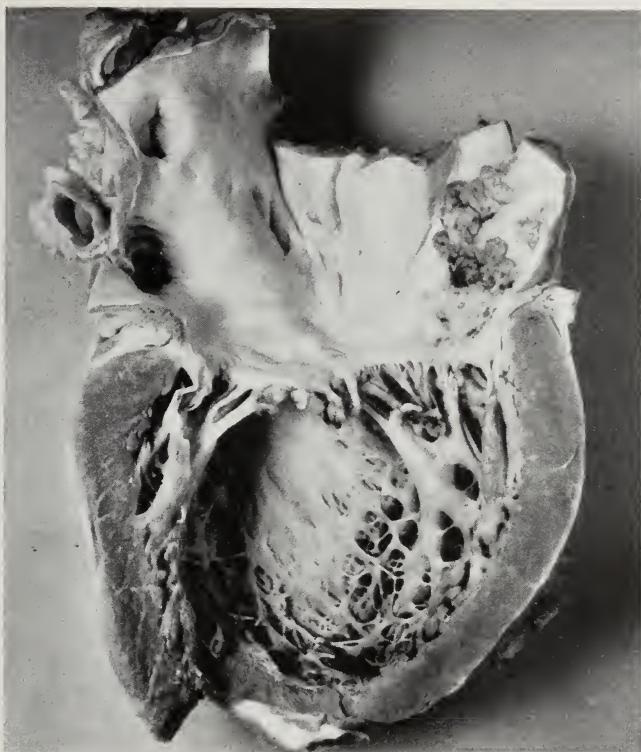


Fig. 270.—Subacute endocarditis (*Streptococcus viridans*) involving mitral and a typical position on the wall of the auricle. The vegetations occupy the site of old rheumatic lesions.

part played by rheumatism in preparing the field for the lodgment of the streptococcus.

The vegetations are usually rather small and rough, but very numerous and very destructive, so that the valves are extremely apt to appear as ragged, torn shreds covered with rough broken masses of thrombus material (Fig. 270). The chordæ tendineæ of the mitral valve are especially overgrown by the vegetations and soon eaten through, so that loose ends flap about covered and rounded off by the thrombus material. A peculiar result of this, emphasized by Grant, has been very striking in

our recent cases, namely, the infection of the wall of the heart or root of the aorta wherever such loose flapping shreds strike against it. Mycotic aneurysms or excavations by the bacteria appear at such places and are shown in Figs. 110, 111, 271. Their form is influenced by the pressure of the blood, and those in the substance of the mitral valve have an orifice turned toward the ventricle, the sac bulging into the auricle, while in the aortic valve the sacculation projects into the ventricle with its orifice in a sinus of Valsalva. The wall of the aorta seems especially vulnerable and is quickly eaten through by the bacteria, so that a sac protrudes on its adventitial surface.

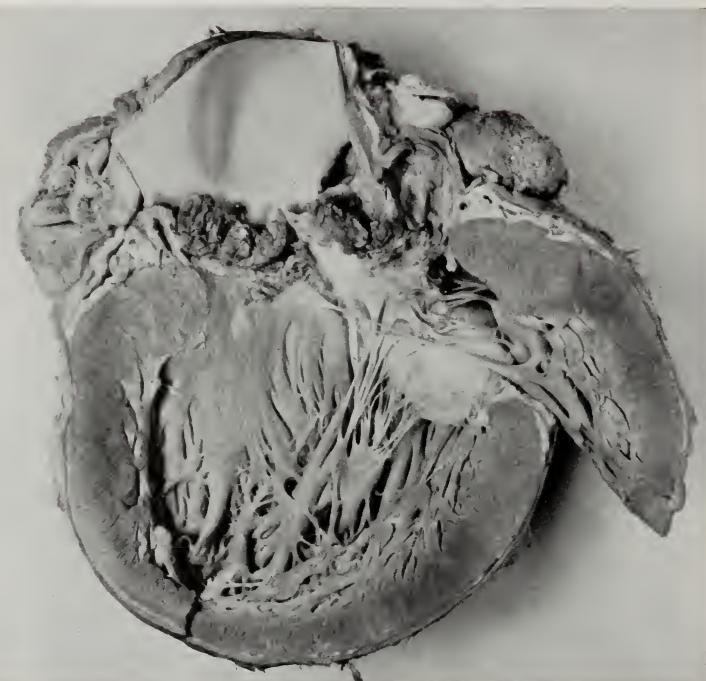


Fig. 271.—Endocarditis due to the *Streptococcus viridans*. Vegetations on the aortic valves have, through contact, produced excavations in the aorta and base of mitral

There is usually a well-defined acute splenic tumor with infarcts, the typical nephritis mentioned above, often infarcts in the brain and general evidence of chronic passive congestion, but hardly the typical picture of acute septicæmia such as accompanies infection with the haemolytic streptococcus and other more virulent organisms. Particularly the extensive blood-staining of the tissue sometimes seen in those cases is lacking here.

LITERATURE

Streptococcal endocarditis:

Baehr: Jour. Exp. Med., 1912, xv, 330.

Clawson: Arch. Int. Med., 1924, xxxiii, 157.

Grant: Heart, 1924, xi, 9 (excellent paper).

- Lewis and Grant: Heart, 1923, x, 21.
Libman: Jour. Amer. Med. Assoc., 1923, lxxx, 813; Trans. Assoc. Amer. Phys., 1912, xxvii, 157; 1913, xxviii, 309.
Löhlein: Med. Klinik, 1910, vi, 375.
Thayer: Johns Hopkins Hosp. Rep., 1926, xxii, 1.
Wright: Jour. Path. and Bact., 1925, xxviii, 541.

General Streptococcus Septicæmia.—Although the clinical and anatomical features of a general septicæmia or invasion of the streaming blood by bacteria have many special characters, depending on the type of organism, there is a great deal in common among them, and at autopsy one frequently recognizes the existence of a general septicæmia from the condition of the organs without being able to say whether it is due to a streptococcus, pneumococcus, staphylococcus, or some other organism. Of course, a staphylococcus septicæmia is likely to be marked by the presence of numerous abscesses, typhoid septicæmia by lesions peculiar to it; septicæmia due to Friedländer's bacillus by peculiarities of the exudate, and so on, but there are still features common to septicæmia in general.

While at times it is possible to find streptococci or other organisms circulating in the blood, this seldom continues for any great length of time unless there is a constant source of supply, such as a large vegetation loaded with growing bacteria, hanging upon a valve of the heart, and shedding the bacteria continuously into the blood-stream. For this reason we have become skeptical of the existence of a septicæmia as such, and think of the presence of bacteria in the circulating blood as the temporary result of their discharge from a focus of infection which is in close or direct communication with the blood-stream. That the bacteria grow and multiply in the blood, so as to constitute a true bacteriæmia, seems in most instances extremely unlikely, and occurs, if at all, shortly before death in the fatal cases in which we may suppose the antibacterial powers of the blood at a low ebb. After death the blood becomes filled with them, so that cultures from the heart's blood at autopsy, unless immediately after death, are of very little interest. These statements seem to be supported by the experiments of Hopkins and Parker who observed the fate of streptococci injected into the blood-stream in cats which are insusceptible and rabbits which are susceptible to infection. In both, the bacteria disappeared from the blood very quickly, but in the rabbits, after foci of infection were established in the tissues, the organisms were once more shed into the blood. Nevertheless the instances in which there are foci of infection quite adequate to allow a more or less continuous escape of bacteria into the blood are so numerous that we are justified in describing the symptoms and anatomical effects of a general septicæmia.

The symptoms begin with a chill and high fever, which continues in various forms, sometimes continuously high, but more often with remissions and daily exacerbations with chills. The blood is quickly and profoundly altered. There is a great increase in the number of leucocytes, although in the severe cases, in which resistance fails, the lack of any increase or an absolute decrease in their numbers may be an index

of an unfavorable outlook for the patient. The destruction of blood-corpuscles proceeds rapidly, and extreme pallor may quickly ensue. In the skin and in the retinae the clinician is made aware of the presence of bacteria by the appearance of minute points of yellow opacity, surrounded by little flecks of haemorrhage. These are due to the plugging of tiny blood-vessels with emboli of bacteria, or, when there is endocarditis, with fragments of the vegetations loaded with bacteria. In the skin the thickness of the tissues makes them appear as homogeneous petechial haemorrhages, but in the conjunctiva or retina, or in the serous surfaces at autopsy, it is usually possible to distinguish a central necrotic fleck. In the skin such emboli may produce no haemorrhage, but instead tender, nodular swellings, which on section reveal a focus of inflammatory infiltration around the obstructed vessel. Extensive purpuric haemorrhages may spread throughout the skin, sometimes becoming con-

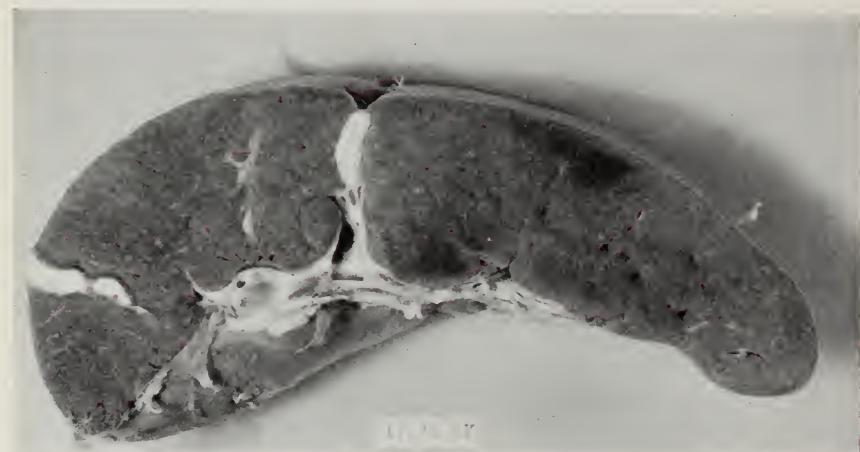


Fig. 272.—Acute splenic tumor associated with subacute endocarditis, *Streptococcus viridans*. There are two rather old infarcts.

fluent over considerable areas. In other cases erythematous rashes appear, resembling those of scarlatina or of measles.

In the case of streptococcus septicæmia there are found relatively few focal internal lesions produced by the lodgment of the bacteria. The most common are those in the lungs, which may take the form of bronchopneumonic patches or abscess-like infiltrations, and those in the joints, where at times there is found an intense inflammatory reaction with a purulent exudate in the synovial cavity.

In many cases these focal affections are absent. Endocarditis is, of course, focal in this regard, and, as stated, the dislodgment of fragments of the vegetations mechanically produces lesions elsewhere. But the more direct effects of the diffusion of bacteria in the blood are seen in the cloudy swelling of the liver and kidney, and such other organs as are composed of tissue capable of showing a cloudiness from changes in the water or granule contents of the cells. The nature of this is dis-

cussed elsewhere (Chapter VII). The heart muscles partake of this dull, opaque appearance, which is intensified there, as in the liver and kidney, by the appearance in the cells of many minute globules of fat. The acute and subacute nephritis which has been described elsewhere requires time to develop, and is rather an accompaniment of those streptococcal infections which have already lasted for some time. The bone-marrow, actively exercised in the production of leucocytes, is often found to have assumed the opaque cellular appearance which is also found in anaemias, where active regeneration of the blood is required. In septicaemia death may occur before this stage of activity is reached, but if the patient survives long enough, examination of the marrow will reveal a great increase in the number of myelocytes which form the polymorphonuclear leucocytes, and also of those cells which go to form red corpuscles.

The spleen is enlarged and soft, with peculiar alterations of its substance which are discussed under the non-committal phrase *Acute Splenic Tumor*.

Acute Splenic Tumor.—In practically all acute infectious diseases, but especially in such intense forms as the septicæmias under discussion, the spleen becomes tumefied, so that it is readily palpable beneath the margin of the ribs. Its size varies greatly, but its weight may reach 600 to 700 grams or more. The capsule is tense, but the organ is soft, so when it is cut through the cut surface swells forward, evertting the edges of the capsule (Fig. 272). One may scrape off with the knife or even with the finger a quantity of smeary, paint-like pulp. Indeed, the spleen is so soft sometimes that it spreads out on the pan or even flows as a semifluid material. The trabeculæ are sunken below the swollen surface, or else, if the cut surface has been scraped, they alone may be left as shaggy threads after the pulp has been wiped away to a considerable depth. In such extreme examples of softness it is difficult even to see the Malpighian bodies. In other cases they are much enlarged and conspicuous, sometimes with an opaque, yellowish, central fleck in each. Ordinarily the splenic pulp in such swollen spleens has a velvety or pasty appearance, and is very opaque and of a dull, pinkish-gray color. In these latter particulars the acute splenic tumor of septic conditions is very different from that of typhoid fever, which is deep red in color, and almost jelly-like in consistence, owing to the great quantities of red corpuscles held in its pulp. In order to give any idea of the nature of the change in the spleen it is necessary, first, to refer briefly to the main points in its structure, as worked out by Weidenreich, Mollier, and others. The Malpighian bodies, rather sharply marked out from the actual splenic pulp, are collections of lymphoid cells in a reticulum formed from the adventitia of the arterioles, so that they are periarterial lymphoid nodules. After leaving the Malpighian body the branches of the arteriole empty into one of the peculiar wide venules, which, entangled together, make up the bulk of the splenic pulp. These venules have walls which are formed of peculiar, elongated endothelial cells, whose central nucleus is relatively large, causing a bulging at the middle point of the long tapered cell, which projects somewhat into the lumen. Cross-sections of the venules sometimes pass through many of the nuclei; sometimes, on the contrary, they show chiefly sections of the protoplasm of the cell. Outside these each venule is surrounded by a basketwork of elastic reticulum fibrils, which are connected with the general reticulum of the pulp. Whether there is also an intervening structureless membrane, upon which the endothelial cell lies, is not perfectly clear. Weidenreich states that there is such a membrane perforated here and there. In the spaces between these venules there lie the cells of the splenic pulp, which are of various sorts, and it is in connection with them that our information seems least precise. Many red corpuscles are normally found there, and many mononuclear cells of various forms. Polymorphonuclear leucocytes occur, but are less abundant. It is

difficult to say whether any of these mononuclear cells are peculiar to the spleen, or whether they contribute largely, or at all, to the circulating blood. Morris found them swept out in numbers in the blood of the splenic vein, while others have found the reverse, *i. e.*, the mononuclear cells which entered the spleen with the arterial blood retained there, while polymorphonuclear leucocytes pass through. There seems to be no doubt that in cases of extreme anaemia, especially when the function of the bone-marrow is interrupted, myeloid cells appear in the spleen. Further, it is clear that some cells, especially large pale branching cells with pale vesicular nuclei, act greedily as phagocytes in the splenic pulp and often contain pigment which gives the reactions for iron. But in most instances the endothelial cells which line the venules are not phagocytic, although generally believed to be so. Any study of the spleen in a long series of cases shows such a bewildering variety of activities and cell accumulations, however, that it is impossible to make a satisfactory brief statement about it.

The acute splenic tumor accompanying streptococcal and similar infections shows microscopically relatively slight changes in the Malpighian bodies, but a very great

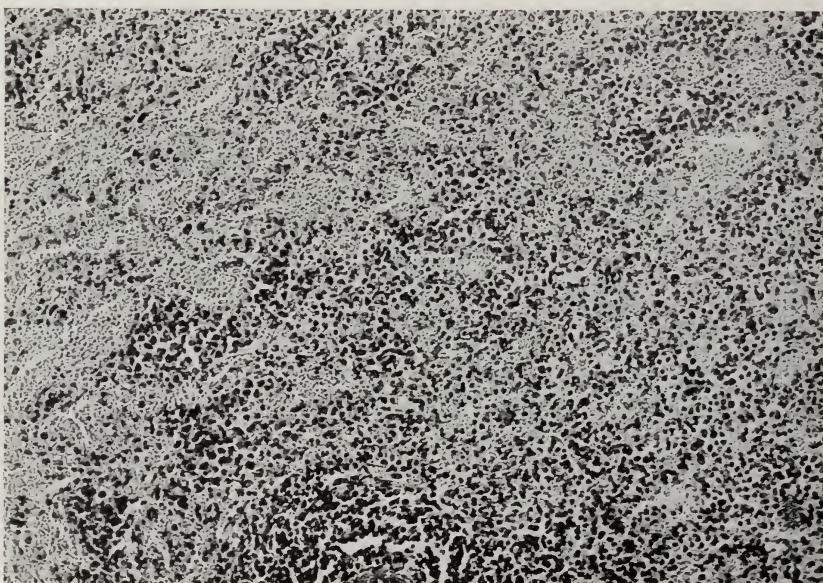


Fig. 273.—Acute splenic tumor associated with acute streptococcal endocarditis.

accumulation of cells in the meshes of the reticulum between the venules, while the walls of the venules are unchanged (Fig. 273). In a few cases neutrophile and eosinophile polymorphonuclear leucocytes are quite abundant there, but this is exceptional. Generally the majority of the cells, which seem accumulated in groups or masses and not uniformly distributed, are mononuclear. There are, besides the large pale branching phagocytic cells described above, numerous small mononuclear cells little larger than lymphocytes, with others of slightly larger size. Conspicuous among them, however, are groups of still larger cells which are rounded or pear-shaped, never phagocytic, with rather large, deeply stained nucleus with clumps of chromatin. This is usually eccentrically placed and surrounded in part, at least, by an unstained halo, while the rest of the cytoplasm takes a bluish stain with methylene-blue. In other words, these are morphologically identical with plasmacells. Red corpuscles are present, but not in greatly increased numbers. It is this great accumulation of nucleated cells which gives the pastiness and gray opacity to such spleens.

In our ignorance of the exact nature of the process one gains the impression that this great hyperplasia is analogous to that seen under similar conditions in the bone-marrow, where hyperplasia of cells is associated in our minds with the furnishing of necessary elements to the blood. Jawein, however, regarded the swelling of the spleen as a process associated with the destruction of red corpuscles, and found that it occurred only in those intoxications and infections in which there was much blood destruction. The advent of so many cells would, for him, represent a phagocytic function.

While in the typhoid spleen this phagocytosis of red cells and other débris is a very obvious feature, and most extensively carried on, it is by no means conspicuous in the spleens of septic infections, and, indeed, one sees relatively little phagocytosis in this pulp. Bernhardt, who studied especially the spleens of cases of scarlet fever and typhoid fever, draws this same contrast in another connection. He finds that in scarlet fever huge numbers of blood-platelets accumulate and are engulfed by phagocytic cells. Probably this occurs also in other infections, but in order to



Fig. 274.—Acute splenic tumor associated with streptococcal endocarditis.

prove that these platelets are not merely the débris of red corpuscles, he shows that in typhoid fever, where there is such active phagocytosis of red corpuscles, platelets are relatively few in number in the spleen. This is another theory of phagocytosis to explain the swelling of the spleen, but hardly more completely satisfactory than that of Jawein.

In diphtheria Washkewitz points out that the especial enlargement of the Malpighian bodies is due to the appearance of a central mass of large, pale phagocytic cells, which she thinks are probably derived from the lymphoid cells and not from the reticulum, as Ziegler had thought. These conspicuous pale central masses of large cells in the Malpighian bodies are by no means confined to diphtheria, but occur in many types of infections, especially in children and young people. We have reviewed the last 500 autopsies in this regard, and have found many cases in which they occur. They are all in cases of infection of one sort or another, with bronchopneumonia, tuberculosis, diphtheria, peritonitis, and many toxic processes, among which skin burns are notable. But they are not particularly a feature of

the acute splenic tumor, in which the splenic pulp is especially swollen. The large cells have pale, vesicular nuclei, abundant pale-staining protoplasm, and are frequently loaded with fragments of other cells which they have engulfed. They themselves often show degenerative changes; their nuclei become fragmented, and in time the mass may come to look like a focal necrosis with clumps of broken nuclei.

F. A. Evans has carried out in our laboratory a study of the forms of acute splenic tumor in human beings and those produced experimentally in animals, employing vital stains and the oxydase reaction in the attempt to distinguish the various cells found there. He confirms the sharp distinction made between the red type found in typhoid fever and the gray one in the infections with all the pyogenic bacteria. The red type is distinguished by hyperplasia and phagocytic activity of the reticulo-endothelial macrophages and decrease in the number of the other cells of the pulp. The gray type, on the contrary, shows a great increase in the pulp cells, especially the oxydase-containing myeloid elements, with no change in the reticular and endothelial cells.

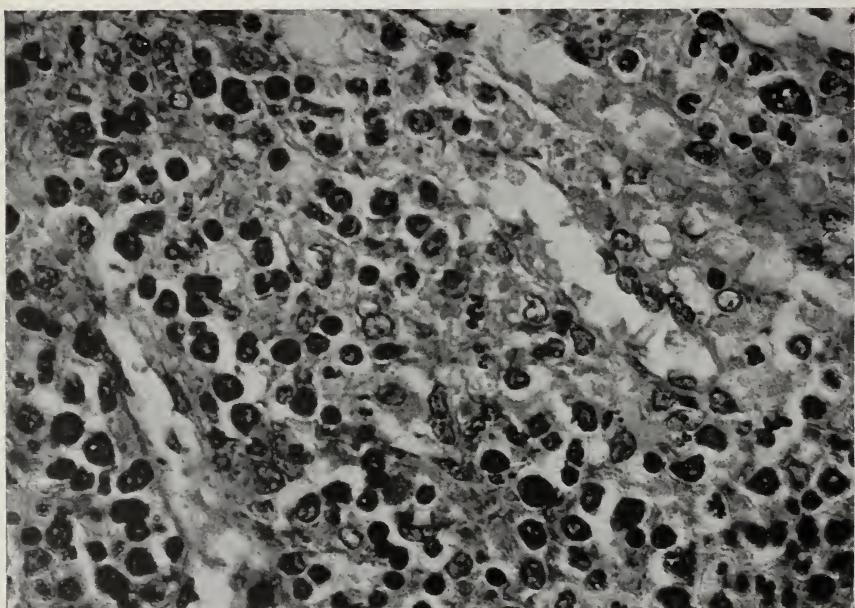


Fig. 275.—Acute splenic tumor, higher magnification of splenic pulp to show the character of the cells between tissues.

It must be said that further work is required to make clear the complex nature of acute splenic tumor, which in some cases seems to be a response to the presence of the débris of red corpuscles or other cells; in others, to the diffusion of a toxin or bacteria. The part of the spleen in reconstructing the blood seems to be little understood in spite of numerous studies which have been made recently, but more will be said on this point in connection with the diseases of the blood. On the whole it seems probable that the changes in the spleen represent its activity in producing defensive substances in response to the infection but we have no precise information.

Rich, however, has found that by injecting egg-white or horse serum into rabbits with antibody formation, he could produce a great enlargement of the spleen with proliferation and enlargement of mononuclear cells in the marginal zone of the Malpighian bodies, exactly as occurs in the early stages of acute splenic tumor in bacterial infection. These cells spread into the pulp and give the recognized histological picture of acute splenic tumor. Isolated in tissue culture and studied

with the aid of motion pictures, they prove to be identical with those developed in culture of lymphocytes.

LITERATURE

General Studies of Streptococci:

- Avery and Cullen: *Jour. Exp. Med.*, 1919, xxix, 215.
 Ayers and Rupp: *Jour. Infectious Dis.*, 1922, xxx, 388.
 Brown: *Monograph*, Rockefeller Institute, No. 9, 1919. *Jour. Exp. Med.*, 1920, xxxi, 35, 49. *Jour. Infectious Dis.*, 1926, xxxviii, 381.
 Capps and Davis: *Trans. Assoc. Amer. Phys.*, 1914, xxix, 279.
 Dochez, Avery, Lancefield: *Jour. Exp. Med.*, 1919, xxx, 179.
 Gay: *Jour. Laboratory and Clin. Med.*, 1918, iii, No. 12. (Extremely good review of recent literature.)
 Holman: *Ibid.*, 1916, xxiv, 377.
 Hopkins and Parker: *Jour. Exp. Med.*, 1918, xxvii, 1.
 Kinsella, Kinsella, and Swift: *Jour. Exp. Med.*, 1918, xxviii, 169, 181. *Arch. Int. Med.*, 1917, xix, 367.
 Lenhardt: "Septische Infektionen," Nothnagel, *Spec. Path. u. Therap.*, 1899.
 Libman: "Otitis," *Amer. Jour. Med. Sci.*, 1909, cxxxviii, 409.
 MacCallum: *Monograph*, Rockefeller Institute, No. 10, 1919.
 Smillie: *Jour. Infectious Dis.*, 1917, xx, 45.
 Smith and Brown: *Jour. Med. Research*, 1915, xxxi, 455.

Erysipelas:

- Amoss and Birkhaug: *Trans. Assoc. Amer. Phys.*, 1925, xl, 5.
 Birkhaug: *Johns Hopkins Hosp. Bull.*, 1925, xxxvi, 248; xxxvii, 85, 307.
 Erdmann: *Jour. Amer. Med. Assoc.*, 1913, lxi, 2048.
 Fehleisen: *Aetiologie des Erysipels*, Berlin, 1883.
 Gay and Rhodes: "Erysipelas," *Jour. Infectious Dis.*, 1922, xxxi, No. 2.
 Holmes: *Ann. Otol., Rhin., and Laryngol.*, 1907, xvi, 457.
 Jochmann: *Mohr u. Stachelin. Handb. d. inneren Medizin*, Berlin, 1911, i, 578, 717.

Acute Splenic Tumor:

 Bernhardt: Ziegler's *Beiträge*, 1913, lv, 35.
 Evans: *Johns Hopkins Hosp. Bull.*, 1916, xxvii, 356.
 Jawein: *Virch. Arch.*, 1900, clxi, 461.
 Mollier: *Arch. f. mikr. Anat.*, 1911, lxxvi, 608.
 Rich, A. R.: *Proc. Soc. Exp. Biol. and Med.*, 1935, xxxii, 1349.
 Washkewitz: *Virch. Arch.*, 1900, clix, 137.
 Weidenreich: *Arch. f. mikr. Anat.*, 1901, lviii, 247.

CHAPTER XXVI

TYPES OF INJURY.—BACTERIAL DISEASE (Continued).— STAPHYLOCOCCUS INFECTIONS

General character. Furunculosis. Paronchyia, impetigo, etc. General septicaemia, pyæmia, suppurative nephritis, endocarditis, lobular pneumonia, osteomyelitis.

THE *Staphylococcus pyogenes aureus*, *Staphylococcus albus*, and other less important forms, including the *Staphylococcus citreus*, are concerned in these infections. Much of their peculiar effect is dependent upon their tendency to grow in clumps and to cling together, rather than to spread diffusely. Hence in the tissues there is a focal character in the lesions they produce, in contrast with the more spreading lesions of the streptococcus. For the same reason the entrance of the staphylococcus into the circulating blood results in its deposition at numerous points, where it grows into compact colonies which produce focal lesions. Unlike the streptococcus, which grows most commonly on mucous membranes, such as that of the pharynx, and enters the body thence, the staphylococci are dwellers on the skin, and infection is usually from abrasions or cracks in the skin, although, as shall be stated, infection from the genito-urinary tract is not uncommon.

Owing to the attributes just mentioned the formation of abscesses is the usual effect of the invasion of this organism, a process already described in Chapter XIV. No matter how extensive the lesions, they have the same general character of concentration which makes possible the liquefaction of the tissue and exudate.

Furunculosis.—Cultures from the skin of healthy persons show (J. Koch) a great number of staphylococci, partly saprophytic, partly truly pathogenic. The haemolytic power of these cocci seems to be almost a measure of their pathogenic character. Even in the depths of the skin, probably in the sebaceous glands and the clefts about the roots of the hairs, there are constantly present staphylococci which grow white on culture-media (*Staphylococcus epidermidis albus*, Welch), and it is thought that these are responsible for stitch abscesses when sutures are made through the skin. To avoid them, subcutaneous sutures have been employed by surgeons with great success. With such a flora present, it is very easy to understand that abrasions, or even a constant rubbing which does not erode the skin, as in the case of a collar or cuff, might give an opportunity for the beginning of furunculosis which is so familiar. It depends evidently upon a predisposing lowering of resistance, which, according to Wright, may be recognized in the decreased activity of phagocytic leucocytes (lowered opsonic power of the plasma). At any rate, once begun, furuncles or boils are likely to continue to appear, sometimes in hundreds. Athletes in training, who are roughly rubbed down, are a prey to them, and, on the other hand, persons long ill with

such wasting diseases as typhoid fever are likely to have a crop of boils. The active immunization by the injection of repeated doses of killed cocci usually has an extraordinary effect in raising the resistance and completely stopping their appearance. They begin usually about a hair, and the abscess develops until the hair can be seen standing up in the middle of a small, opaque yellow fleck. From that the infection burrows deeper and spreads laterally a little under the corium, which in the thicker parts of the skin prevents for some time the complete evacuation of the pus to the outside. In time, however, through the bursting of the central necrotic cap of skin, it escapes and the hole thus left heals up by the formation of granulation tissue. The surgeon can hasten this process by stretching or bursting open the hole with as little injury as possible to the adjacent tissue. If he squeezes or cuts that adjacent tissue so as to impair its blood-supply, extension of the infection is almost inevitable.

When the resistance is very low, the cocci may quickly extend to form a whole group of connected abscesses, with several projecting necrotic points side by side in the skin. The whole swollen mass is honeycombed with channels full of pus in the necrotic tissue, and the further expansion proceeds rapidly. Such a threatening affection is known as a carbuncle, and requires prompt surgical intervention. They occur anywhere, but most commonly on the back of the neck or on the lip or buttocks. Those on the upper lip are particularly to be feared, since extension along the lymphatics or thrombophlebitis extending upward through the nose to the cavernous sinus may lead to meningitis.

Infections of the finger extending about the nail (*paronychia, panaritium*) or of the palmar surface are guided in their extension by the fasciae of the finger and hand. Involvement of the tendon-sheaths is a particularly destructive complication.

Impetigo contagiosa, a skin disease of children, appears to be caused by the staphylococcus, although, as shown recently by Burky and Smith, many cases give cultures of a streptococcus. It produces pustules about the face, especially around the nose and mouth, which burst and dry up into a honey-yellow crust without much surrounding reaction. It may spread over the entire body, especially where the child can scratch the skin, and is contagious for other children, although not all are susceptible.

General Septicæmia.—While the *Staphylococcus aureus* is perhaps the most common cause of the forms of furunculosis just described, the *Staphylococcus albus* takes part, and in infections which become general, it, too, is quite often found. General distribution of staphylococci through the blood-stream occurs readily, even from small infected scratches or cuts, or from some other local infection, all of which may heal up and disappear before the general infection is well under way. The wide-spread character of such general infections may be most clearly brought out by describing cases which have recently come to my attention at autopsy.

A man fell in a Pullman car against some projection which caused an abrasion between his shoulders; death occurred two weeks later, and

at the autopsy, although the abrasions were partly healed, huge abscesses were found among the muscles of the back; the right knee was distended with a purulent fluid, and an abscess, filled with thick greenish pus, burrowed among the muscles of the thigh.

A plumber, who had cut his finger with a piece of tin some weeks before his death, making a trifling wound which had healed completely, was brought to the hospital in a condition of delirium without definite localizing symptoms. At the autopsy there was found a general infection with the *Staphylococcus aureus*, which was cultivated from the blood. There were small abscesses in nearly all the organs, everywhere



Fig. 276.—Multiple abscesses in the heart-wall from a case of general staphylococcus septicæmia.



Fig. 277.—*Staphylococcus* septicæmia. Minute abscesses in the pericardium surrounded by haemorrhagic flecks.

presenting themselves as opaque yellowish spots surrounded by a zone of haemorrhage. The heart muscle was studded everywhere with them (Fig. 276), while upon the aortic valves there were soft vegetations. The pericardium showed numerous haemorrhagic flecks (Fig. 277), with central opacities, as did the pleural and peritoneal surfaces. Throughout the intestinal mucosa there were haemorrhagic nodules, and similar foci appeared in the kidneys and liver. In the lungs the abscesses were larger, with central softening, and a zone of haemorrhagic pneumoniae consolidation about each.

Sometimes it is difficult to determine upon the portal of entry of the cocci, as in the case of a sailor brought off a ship to the hospital. He, too, was in a state of coma, extremely anaemic, with signs of patchy bronchopneumonic consolidation, and with abundant staphylococci in a culture from the circulating blood. At autopsy practically the same wide-spread focal lesions were found as described in the preceding case, the heart muscle and kidneys being especially thickly set with small abscesses (Fig. 278). No source of infection could be found after the most minute search, until a decayed canine tooth was pulled from the upper jaw, when a gush of pus came from the antrum, which evidently represented the portal of entry.

It should be noted that in such infections, especially when they are not quite so severe and rapidly fatal, localization of the bacteria in the joints with the production of a purulent synovitis is not uncommon.



Fig. 278.—Staphylococcus septicæmia. Multiple abscesses of the kidney.

Suppurative Nephritis.—Aside from their appearance as part of a general pyæmia, staphylococcus infections of the cortex and medulla of the kidney, transported there by the blood-stream, come to the attention of the surgeon more commonly than is generally thought. Jordan, Brewer, and others have described them as multiple foci, involving necrosis of the renal tissue in the cortex, and extending into the pyramids. They are probably formed in the effort of the kidney to excrete the staphylococcus brought by the blood-stream, and may develop about the bacteria which accumulate with casts in the tubules (staphylococci are known to be abundantly excreted in the urine in general infection). Brewer looks upon them as rather of embolic origin, and therefore starting from the neighborhood of the plugged arteriole or glomerulus. Similarly, as the only internal lesion produced by transportation of

cocci from some cutaneous infection, there may be formed a perineal abscess which can later encroach upon the kidney.

There is always the question as to whether such haematogenous infections of the kidney are to be regarded as the basis for the forms of suppurative pyelonephritis associated with infections of the urinary bladder. As in the case of tuberculosis of these organs, there are those who regard the process as the result of ascending infection from the bladder, while others assume it to be haematogenous or indirect. It seems that both types may occur, although when abscesses appear in the kidneys as the direct continuation of an illness which begins with obstruction to the outflow of urine from the bladder, infection by catheterization, cystitis, and ureteritis, it is almost impossible to resign oneself to the idea that in those cases the bacteria enter the kidney by the blood-stream. All



Fig. 279.—Abscesses in both kidneys caused by the *Staphylococcus aureus*.

this can be more appropriately discussed in another place, since the staphylococcus is not often primarily concerned in such cases. On the other hand, the chills which follow catheterization are perhaps in some cases the expression of a general staphylococcus septicæmia of mild character initiated by the trauma in the operation.

Endocarditis forms an accompaniment of staphylococcus infection, the mitral and aortic valves being especially affected, while the vegetations are occasionally found upon the tricuspid or upon the walls of the heart. They are usually rather large, soft thrombus masses, which readily crumble and give rise to emboli.

Lobular Pneumonia.—As in the case of streptococcal infections of the lung, there is nothing especially characteristic about many of the cases in which the staphylococcus forms the infectious cause of bronchopneumonia, except in those instances in which the concentration is such as

to produce definite abscesses. The mode of entrance into the lung tissue is probably in part responsible for this. Chickering and Park describe an epidemic of pneumonia following influenza in the course of the great epidemic, caused by the *Staphylococcus aureus*, and characterized by the presence of many minute abscesses throughout the lungs.

LITERATURE

Chickering and Park: Jour. Amer. Med. Assoc., 1919, lxxii, 617.

Osteomyelitis.—It is in producing a destructive lesion in the bones, involving periosteum, cortex, marrow, and even extending to the cartilages, that the staphylococcus plays one of its most characteristic rôles, although here, too, other organisms, such as the pneumococcus, the typhoid bacillus, and others, may take its place and cause similar lesions. In the great majority of the cases, however, the staphylococcus is found. Here it shows particularly well its tendency to localize itself and grow in a place already injured mechanically. If several ribs or other bones are fractured in a rabbit, it is said that a subsequent injection of a culture of the *Staphylococcus aureus* will produce an abscess at the site of each fracture. These may be considered as points of lowered resistance, or perhaps the interruption of blood-vessels allows the bacteria to be caught there instead of being swept on by the blood-stream. In the same way in human beings a blow upon a bone appears to predispose it to the settling there of bacteria.

The organisms reach the bone either from a recognized focus of infection, or from some small infected abrasion or wound which heals and is forgotten before the disease of the bone is evident. It is the latter case which has given rise, no doubt, to the idea that there may be a primary osteomyelitis, a situation which is realized in cases of infected compound fractures. The long bones are affected far more often than the others; nevertheless osteomyelitis involving the tarsal and carpal bones, the vertebræ, the clavicles, and the bones of the pelvis is not rare. The disease occurs most frequently in children and young persons, the cases being most numerous in those between the ages of thirteen and seventeen, after which they fall off rapidly.

The cocci usually lodge in the shaft of one of the long bones in such a position as the upper third of the tibia or the lower third of the femur, and there produce abscesses in the cancellous substance of the bone (Fig. 280) which involve the cortex and the periosteum, lifting up the latter from the surface of the bone. As in other abscesses, the presence of the bacteria leads to necrosis of the tissue round about, and from the fact that this necrosis extends far wide of the clump of cocci, it may be agreed that they produce a toxic substance. (This, in fact, is well proved for the staphylococci.) The leucocytes which accumulate liquefy the necrotic tissue and attack the bony lamellæ, which they reduce to fragments. Frequently large portions of the cortex thus become necrotic and rarefied, and finally isolated from the still living bone as a sequestrum (Fig. 281) which practically floats in a pus-filled cavity. Generally it is not so completely loosened for some time, but in its extent it may amount to nearly the whole shaft of the bone. I recall vividly one such case from my assistant time in the surgical wards, upon which I was allowed to operate. It was a boy of about twelve, whose left leg, as he was brought into the hospital, was greatly swollen below the knee, tense, and oedematous. He was

suffering a great deal of pain and had a high temperature, but there was found no obvious point of infection elsewhere, from which the disease of his leg might have started. A long incision was made, and quantities of rather gritty brown pus flowed out. The periosteum had been lifted up from nearly the whole length of the tibia, and evidently had been torn to let the pus escape into the intermuscular tissues. The bone itself was already rough, and some portions of it were easily pulled away. These were ragged, as if worm-eaten. Much of the rest was chiseled or gouged away, leaving, as I remember it, the posterior half of the bone exposed in the wound which remained open. Healing occurred in a remarkable fashion by the growth of the most luxuriant granulation tissue, from the crevices in which tiny fragments of bony lamellæ were discharged for some time. Even when the skin covered most of the granulating surface, a fistula extending to the bone at one point remained for a time and discharged bony granules, but this in time healed up. This boy remained well, but it is frequently the case that before one focus is completely cleaned out and healed, another appears in some far-distant bone.



Fig. 280.—Irregular fresh areas of osteomyelitis in the cancellous bone caused by the *Staphylococcus aureus*.

Occasionally they follow one another in rapid succession, destroying or mutilating one bone after another, and ending often in the development of a general septicæmia with hundreds of small abscesses in the internal organs.

When not treated by radical surgery, the most remarkable results may ensue, especially when the infective agent is not so virulent as to lead rapidly to very extensive destruction or to general septicaemia. While in the acute forms the necrotic bone is rapidly rarefied and partly disintegrated, it may happen that in the more slowly progressing forms there is time for prolonged activity on the part of the osteoblasts which cover the bony lamellæ in the neighborhood of the focus of infection, before that surrounding bone tissue is involved in the necrosis. Then each lamella becomes greatly thickened, and the bone becomes compact as ivory (eburnation or sclerosis). It is for this reason that the necrotic sequestrum is sometimes found to be extremely dense and hard. In such subacute cases, which are more localized, the extension of the infection and inflammatory exudate to the periosteum lifts up and ruptures only a small part of it. The pus then burrows in a channel among the muscles to the skin, where it causes a bluish-red bulging,

which finally ruptures like an abscess. In this way a sinus is formed through which a probe can be passed down until it scrapes upon the rough dead bone. Through this sinus fragments of bone may be discharged with pus for a long time. If any



Fig. 281.—Large necrotic fragment of bone or sequestrum from the tibia in osteomyelitis.



Fig. 282.—Osteomyelitis showing the sequestrum, the involucrum with orifices which represent the sinuses, and periosteal osteophytes.



Fig. 283.—Chronic perios-
titis with osteophytes.

considerable mass of the cortex has been thus converted into a loose sequestrum, extensive healing processes go on about it, even though it maintains a constant source of infection. It is true that the bacteria may die out, but even then the mass of dead bone acts as a foreign body of which the tissues cannot get rid. In-

stead, abundant new bone with much granulation tissue is formed about it, usually still perforated by the sinus or sinuses which extend to the skin. In time there may be produced in this way (Fig. 282) a sheath of new bone which practically represents the old shaft (the involucrum) inside which the sequestrum persists. A great part of this is formed by the periosteum, but those portions of the shaft which remain alive produce much new tissue by the aid of their endosteal cells. It is easy to understand that if that portion of the cortex of the shaft which is destined to become necrotic and sequestrated can, in the meanwhile, undergo sclerosis or eburnation by the new formation of layers of bone in all its Haversian systems and on the surfaces of all its lamellæ, the rest of the bone will do the same. It is for this reason that whatever remains of such a shaft is found to be heavy and dense. Indeed, if the infectious process proceeds very slowly and without gross destruction of the cortex, the whole bone may preserve its form, but become almost solid and very dense and heavy. One type of abscess which occurs in the cancellous bone of the femur, or in the lower end of the tibia, is known as *Brodie's abscess*. Caused also by the staphylococcus, it progresses so slowly that it becomes encapsulated and is less destructive than the usual form of osteomyelitis. Quite aside from the actual area of necrosis or in its absence, the inflammation which involves the periosteum results in its producing a great deal of new bone superficially applied to the shaft, so that the surface of a bone in old osteomyelitis is usually greatly roughened by such osteophytes (Fig. 283). As we shall see, a quite similar process of periosteal bone formation is frequent in other slowly progressing inflammatory affections, and is especially striking in syphilis.

When osteomyelitis caused by the staphylococcus involves the bones of the skull, or in the cases in which otitis media is due to its agency (it is very frequently active here, and the cause of nearly all the chronic forms), when metastatic abscesses occur in the brain, or when extension of the infection takes place from furunculosis of the nose or lip, acute meningitis may arise, involving the coverings of the brain and extending to the pia-arachnoid of the spinal cord. Its nature is similar to that caused by the streptococcus, pneumococcus, and other organisms, and it will more conveniently be described elsewhere. One form of meningitis is of interest, however, in this connection, namely, the purulent pachymeningitis or inflammation of the dura. That this should occur with osteomyelitis of the bones of the skull is self-evident, but one occasionally sees cases of another type in which, from an abscess in the perirectal tissue, extension of the infection occurs along the nerves, to enter the sacral foramina or even the lumbar foramina to the space outside the dura and within the spinal canal. The outer surface of the dura then becomes bathed in pus.

LITERATURE

- Brodie, Benjamin: Works of, London, 1865, vol. iii, 403.
Koch, Jos.: Ergeb. d. allg. Path., 1909, xiii, 205.
Lenhardt: Nothnagel's Handb. d. spez. Path. u. Therap., 1903, iii, Teil 2, 329.
Lexer: "Osteomyelitis," Volkmann's klin. Vorträge, 173.
Neisser and Lipstein: Handb. v. Kolle u. Wassermann, 1903, iii, 105.

CHAPTER XXVII

TYPES OF INJURY.—BACTERIAL DISEASE (Continued).— PNEUMOCOCCUS INFECTION

Character of organisms. *Lobar pneumonia:* consolidation, resolution, organization, etc. *Septicæmia.* *Endocarditis.*

Character of Organisms.—The pneumococcus or Micrococcus lanœlatus is best known on account of its preëminent relation to the clear-cut disease, lobar pneumonia. It is true that it is concerned in many other infectious processes, including otitis media, meningitis, various inflammations of the nasal sinuses, pleurisy, pericarditis, general peritonitis and even general septicæmia, as well as the more indefinite forms of lobular or patchy pneumonia. On the other hand, a few other organisms, such as Friedländer's capsulated bacillus, have been detected at times as the cause of unmistakable acute lobar pneumonia.

The pneumococcus is very widely distributed, and occurs in the mouths and upper respiratory tracts of most normal persons. It varies greatly in virulence, as has been shown by animal inoculations, and those cultivated from pneumonic lungs are not necessarily more virulent than those from the mouths of healthy persons. It produces a toxic substance which is feebly haemolytic, but which must be extracted from the dissolved bodies of the organism. It has the power of converting haemoglobin into methæmoglobin, and can be neutralized by cholesterine. Studies of Neufeld, and especially of Cole and his assistants, have revealed the fact that there are several kinds of pneumococci which can be distinguished sharply from one another by their biological characters, although morphologically and culturally they are alike. By the aid of sera produced by inoculating living pneumococci of different strains into large animals Cole, Dochez, and Gillespie have been able to distinguish sharply at least four types, which have been found to occur in 150 cases of pneumonia in the following proportions:

Type I	57
Type II	44
Type III (Pneumococcus mucosus)	17
Type IV (heterogeneous)	32

A potent serum was obtained for Type I, a less satisfactory one for Type II. Attempts to produce a protective serum against Type III failed completely. This organism, which is the Streptococcus mucosus of Schottmüller, is readily distinguished by its very large capsule, its stringy growth in culture, and by the glutinous exudate in the lungs in pneumonia caused by it. It produces the severest infections. Type IV is made up of a great many different strains, none of which ordinarily produces a very severe pneumonia. They are the forms found in the mouths of healthy persons; they are overgrown by Types I, II, or III in pneumonias caused by those types, but reappear in the mouth on convalescence after the infecting type has disappeared. Protective sera can be produced for each member of Type IV, but they are quite specific, and powerless against any other members of the group. So, too, the sera for Types I and II have no protective effect against Types III or IV, nor against one another, but are quite specific for the homologous organisms. Although infections produced by Type III are so far insusceptible of treatment by any serum, the serum for Type I is used in large doses, with excellent effect. Infec-

tions with Type IV are so mild as scarcely to require serum treatment. Felton has by a newly contrived method concentrated antipneumococcal sera so that treatment with such sera is very effective in some types. With the aid of these specific sera the organism in any case of pneumonia can be referred to its type either by inoculating mice and ascertaining which protective serum causes them to survive, or by testing the agglutination of the organism with each serum. It is impossible to discuss here the rather indefinite toxins which have been extracted from various types of pneumococcus. The student is referred to the papers of Cole and Felton.

Avery and his co-workers have recently shown that there is a soluble specific substance probably related most closely with the capsule of these organisms, which is a carbohydrate! It reacts to immune serum, but is not itself antigenic. The surprising nature of this discovery prepares one for further revelations as to the specific substances produced by other bacteria, such as the Streptococcus viridans (Lancefield). Avery and Dubos (Jour. Exp. Med., 1931, liv, 51, 73) have even found in a cranberry bog a bacillus which develops an enzyme which breaks up the specific carbohydrate of Pneumococcus Type III, and, further, that by injecting this enzyme they can protect mice against infection, with that organism or even influence favorably an infection already established.

Felton having concentrated the potent antibacterial serum of Cole for Type I Pneumococcus in horses, found that the severe reaction which followed its injection in patients was due to the more acid of several protein constituents of the serum. This could be precipitated and removed from the serum by mixing with a fluid iso-electric for that protein, leaving the protective protein which was of a quite different pH. Felton found that the polysaccharides free from protein were actively antigenic and that the specific antibacterial serum can be neutralized by the corresponding polysaccharide which in itself is toxic in its action. A definite toxin has been isolated by Parker and associates and has been shown by Blackman to produce acute nephritis in rabbits.

LOBAR PNEUMONIA

Pneumonia is an acute infectious disease which begins suddenly, usually with a sharp pain in the chest and with a chill and high fever. It proceeds with extensive consolidation of the lung, evidences of intoxication, and various metabolic disturbances, to the death of the patient or to sudden disappearance of the symptoms and rapid passing away of the consolidation (crisis), or to a slower and more gradual defervescence and relief from the symptoms of the disease (recovery by lysis). Occasionally, while the symptoms of the acute illness disappear completely and convalescence seems complete, a form of consolidation of the lung persists and is found to be due to a replacement of the exudate by fibrous tissue. Other complications which delay recovery or lead to death will be discussed later. Since most persons harbor pneumococci in their mouths, and since pneumonia seems not to be a particularly contagious disease, although rarely occurring in small epidemics, the question arises as to the mode of entry of the organisms into the lungs and the conditions under which they produce pneumonia. It is shown that many persons who do not contract diphtheria are carriers of virulent diphtheria bacilli, and the same is true, in a modified way, of other organisms. Therefore unless it should prove that those who develop pneumonia do so always from the invasion of a pneumococcus of a type different from that which they have harbored in their mouths, we must search for some predisposing cause for their invasion. It has long been known (Litten) that crushing or contusion of the thorax is frequently followed by pneumonia, and there is also the general impression that

alcoholism predisposes to it, and that some sudden exposure to cold is likely to precipitate invasion of the infection. Blake and Cecil have shown in an important series of experiments that a sufficiently virulent pneumococcus will produce lobar pneumonia in susceptible animals when a very small number of organisms are allowed to trickle down into the trachea and bronchi. They find that the pneumonia begins near the hilum of the lung and spreads peripherally, and think that the organisms invade primarily the lymphatics and interstitial tissues through the walls of the bronchi and bronchioles and are thus quickly spread. They base this on the fact that they find a striking interstitial inflammation in the beginning which is later masked by the exudate in the alveoli. Unfortunately they studied the very early stages in only one or two monkeys, leaving the rest to develop the later and more complex conditions. Permar has repeated this work in rabbits, studying especially the conditions found from one-half to four hours after inoculation. He concludes that pneumonia arises as an acute inflammatory reaction of trachea, bronchi, alveolar ducts, atria, and alveoli, the severity of the reaction being greatest in the terminal bronchioles and alveoli, but that acute interstitial pneumonia does develop early in the course of this as an acute lymphangitis, arising in the peripheral lymphatics and extending to the subpleural network and to the hilum. This augments the primary bronchogenic inflammatory process and tends to hasten the complete involvement of the affected lobe. Lauche, in his chapter on pneumonia, discusses at length the reasons for the remarkable homogeneous consolidation in one lobe of the lung in lobar pneumonia, and favors the idea that there must be a local influence which guides the spread of the bacteria into one lobe only and that this spread must therefore take place by way of the lymphatics since it would not be uniform by way of the bronchi and would affect both lungs if by way of the blood-stream. The other factor, which has also been emphasized by other writers, is the existence of allergic hypersensitization which is essential to the production of such a widespread inflammatory reaction. All these arguments are a little lame and the spread up-stream by way of the lymphatics is especially hard to believe. Indeed, it requires the support of Tendeloo's idea of an ebb and flow produced by the respiratory movement and overcoming the action of the valves.

Ether Pneumonia.—Pneumonia which occurs after a surgical operation with general anaesthesia is not infrequent, and presents some problems of interest. It was thought to be lobular in character, and due to the aspiration of various bacteria with saliva, etc., during the anaesthesia, owing to the abolition of the normal reflexes which would prevent the access of such materials to the lungs. A. O. Whipple has shown, however, in an interesting study of many cases of this kind that some of these consolidations are lobar in type and that they are usually caused by infection with pneumococci of Group IV, which are known to be common in the throats of persons who are not ill.

LITERATURE

- Armstrong and Gaskell: Jour. Path. and Baet., 1921, xxiv, 369.
Avery and Goebel: Jour. Exp. Med., 1933, lviii, 731.
Blake and Cecil: Jour. Exp. Med., 1920, xxxi, 403-708.
Cecil and Steffen: Pub. Health Reports, 1922, xxxvi, 2735; Hygienic Lab. Bull., 1925, No. 141; Jour. Exp. Med., 1921, xxxiv, 245; 1923, xxxvii, 149.
Cecil and Sutliff: Jour. Amer. Med. Assoc., 1928, xci, 2035.
Felton: Jour. Infect. Dis., 1925, xxxvii, 199, 309; 1928, xlivi, 531; 1935, lvi, 101.
Johns Hopkins Hosp. Bull., 1926, xxxviii, 33. Jour. Amer. Med. Assoc., 1930, xciv, 1893. Boston Med. and Surg. Jour., 1924, cxc, 819. Jour. Immunol., 1930, xix, 511; 1931, xxi, 341; 1932, xxiii, 405; 1934, xxvii, 379; 1935, xxix, 149.
Lauche, A.: Henke and Lubarsch, Handb. d. spez. Path. Anat., 1928, iii, 864, 915.
Parker, J. T.: Jour. Exp. Med., 1928, xlvi, 531; 1929, I, 103, 161.
Permar: Jour. Med. Research, 1923, xliv, 1.
Whipple, A. O.: Surg., Gyn., and Obst., 1918, xxvi, 29.

Anatomical Changes.—The inflammatory reaction is commonly divided into several stages. Of these, the first, the so-called *stage of engorgement*, is rarely seen at autopsy, except perhaps at the edges of an advancing consolidation, and it must be conceded that its characters are to some extent constructed from the known course of inflammation elsewhere. The capillaries of the alveolar walls are dilated with blood, and there exudes into the air-cells fluid from the blood, together with leucocytes and red corpuscles. The second stage, which is the earliest one commonly seen, is called the *stage of red hepatization* (because the lung is red and solid, like the liver). At this stage an abundant inflammatory exudate is found to have filled the alveoli and to have clotted. As in the case of a perfectly fresh clot of blood in a glass dish, which is so firm and dry that the dish can be inverted without spilling it, these clots in the air-cells are firm and dry. In sections they are seen to fill the air-cell (Fig. 284) and to be composed of a coarse-meshed network of fibrin in which are entangled numerous pneumococci, many red corpuscles, many polymorphonuclear leucocytes and some desquamated epithelial cells. Furthermore, at this stage, and even in the earlier stage there are seen quite numerous mononuclear wandering cells or lymphocytes. This feature has been pointed out by Pratt, and is far less characteristic of later stages. Perhaps the most distinctive thing about the exudate from the microscopical point of view is its freshness and good state of preservation. The red cells are intact, and stand out clearly with their normal haemoglobin content; in other words, they show as yet no sign of laking or haemolysis. The leucocytes are clearly outlined and turgid. All these cells can be seen clearly because they are relatively few in numbers and stand out distinctly in the fibrin network. Many of the leucocytes show active phagocytosis and contain several pneumococci.

In its gross appearance at this stage a lung is very characteristic. The consolidation may involve one or more lobes, which are dense and hard and heavy. Their pleural surface has lost its normal gloss and is seen to be covered over the consolidated area, with a delicate, scarcely perceptible layer of yellowish fibrin. On section the bronchi are reddened and may be plugged in their smaller branches with moulds of

fibrin. The cut surface of the lung is usually dry, rough, and of a deep red color. The roughness is due to the slight projection from each alveolus of its plug of coagulated exudate. In sharp contrast with this flat plateau of consolidated lung, the remainder collapses and allows the escape of some of its content of air. It still crackles and crepitates under the finger, while, of course, the consolidated lobe is firm and airless. In spite of what was said about the stage of engorgement, it is rather rare to find anything but an abrupt transition from the consolidated to the unaffected lung substance.

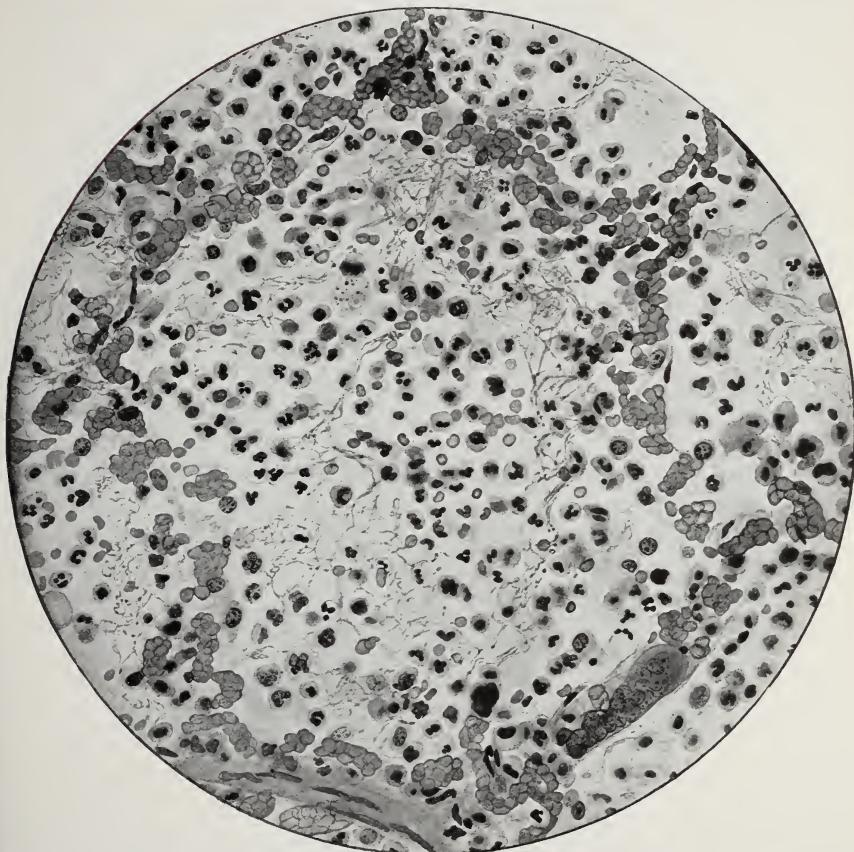


Fig. 284.—Lobar pneumonia; red hepatization. A single alveolus showing fresh exudate with well-preserved cells. A megalocaryocyte in one of the capillaries.

The third stage is the stage of gray hepatization, although it is usual—indeed, almost the rule—to find the consolidated lung in an intermediate condition, and of a color half-way between red and gray. The nature of that intermediate stage will be readily understood from a description of the gray hepatization.

In section the alveoli are found to be densely packed with a cellular exudate (Fig. 285). By this time, although the bacteria have increased

in number and the alveoli are crowded tightly with many more poly-nuclear leucocytes, which frequently contain the cocci, the fibrin is not observed to have increased specially in quantity. Instead, it is packed together, often in pretty compact masses, and scarcely shows any longer the graceful network which was to be seen in the earlier stages. Red corpuscles are hardly to be found in the advanced stage of gray hepatization, except that with careful scrutiny the shadowy outlines of those

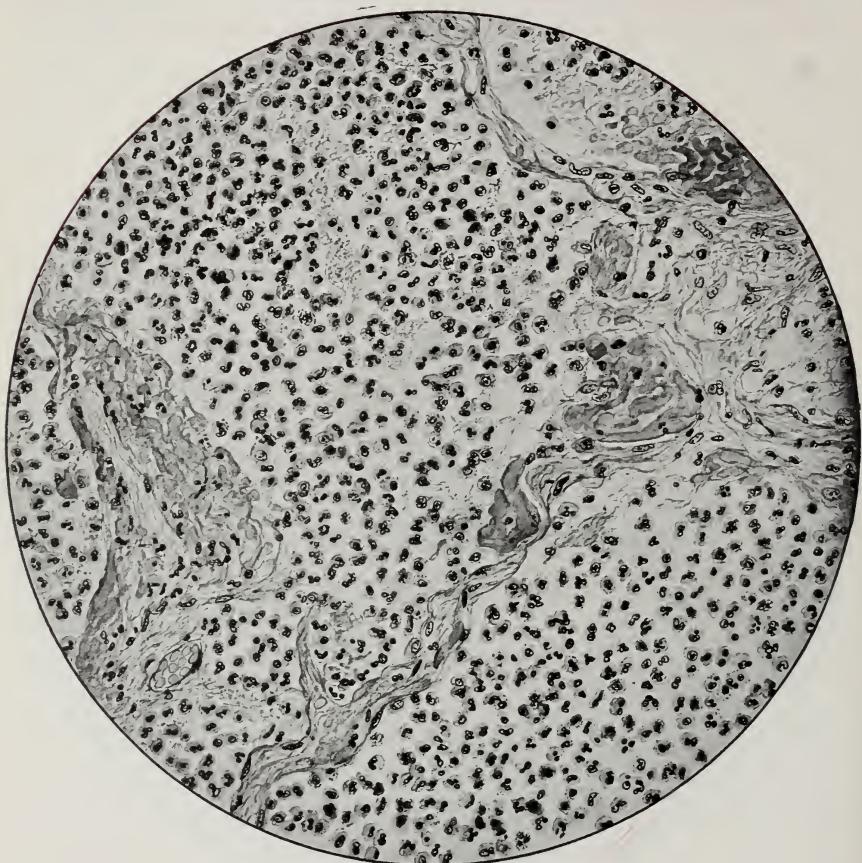


Fig. 285.—Lobar pneumonia; gray hepatization, showing retraction and consolidation of fibrin and partial disintegration of leucocytes.

which have lost their haemoglobin may be made out here and there among the closely crowded leucocytes. The capillaries of the alveolar wall are quite patent, as can be shown easily by injection, but they seem compressed by the mass of exudate and no longer look distended with blood. In this stage and in the stage of red hepatization one may often find capillaries obstructed by a huge cellular mass which proves to be a megalocaryocyte from the bone-marrow, swept into the lung in the general rush of leucocytes from the marrow (Fig. 286). In both stages,

too, one may make out the fact that the fibrin threads in any one air-cell often seem to twist themselves into a thin cord, and pass directly through the alveolar wall, to spread out again into the network of the next air-cell. This is because of the presence of the so-called "pores of Cohn," which may be normal apertures in the wall, although it has been contended by many that they occur only in lungs somewhat altered by emphysema.

The most distinctive feature of the stage of gray hepatization from the microscopical point of view is the degenerated condition of the cells



Fig. 286.—Lobar pneumonia; red hepatization, showing megalocaryocytes in the capillaries.

of the exudate. Not only have the red cells undergone laking and disintegration, but the leucocytes have lost their clear outline, if not their whole protoplasm, and have become granular, ragged, partly disintegrated cells, which, however, still show evidences of their phagocytic activity. Most of them contain fine droplets of fat, and some contain yellow pigment, evidently produced at the expense of the haemoglobin of the broken red corpuscles. Desquamated epithelial cells are rather more abundant, and they too contain fat-droplets and pigment-granules.

It is especially important to observe also that the pneumococci degenerate, disintegrate, and lose their power to stain brilliantly as they

did in the stage of red hepatization. Indeed, they have also largely lost their power to infect, and a rabbit will survive when inoculated with a mass of exudate from an area of gray hepatization, but succumb to the same dose from an area of red hepatization. Armstrong and Gaskell suggest that the completion of this destruction may be the occasion for the crisis in pneumonia.

In the gross appearance (Fig. 287) the lung at this stage is still more enlarged, dense, and heavy. Its surface is covered with a much thicker layer of fibrin, which can be peeled off, leaving a dull pleural membrane. Not only does this cover the consolidated lobe, but it often extends over the whole lung and the parietal pleura. Frequently there is a considerable accumulation of turbid fluid in the pleural cavity, separating the surfaces, which elsewhere may be found glued together by the exudate. On section the cut surface of the consolidated lung is found to be gray, yellowish gray, grayish white, or yellowish white, although, as mentioned, the cases in which some redness persists at death are much more common. The surface is not dry nor so rough as before, but gives the impression that the alveoli are filled with coarse plugs of softer, almost unctuous material, a condition which is doubtless due to the retraction of the fibrin setting free serum in each alveolus, and to the much greater number of leucocytes, together with the accumulation of fat-droplets in their substance. The color is easily explained by the laking of the red corpuscles, the yellowish tint being contributed, no doubt, by the hemosiderin which is produced from their haemoglobin, and by the fat-content of the leucocytes, aided by the generally anaemic state of the lung.

A later stage, that of *resolution*, is seldom seen at autopsy, but it can occasionally be studied when the person dies from some other cause, as, for example, the development of pneumonia in the other lung, meningitis, or pericarditis. In two cases which I have seen in this stage the change in the lung was quite wonderful. The enormously enlarged organ was in each instance very soft and friable, and had assumed a very distinct translucence, so that one could discern blood-vessels in the depths of the tissue. The alveolar contents had lost to a great extent their appearance of being in the form of plugs, and the whole lung appeared gray and jelly-like.

In section the change was not so obvious, since it apparently consisted only in a more advanced disintegration of the leucocytes and fibrin. It is well known, however, that, through the agency of the proteolytic ferments of the leucocytes themselves, the whole mass of exudate is liquefied in a few days, and while some of it is expectorated, the greater quantity is absorbed by the lymphatics and carried away.

The stage of *healing* is even more rarely recognized. It must consist in the relining of the alveoli with alveolar epithelium after the complete removal of the exudate. It is to be noted that throughout this intense inflammatory affection of the lung there is very little infiltration of the lung tissue itself with the exudate. The alveolar walls, bronchial walls, and perivascular tissues remain throughout almost free from bacteria and exudate. It is rather as though the whole process were taking place

upon a mucous membrane without any invasion into the depths, and it results that after the exudate is removed there is no damage to repair



Fig. 287.—Lobar pneumonia; gross appearance of the lung in early gray hepatization with involvement of both lobes.

other than the loss of the epithelial cells, which are quickly made good by those which remain, so that it would be impossible to say two weeks later that that lung had been the seat of a pneumonia.

In sharp contrast to this are the effects of the streptococcus and influenza bacillus, described elsewhere.

Lobar pneumonia caused by the Pneumocoecus mucosus differs from that produced by the members of the other types in the viscosity of the exudate and in the severity of the disease, and the same may be said of the rarer cases, in which the capsulated bacillus of Friedländer is the cause. In one case of this kind which we saw, the exudate was so glutinous that it could be lifted up from the cut surface in long strings which hung from the knife.

Complications of pneumonia, which are perhaps commoner in the case of various types of lobular pneumonia, are abscess formation, organization of the exudate, and gangrene.

Abscess Formation.—In the late stage of a severe pneumonia the consolidated tissue appears to succumb sometimes, to an especially intense injury on the part of the bacteria, so that the alveolar walls give way throughout a limited area, and the lung substance breaks down into a purulent fluid. Such an abscess-like focus may extend into the pleural cavity, producing a purulent pleurisy or empyema. One is inclined to suspect in such cases the presence of a mixed infection with streptococci or staphylococci.

Organization or Carnification.—Ordinarily, when a fibrinous exudate is thrown out on any such surface as that of the pericardium or the pleura, healing leads to its replacement by granulation tissue, which in those situations is likely to end in the formation of fibrous adhesions between the opposed surfaces. It is, therefore, rather remarkable that in pneumonia the exudate, which is apparently quite the same in character, should be completely removed without the least attempt at such replacement or organization. Possibly the rapidity with which the whole reaction proceeds is accountable for this, or there may be some other explanation. Occasionally, however, the exudate fails to be removed promptly, whether because the bacteria persist or the mechanism of autolysis fails, and blood-vessels and fibroblasts do spring up and invade the fibrinous plugs in the alveoli, finally replacing them with vascularized tissue. The origin of this vascularized tissue is interesting, since it seems not to arise from every point of the alveolar wall. This is partly because the exudate retracts and remains in contact with the walls at certain points only, but even so, it seems that the new blood-vessels fail to spring up from all these points. Instead, it may be found by reconstruction that the connective tissue which replaces the exudate in any given lobule of the lung often springs essentially from the wall of the terminal bronchiole, or from one of those angles of the alveoli where an arteriole is surrounded by more tissue than goes to make up the alveolar wall. Then it follows the exudate, extending into each alveolus, and keeping clear of the walls (Fig. 288). Where the fibrin extends through one of the pores of Cohn the connective tissue follows, thickening itself into a stout cord and stretching the pore. Having penetrated into an alveolus belonging to another bronchiole, it extends to replace the exudate in that system. Consequently in the end it seems that a continuous network of strands of fibrous tissue stretches about in the

alveoli, connected only here and there with their walls, so that if the lung substance could be dissolved away, the new connective tissue might remain as a sponge-like mould of its cavities. When the new connective tissue has replaced the exudate, or even when it has succeeded, as it often does, in forming a sort of mantle about the exudate, epithelial cells creep up from the alveolar walls and cover it. This whole process



Fig. 288.—Organization following pneumonia. Strands of connective tissue extend through several alveoli and are in part covered with epithelium.

gives a dense elastic consistence to the lung, and obviously impedes greatly its expansion. Later, however, with shrinkage of the fibrous tissue, there is left much more air-space in the cavity of each alveolus, although even then the function of the lung must be greatly impaired (Fig. 289).

Gangrene.—Retarded recovery in some cases of pneumonia is accompanied by an exceedingly foul odor from the breath and sputum, which is a recognized indication of the existence of a gangrenous process in the lung. This is a commoner complication of lobular pneumonia, and

is the result of a secondary infection with organisms of a different type. It has already been described in Chapter XIV.

Pneumococcus Septicæmia.—In the course of pneumonia the pneumococcus may gain access to the general blood-stream, and be recognizable in cultures from the blood. Jochmann leans to the view that this is a very frequent occurrence, since by using large quantities of blood in culture he has succeeded in discovering the organism in a large percentage of his cases. Cole, on the other hand, recognizing that occasional cocci may enter the blood-stream, has found that any considerable or even recognizable bacteraemia occurs only in the most severe cases, and near the fatal termination of the disease.



Fig. 289.—Organizing pneumonia; cut surface of lung as seen with a lens, showing scar tissue extending through the lung, and points of yellow opacity produced by fatty cells.

The accompaniments of such bacteraemia are endocarditis, meningitis, and acute arthritis, although other rarer localizations are also recognized.

Endocarditis caused by the pneumococcus resembles closely that produced by the *Streptococcus haemolyticus*, or that of the staphylococcus infections. Large gray or greenish-gray soft vegetations are formed on the aortic or mitral or sometimes the tricuspid valves, and are of such friable consistence as to be a source of emboli. Little mention is made in the literature of acute nephritis in pneumococcal infections but Blackman has found that it is by no means infrequent, not only in children but in adults. His experimental production of typical glomerular lesions with hyaline capillary thrombi and haemorrhage into the tubules by the intravenous injection of an autolysate of pneumococci, affords some explanation of this.

Meningitis is a fairly common accompaniment of such endocarditis and of pneumococcus bacteraemia in general. The distribution of the exudate is usually very general, involving the spinal cord, and extending into the ventricles. In some cases in which the exudate is abundant there is a peculiar arrangement which is shown in Fig. 290. A network of fibrin is rather uniformly stretched throughout the meshwork of the arachnoid but the leucocytes and bacteria are not so evenly distributed for about each blood-vessel and also at a level above the closely placed vessels of the pia, there is a dense layer of leucocytes which when one of the arachnoid blood-vessels is cut transversely, is seen as a ring about it. These closely packed leucocytes contain numbers of agglutinated bacteria. No bacteria are seen between this halo and the blood-vessel but outside it, in the network between the vessels, leucocytes and bacteria appear wandering independently, with little or no sign of phago-



Fig. 290.—Pneumococcal meningitis with thick mantles of exudates about the veins.
Shown in microscopical section in Fig. 291.

cytosis. This is a frequent occurrence and it is quite evident upon gross inspection of the brain, for while the meninges in general are clouded, each vein is thickly surrounded by an opaque mantle so that it stands out prominently (Fig. 291). Sometimes the mid-surface of the vein is uncovered and then shows as a deep red line bounded on each side by the opaque yellowish sheath of phagocytes. Although we have attempted to reproduce this condition experimentally we have not yet succeeded. The experiments were planned on the idea that the bacteria reach the arachnoid meshes with the cerebrospinal fluid from an invasion somewhere in the ventricles—perhaps through the choroid plexus—and that later agglutinins and opsonins are passed out from the blood-vessels into the network of exudate with its free bacteria and leucocytes in the arachnoid meshwork, with this curious result.

Arthritis may take the form of a serous exudate in the joint cavity

in which the pneumococcus is found, or in other cases there is found a purulent exudate with intense swelling and inflammation of the synovial membranes, erosion of the cartilages, etc.

The pneumonia itself is by no means necessarily confined to one lobe, or even to one lung. The whole of one lung may be involved, together with the development of patchy or lobular areas of pneumonia in the other. Or there may be lobar involvement of both lungs. Occasionally the spread or extension of the consolidation may be observed clinically, and in a recent summary of the cases at the Presbyterian Hospital it was noticed that before and during the extension of an area of consolidation the temperature and leucocytosis frequently sank to low levels,

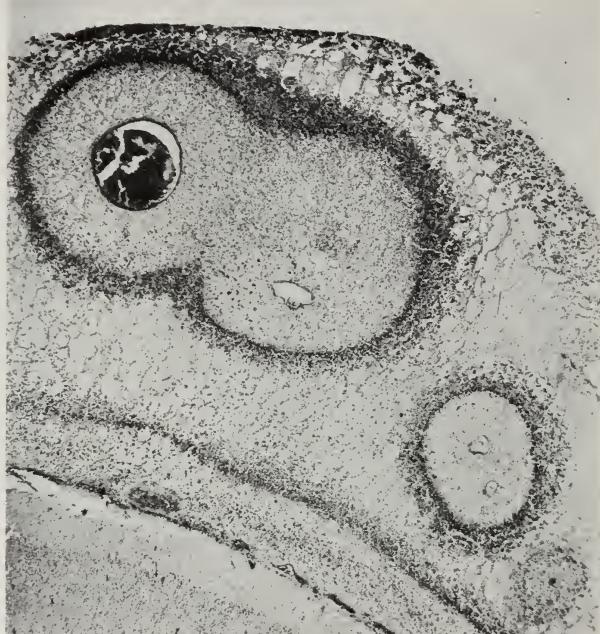


Fig. 291.—Meningitis caused by the pneumococcus with halo formation about blood vessels.

indicating perhaps a lowering of the powers of resistance which allowed the infection to spread.

Pleurisy has been mentioned, and it may be said further that following pneumonia, or in some cases without pneumonia, the pneumococcus gaining entrance into the pleura may cause a suppurative pleurisy or empyema in which great quantities of purulent fluid accumulate, compressing the lung and ultimately requiring surgical intervention.

Pericarditis of serofibrinous or fibropurulent character may be due to extension through the pleuropericardial membranes, and is a serious and often fatal complication.

Similarly, apparently by extension of the infection through the diaphragm, a generalized peritonitis may be set up. Such pneumococcal peri-

tonitis is described especially in children in association with lipoid nephrosis. Its portal of entry is not always clear, since no lesions of the abdominal organs are found, and it may sometimes occur without pneumonia. The exudate is greenish and soft and rich in fibrin, which is loosely attached to the serous surfaces.

Portals of entry for the pneumococcus other than the lungs should be mentioned. The nasal sinuses frequently become infected from the nose, giving rise to a painful and persistent inflammation. Extension of the infection from the nares and pharynx through the Eustachian tube is the cause of those cases of otitis media which are due to the pneumococcus. From the frontal or ethmoid sinuses, as well as from the middle ear, extension may occur to the cranial cavity, with the production of meningitis.

LITERATURE

- Avery, Chickering, Cole, and Dochez: Monograph, Rockefeller Institute, No. 7, 1917.
Avery, Lancefield, and others: Many papers in the Jour. Exp. Med., 1920-28.
Blackman, Brown, and Rake: Johns Hopkins Hosp. Bull., 1931, xlviii, 74.
Cecil and Austin: Jour. Exp. Med., 1918, xxviii, 19.
Cecil, Baldwin, and Larsen: Arch. Int. Med., 1927, xl, 253.
Cole and others: Jour. Exp. Med., 1912, xvi, 644-718; 1914, xx, 346, 363. Arch. Int. Med., 1914, xiv, 56. Jour. Amer. Med. Assoc., 1918, lxxi, 635.
Heidelberger and Avery: Jour. Exp. Med., 1924, xl, 301.
Kline: Jour. Exp. Med., 1917, xxvi, 239.
Lamar and Meltzer: Jour. Exp. Med., 1912, xv, 133.
MacCallum: Ziegler's Beiträge, 1902, xxxi, 440. (Organizing pneumonia.)
Wadsworth: Jour. Exp. Med., 1912, xvi, 54.
Wollstein and Meltzer: *Loc. cit.*, 1913, xviii, 548.

CHAPTER XXVIII

TYPES OF INJURY.—BACTERIAL DISEASE (Continued)

Meningococcus infections: Epidemic cerebrospinal meningitis. Endocarditis.

Gonococcus infections: Urethritis and sequelæ. Salpingitis and sequelæ. Arthritis, ophthalmia, dermatitis, endocarditis, vulvovaginitis in children.

MENINGOCOCCUS INFECTIONS

INFECTION with the meningococcus or Diplococcus intracellularis meningitidis of Weichselbaum occurs sporadically or in epidemics, and usually gives rise to a febrile disease in which the symptoms are due to the predominant affection of the meninges. In England it is called cerebrospinal fever. This disease has been known for a long time and there has always been great interest in its occurrence in epidemics mysteriously arising in widely separated places. Much might be written of the history of its various appearances, of the terror which it has always inspired, and of the prolonged efforts to gain some insight into the mode of transmission and the life history of the organism which causes it. So much has been accomplished in recent years, especially through studies made upon the great numbers of cases which occurred among the troops during the war, that our ideas are now much clearer than before, although many obscurities remain.

The meningococcus itself has been studied by new methods, and especially through the work of Gordon, Hine, Flack, Dopter, and Flexner it has been learned that, as in the case of the pneumococcus, by the application of agglutination tests and especially by the absorption of agglutinins, it is possible to divide the strains into several types. Dopter in 1911 distinguished as parameningococcus one strain, which now becomes one of the types. In brief, Gordon's Type I stands at one end of a series. His Type IV, which corresponds with Dopter's parameningococcus, at the other end. Types II and III occupy places between in the series, but there are many other strains which are intermediate. Indeed, more than fifty different subtypes have been distinguished approaching more or less closely in their agglutinative characters one or other of these main types. It is stated in this form because there is, even with this most accurate method of recognizing a specific organism, a certain amount of cross agglutination, so that it is only an organism which gives the maximum reaction with a serum produced by the arbitrary original Type I and the minimum reaction with the serum of Type IV that is classed with Type I. Doubtless with further study other differences may be found, as in the case of the Pfeiffer bacillus, which will make this differentiation more stable.

Rake has made an analysis of the antigenic complex of the meningococcus and found that there are type specific and group specific substances of which one is a polysaccharide. There are type specific pre-

cipitinogens in the cerebrospinal fluid which aid in determining the type concerned as the precipitin reaction has been confirmed by the agglutination reaction of the strain. Ferry shows that while the anti-meningococcic serum does not protect from live meningococci, it does neutralize the toxin which they produce.

No very sharp distinction can be made between these types as far as concerns their virulence and ability to produce disease. It is true, however, that there is a great difference in the susceptibility of individuals, since many become the healthy carriers of one or other type, probably through mere contact with infected persons. Others after surviving the disease remain as carriers of the organisms which are lodged in the nasopharynx. It was the problem of the recognition and disposition of such carriers which at first occupied so much attention in the various armies. As to the mode of infection, there is little doubt that transmission is by way of organisms which pass from the nasopharyngeal secretion of infected persons or carriers to the nasopharynx of others. The fact that persons known to carry these organisms in the nasopharynx may later develop meningitis, and the further fact that persons exposed to contact with these carriers become similar carriers or quickly develop the disease, support this.

From the nasopharynx invasion may be conceived of as occurring directly through the ethmoid plate, through the sphenoid or ethmoid sinuses, or through the middle ear. Although Andre has shown that prolongations of the subarachnoid spaces extend along the olfactory filaments into the nasal fossæ, apparently offering an easy path, no one has actually demonstrated organisms on their way through. On the other hand, there have been many cases in which an invasion of the blood-stream with the production of septicæmia has preceded the appearance of any organisms in the clear cerebrospinal fluid, but has been followed later by meningitis. This has been especially emphasized by Dopter, many English writers, Worster-Drought, Kennedy, and others, and in this country by Herrick. Indeed, Weed and his collaborators, in studying the infection of the cerebrospinal fluid in general, have shown that after the experimental production of septicæmia the cerebrospinal fluid becomes infected easily when pressure is reduced there, but only rarely if the pressure is normal or heightened. They even suggest that the removal of fluid by lumbar puncture during septicæmia may give opportunity for the development of meningeal infection. On the whole, therefore, in spite of authoritative voices to the contrary, I think the evidence is in favor of the infection of the meninges by the blood-stream, especially since the meningitis has nothing of the local character often seen when infection is obviously by direct extension from a neighboring abscess. From this it appears that we may regard the disease as one in which, while various localizations of the organisms may occur, as in heart valves, joints, etc., the usual local manifestation is in an inflammation of the meninges.

The symptoms most characteristic of this affection are the sudden onset, with chills, headache, and vomiting, with rigidity of the neck, inability to extend the leg while the hip is flexed (Kernig's sign), pete-

chial and purpuric rash, herpes, and slow pulse with high fever. It may run a rapidly fatal course, or be more subacute in its development, or finally become a chronic affection, in which case various complications arise. Diagnosis is made most certainly by the aspiration of the cerebrospinal fluid by lumbar puncture, with the recognition of the meningo-coccus by cultural and morphological characters, and the treatment by injection of corresponding amounts of the antimeningo-*eo*cal serum, which has been developed by Flexner and others, is going far to reduce the mortality due to this disease.

The pathological alterations in the central nervous system vary in their character according to the acuteness of the process. In the acute forms and sometimes even in the hyperacute or fulminant cases there is an accumulation of purulent exudate in the meshes of the pia-arachnoid



Fig. 292.—Cerebrospinal meningitis.

extending widely over the base of the brain and over the convexity of the cerebrum and down over the spinal cord, where it tends to occupy the meninges of the posterior aspect. The dura is smooth, although sometimes hyperæmic, and the surface of the arachnoid, while it may have lost its gloss, is not covered by any noticeable layer of pus. The exudate is collected, especially in the sulci and in those regions where the arachnoid is less closely connected with the pia. The ventricles contain no great excess of fluid, but this fluid is turbid or purulent, and there is swelling of the choroid plexuses, sometimes with minute haemorrhages. In the less acute forms the exudate is often much more abundant, forming a thick, greenish-yellow layer, and then fluid accumulates in greater quantity in the ventricles (Fig. 292). Occasionally distinct foci of necrosis are found in the brain substance bounding the ventricles

or beneath the pia, and the blood-vessels entering the brain are surrounded by exudate.

Histologically, there are found degenerative changes in the epithelium of the choroid plexus, in the more superficial cell layers of the cortex, and even in the nerve roots. The inflammatory exudate (Fig. 293) is composed chiefly of polymorphonuclear leucocytes, although a few lymphocytes and red corpuscles are to be found. Councilman and his fellow-workers have called attention to other much larger cells which

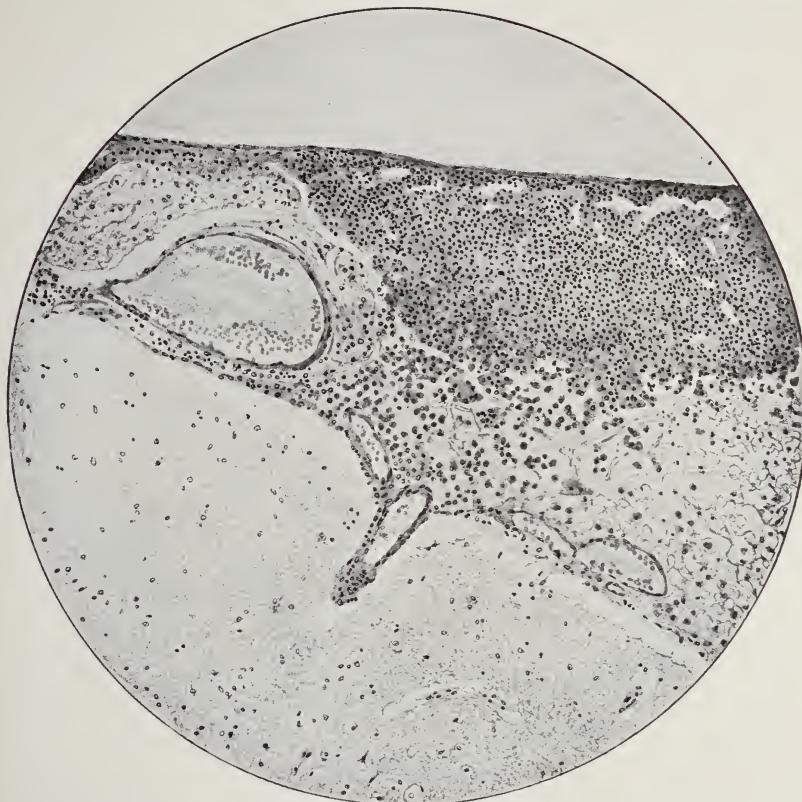


Fig. 293.—Cerebrospinal meningitis showing the limitation of the exudate and the varied character of its cells.

are present in considerable numbers and which are probably to be regarded as large mononuclear wandering cells. These have an abundant cytoplasm and are actively phagocytic, containing often the fragments or whole bodies of several smaller cells. Meningococci are numerous, and in spite of the name, *intracellularis*, are often free. Fibrin forms a delicate network throughout the exudate. The walls of the vessels are markedly affected, being infiltrated with leucocytes which accumulate especially beneath the endothelium. After their entry into the brain their perivascular lymph sheaths are often found filled with leucocytes.

In those cases in which the infection goes on to a chronic course the cerebrospinal fluid may become almost clear, and there arises a chronic progressive hydrocephalus which produces a train of symptoms and mechanical effects resembling those seen in other forms of hydrocephalus. This is due to the fact that organization of the exudate gives rise to adhesions between the surface of the brain and the dura, but more particularly to such as cover the foramina of Magendie and Luschka, or obstruct the communication of the cerebrospinal space about the cerebellum and medulla with that over the cerebral hemispheres. Drainage from the ventricles is interfered with and they become distended with fluid. Retraction of the neck persists with the various pareses which may be found in the acuter stages. Great emaciation, persistent vomiting, a stuporous mental state, with irritability, blindness, and deafness, contractures, and bedsores end finally in death.

Lesions are produced in other organs either by direct extension of the infection or as the result of septicæmia. The infections of the eye may be thought of as the result of the wandering of the bacteria along the lacrymal duct to the conjunctiva, or along the optic nerve with its accessory tissues. These have not been actually demonstrated, and Worster-Drought and Kennedy think infection by way of the blood-stream most probable. Conjunctivitis, keratitis, iridochoroiditis, and even panophthalmitis are observed. The latter processes, through organization of the purulent exudate which accumulates in the chambers of the eye, lead to various forms of distortion of the eye, with blindness. Blindness may also follow hydrocephalus or destructive lesions in the occipital cerebral cortex.

While otitis media is uncommon, permanent deafness results in many cases of meningitis from direct involvement of the eighth nerve by extension of the infection and exudate from the meninges. Its atrophy leads to absolute deafness, which is usually bilateral, and in young children is followed by mutism.

Various more or less transitory paralyses may occur. Hemiplegia, possibly from a destructive lesion in the internal capsule, and monoplegias, more distinctly due to injuries in the lower motor segment involving nerve roots or even the spinal cord, have been observed.

Arthritis affecting any joint, but most commonly the knee- or shoulder-joint, is another complication, or may occur in the course of a meningococcal septicæmia without any meningitis. The same may be said of endocarditis.

We observed one case (Cecil and Soper) in which the meningococcus was present in the crumbling vegetations on the heart valves, and Fairley and Steward, Worster-Drought, and Kennedy report others. The other organs show, as a rule, only such changes as are common to many acute infectious processes.

LITERATURE

Councilman, Mallory, and Wright: Report of State Board of Health of Massachusetts, Boston, 1898.
Ferry: Jour. Immunology, 1934, xxvi, 133.

- Flexner: Mode of Infection, etc., of Epidemic Meningitis, Rockefeller Institute, New York, 1917.
- Flexner with Jobling and Amoss: Jour. Exp. Med., 1907, ix, 105, 142, 168; 1908, x, 141, 690; 1913, xvii, 553; 1916, xxiii, 683. Jour. Amer. Med. Assoc., 1906, xlvi, 560; 1913, ix, 1937.
- Gordon, Hine, Flack: Medical Research Committee Report on Cerebrospinal Fever, 1916-17, London.
- Herrick: Arch. Int. Med., 1918, xxi, 541.
- Rake: Jour. Exp. Med., 1933, lviii, 341, 361, 375; 1934, lix, 553.
- Weed, Wegefarth, Ayer, and Felton: Monograph No. 12 of Rockefeller Institute, 1920.
- Worster-Drought and Kennedy: Cerebrospinal Fever, London, 1919.

GONOCOCCUS INFECTION

The realization of the extent to which gonococci may infect the body is a matter of very recent years. The portal of entry is, in the majority of cases, the mucosa of the genito-urinary tract, since the infection is commonly transmitted by coitus. But it may occasionally be transferred by infected clothing, towels, etc., in spite of the ease with which the organism is destroyed by drying and exposure. Especially in infants and children is this possible, and in orphan asylums and hospitals epidemics of gonorrhœal vulvovaginitis are of extremely common occurrence. In direct or indirect ways the infection can also be introduced into the mucosa of the mouth, nose, rectum, conjunctiva, and especially in the eye may produce serious results.

Gonococcal Urethritis and its Sequels in the Male.—There is, after exposure to infection through coitus, during which the organisms reach the orifice of the urethra, a short period of incubation, averaging two to eight days. Then there begins a thin, mucopurulent exudate from the urethra, which in a short time becomes definitely purulent. The orifice, with its tumefied edges, oozes thick, greenish pus, which besides desquamated epithelial cells, contains abundant leucocytes, both neutrophile and eosinophile. Gonococci are found in great numbers, many of them, if not the majority, contained in the bodies of the leucocytes, where they seem to suffer no harm. Ordinarily this inflammatory process may affect only the anterior portion of the urethra, where it passes through a florid stage, with profuse exudate, gradually to recede after several weeks. In this latter stage, which may end in healing and the disappearance of the cocci, the exudate becomes less abundant and mucoïd, gluing together the edges of the meatus. But in many cases there is an extension to the posterior urethra, where healing is more difficult, and from which the important complications in other organs arise.

There are, in the course of the urethra, many accessory structures, some, such as the paraurethral channels, partaking of the character of malformations, while others, the lacunæ or glands of Littré and the glands of Cowper and various folds of mucosa, are normally present. Directly communicating with the urethra there are, of course, the more developed accessory structures—the prostate and seminal vesicles. All of these are commonly involved in the more chronic or persistent gonorrhœal infections, and serve to maintain the infection in spite of thorough disinfection of the urethra itself. In connection with the anterior urethra the follicles or glands of Littré may become converted into hard, inflamed nodules.

The mucosa in the acute inflammation is swollen, with desquamation of many epithelial cells. The gonococci penetrate among those which remain, and extend even into the subepithelial tissues. Where there are patches of stratified epithelium, such as often occur normally, the cocci obtain an especially good foothold and resist disinfection. When the process has become more chronic, especially in the posterior urethra, there appear ulcerations, with scarring and polypoid excrescences. The scarring results in strictures or stenoses (see Fig. 223) of the urethra, which cause obstruction to the outflow of urine and render catheterization necessary. Not only is cystitis a common result of this, but in attempts to pass instruments through the stricture, wounds of the adjacent tissue are produced, which may become the origin of intense infections. These may assume a phlegmonous character, or there may develop an abscess in the perineal region. The extravasation of urine into such wounded areas favor the development of the infection.

Chronic gonococcal urethritis is commonly recognized by the presence of shreds or filaments of mucus with leucocytes and epithelial cells in the urine. These may contain gonococci, but often the organisms are rare and difficult to demonstrate.

Cystitis, while it can be produced by the gonococcus alone, is rarely due to that organism, but usually to secondary invaders. Ureteritis and pyelonephritis are reported as due to ascending infection with the gonococcus, but are rare.

Prostatitis and Vesiculitis.—Various types of infection of the prostate by the gonococcus are described arising in connection with posterior urethritis. These differ greatly in intensity, for while there may be a sort of catarrhal inflammation of the ducts and acini of the gland, there may, in other cases, be far more intense and destructive changes involving abscess formation. A chronic persistent inflammation with a secretion containing cocci, and leading to the enlargement, or in other cases to scarring and atrophy of the gland, is most frequent. The seminal vesicles may in the same way present acute inflammatory changes or more chronic alterations, including scarring and obliteration of their lumina.

Epididymitis.—A common sequel of urethritis is produced by the wandering of the gonococci along the vas deferens to the epididymis, where an intense inflammation involving the neighboring tunica vaginalis in many cases leads to great swelling and induration. The gonococci can be found in the exudate, even though in some cases they cannot be recognized in the vas deferens and have produced no lesions there. Scarring and stricture or obliteration of the canal of the epididymis and of the vas deferens may lead to complete azoospermia if the epididymis has been affected on both sides.

Gonococcal Infection in the Female.—In the female the urethra, the vagina, Bartholin's glands, and the cervix become infected and react in the same way as does the mucosa of the male genito-urinary tract. The urethra being shorter and without complicated accessory structures, the inflammation does not lead to such serious results. A swelling of the mucosa, with the exudation of the characteristic pus, occurs. Bartholin's

glands become greatly swollen and indurated, and from them there can be expressed a similar purulent exudate. These things may occur without the extension of the infection into the internal genitalia, and, indeed, in the vulvovaginitis of children, this more external type of inflammation, with reddening and swelling of the nymphæ, is relatively common.

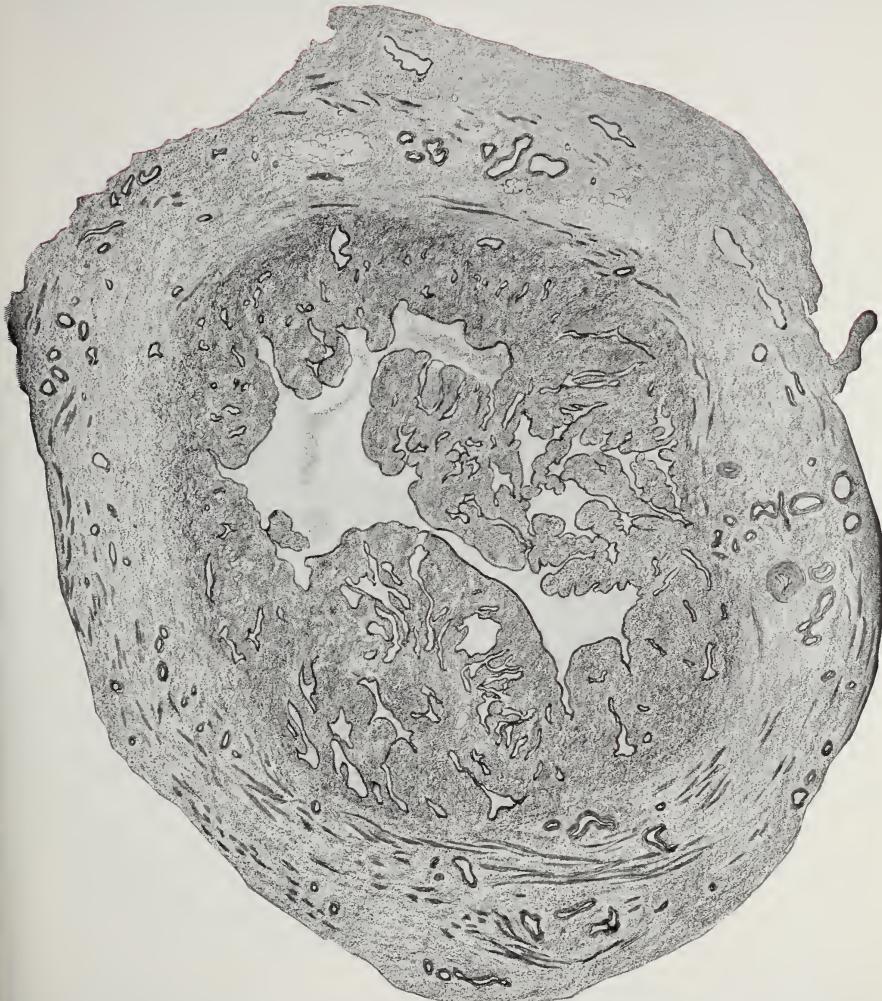


Fig. 294.—Subacute gonorrhœal salpingitis with great thickening of the folds of mucosa by the cellular infiltration.

In the child the vagina is more intensely involved than in the adult, where its epithelium is much more resistant. Recently, however, realizing the keratinizing process which in the vagina is characteristic of one stage in the menstrual cycle, it has been found possible to produce such keratinization in the vagina of children by administration of theelin or amniotin. This renders the vaginal lining far more resistant

*Give theelin to children → Keratinization of vagina
to treat Gc.*

and the gonococcal infection soon disappears as in the adult. Indeed, in the adult, gonorrhœal vaginitis occurs practically only as an acute process and is then relatively unimportant. A chronic gonococcal vaginitis is uncommon. On the other hand, the cocci readily pass into the cervical canal, and establish themselves in the mucosa with its glands, extending also to those of the fundus. Slight erosions, a tume-

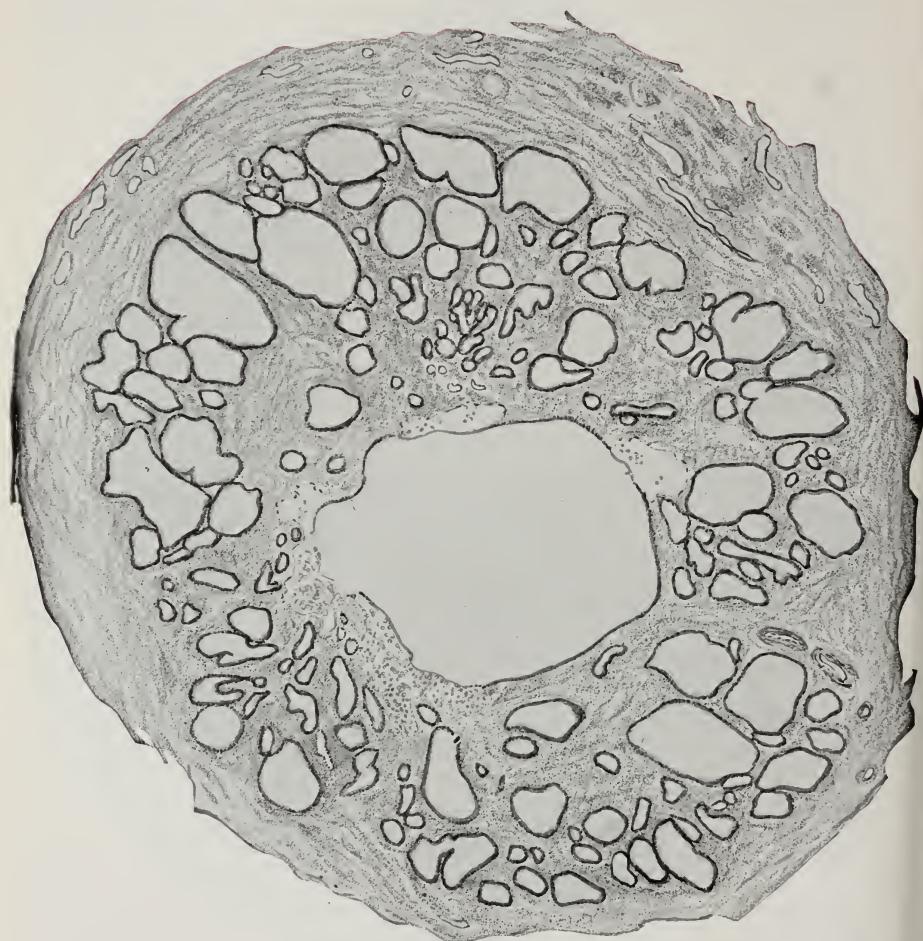


Fig. 295.—Pseudofollicular salpingitis. The appearance of closed cavities is produced by fusion of the folds of the mucosa.

faction of the mucosa, and the secretion of a purulent exudate mark their presence there. More important is the effect of their further wandering into the Fallopian tubes.

Gonococcal Salpingitis.—In the acute stage the tubes become swollen, hyperaemic, and œdematosus, the change being especially striking in the fimbriated extremity. In the mucosa alterations due to the presence of the organisms among the epithelial cells of the complex folds are in

general similar to those in the urethra. Later chronic alterations appear, dependent upon the deeper invasion of the cocci into the tissues. Adhesions are formed about the tube, and through the organization of exudate there is occlusion of its lumen at both ends and the accumulation of a quantity of pus in its cavity. Kinking of the tube may be partly responsible for these occlusions. The progress of the infection leads to great changes in the mucosa, which in operative cases are usually seen in their subacute stages. The folds of the mucosa, ordinarily so delicate and complicated, become distended into thick lamellæ (Fig. 294), which often adhere to one another and grow together so that they cover over the intervening spaces, which then, in cross-section, look like epithelium-lined channels in the tube wall (Fig. 295). Microscopically, these thick folds are found to be stretched by great numbers of wandering cells, among which lymphocytes and plasma cells are very numerous and conspicuous. Eosinophile cells are often abundant. Schridde and Amsbacher claim that the finding of such an infiltration of lymphocytes and plasma cells is sufficient proof of the gonococcal nature of the infection, but this is, probably rightly, contradicted by Müller and Menge, who state that other organisms, such as the streptococcus, may produce the same lesion if time is allowed for the development of a subacute or chronic salpingitis. The distention of the obstructed tube with pus (pyosalpinx) may greatly separate and flatten the folds of the mucosa, and the tube itself assumes then a variety of forms, according to the arrangement of the adhesions which may attach it to the uterus, to the ovary, to the rectum, or the pelvic wall (Fig. 296). Most often it is roughly retort shaped. Rupture of such a sac may occur through violence with discharge of the pus into the peritoneum. Ordinarily, there is not produced any very severe peritonitis, and this is explained by the fact that cultures from the pus are usually sterile. In other cases the exudate may lose its purulent character after the occlusion of the ends of the tube has occurred and become more serous. Such a tube may develop into a large, thin-walled sac full of clear fluid (hydrosalpinx) (Fig. 297). Naturally, either of these results ends in the complete loss of function of the tube, and if both tubes are affected, sterility follows.

Gonococcal infections of the ovary occur in the form of abscesses or false abscesses, caused by the invasion of the cocci into freshly ruptured follicles or corpora lutea.

Gonococcal peritonitis is an outcome of the acute stage of infection of the uterus and Fallopian tubes, the cocci entering through the fimbriated extremities. It may also be produced by transfer of the organism by the blood-stream. The exudate is fibrinous or serofibrinous, and is likely to lead to extensive adhesions among the loops of intestine. This condition is not of common occurrence, except in the more localized form of pelvic peritonitis, which is extremely common in association with salpingitis, and in its late stages is found to have bound the pelvic organs together by firm or lax adhesions.

Gonococcal Arthritis.—Somewhat late in the course of an acute urethritis, that is, after the inflammation has reached the posterior

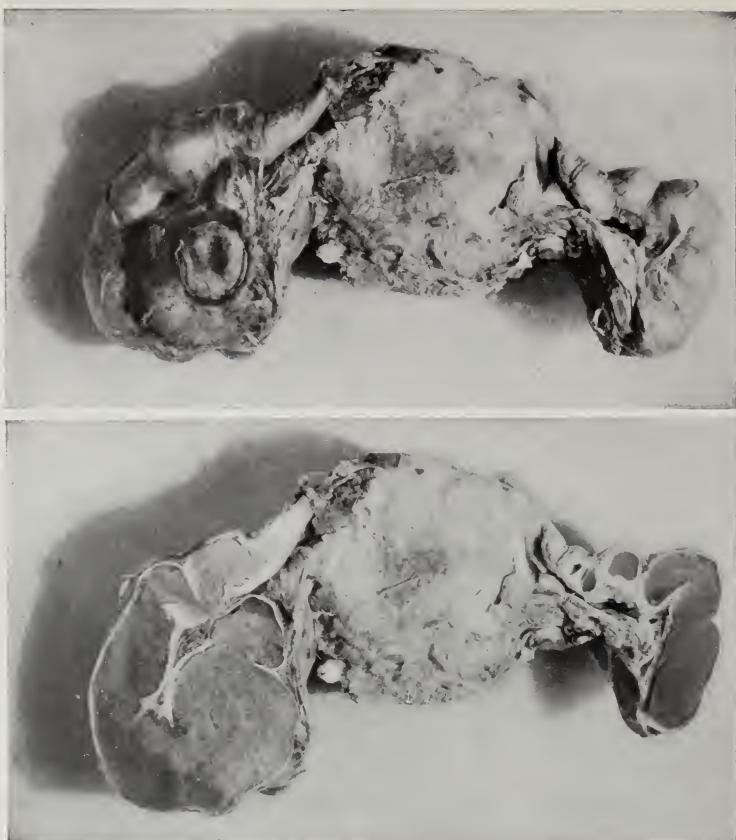


Fig. 296.—Bilateral chronic gonococcal salpingitis. Much of the purulent exudate has been replaced by a gelatinous mass.



Fig. 297.—Hydrosalpinx. In the uterine wall and projecting into its cavity are several small myomata.

urethra and has lasted several weeks, there often arises a painful involvement of a joint, which is due to the transportation of the gonococci by the blood-stream to the synovial membrane. This appears to be commoner in men than in women, and usually only one joint is involved, although others may be affected in succession later. The joint most commonly infected is the knee, and the inflammation may take several forms. The mildest is that in which there is a mere accumulation of fluid without pain or marked impairment of function. More frequently there is formed a serofibrinous or even purulent exudate, with infiltration of the surrounding tissues and extreme pain, so that the joint is held flexed. Erosion of the cartilage and rarefaction of the cancellous bone may occur, and fixation of the joint with ankylosis of the bones sometimes follows. Gonococcal infection of the bones themselves is reported, but is rare.

Gonococcal Ophthalmia.—Infection of the eye with this organism is extremely serious, and often leads, even under the most careful treatment, to destruction of the eye. It occurs in infants from infection during birth from the inflamed genitalia of the mother, and this so-called *ophthalmia neonatorum*, although relatively easy to guard against or cut short by instillation of nitrate of silver into the infant's eyes, is nevertheless the cause of an enormous number of cases of blindness among children everywhere in the world. In other children—and this probably includes the cases of "late birth infections," which develop after five days postpartum—gonococcal conjunctivitis is a fairly common accompaniment of the epidemic gonococcal vulvovaginitis.

In adults such conjunctivitis is caused by the introduction of the organism into the eye with the soiled fingers, towels, etc., or, especially in physicians, by the spurting of gonorrhreal pus into the eye. It is said that there may also arise an infection of the deeper parts of the eye through transmission of the organism by the blood-stream, and in this case there are no cocci in the conjunctival sac.

The conjunctivitis begins with the injection of the blood-vessels, swelling of the lids, and the pouring-out of a thick, purulent exudate, which tends to glue the eyelids together. The conjunctiva over the bulb swells, so that the cornea is sunken beneath it. The slightest touch upon the cornea is sufficient to start an erosion there, which progresses to ulceration and often to infection of the anterior chamber, which fills up with a purulent exudate. Healing of these ulcerations is likely to cause such scars or opacities in the cornea that the eye becomes useless. But there also may be produced extensive infiltration of the iris and neighboring tissues, resulting in distorting adhesions. Indeed, the whole eye may be invaded and extensively injured by the infection.

It is conceivable that infection of the nasal sinuses or even meningitis might arise from such a process, but although deJong and others have described cases of gonococcal meningitis, the proof of the identity of the organism which is so similar to the meningococcus is not satisfactory enough to allow these cases to be generally accepted.

Gonococcal Dermatitis.—Lesions of the skin said to be caused by the gonococcus assume many forms, among which are erythematous rashes,

urticaria, erythema nodosum, haemorrhagic and bullous exanthemata, and hyperkeratoses. Of these, perhaps the latter are most characteristic.

Gonococcal Endocarditis.—It is evidence of the transportation of the cocci by the streaming blood, and therefore of the existence of a general gonocoecal septicaemia, that endocarditis may owe its origin to this organism. Gonococcal septicaemia is particularly characterized by the occurrence of the arthritis already mentioned, and of the endocarditis, and is not an absolutely fatal occurrence. Cases have been reported as recovering even after the valvular lesions were very evident, and the cocci repeatedly demonstrated in the blood.

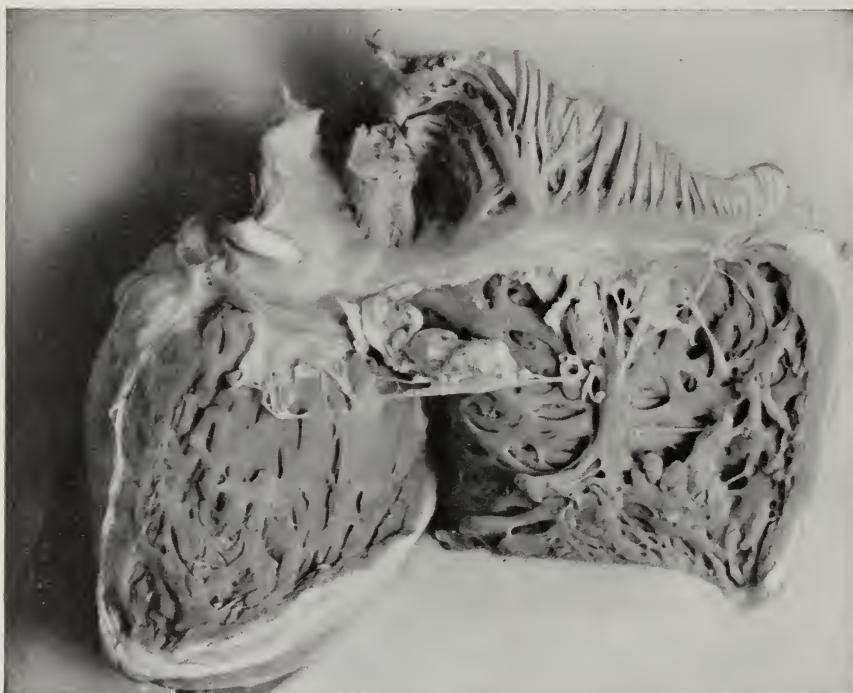


Fig. 298.—Gonococcal endocarditis, tricuspid valve.

The alterations of the heart-valves are rather characteristic, in that the vegetations are frequently extremely large and friable. They seem to effect the destruction of the valves with great rapidity, for in three cases which I have seen the valves were reduced to ragged strands, which flapped in the stream, bearing on their ends large crumbling remnants of the vegetations. Apparently the aortic and the mitral valves are most often affected, but we were impressed with the occurrence of these vegetations in our own cases on the tricuspid and pulmonary valves. Pericarditis and myocarditis of focal or diffuse character often accompany the endocarditis. The organisms are found in abundance in the vegetations. Mycotic aneurysms of the aorta have been observed in some of these cases and we are inclined to agree with Grant as to their mode of

production. They appear, as he found, in cases of endocarditis due to the *Streptococcus viridans* where partially detached portions of the ulcerated valve covered with bacteria-laden vegetations flap against the adjacent aortic wall, or against the wall of the heart. In one instance which we saw at autopsy there was a large sac filled with purulent material containing the gonococcus and extending outward from an ulcerated opening in the aortic lining just above the infected valve (Thayer).

Vulvovaginitis in Children.—With regard to the infection itself, there are some interesting features. It has been pointed out that epidemic vulvovaginitis in little children is a very common thing, and that in some orphan asylums it is never absent, but is known to produce so little real harm that it is somewhat ignored. Dr. Northrup tells me that in contrast to this familiar mild infection, the incomparably more serious effects of infection from the gonococcus from urethritis in the adult impressed him strongly in two cases. These were in two young girls, who were infected in some way from their mother, who had been infected from the acute urethritis of the father. They became profoundly ill, with circulatory collapse and symptoms that were thought to indicate appendicitis. One was operated upon and the appendix removed. Although it was normal, the whole peritoneum was intensely reddened, and there was a slight serous exudate. There were no other complications and they recovered. Recently, apparently with this idea in mind, Dr. Pearce has investigated the organisms concerned in an epidemic in a children's asylum, and has found that they do differ biologically from those isolated from urethritis in the adult. Her conclusions are in part as follows:

Two principal types of gonococci may be recognized by the methods of agglutination and complement fixation, and correspond to the adult and infant types of infection seen clinically. The gonococci isolated from cases of ophthalmia belong to the adult type. It appears that there may be many more varieties, and that these two types are not sharply marked out, but are connected by intervening forms.

Boor and Miller, in their study of the gonococcus, find that a nucleoprotein extracted from the organisms is responsible for their toxic action and their antigenic activity. A protein-free polysaccharid from the gonococcus seemed non-toxic, failed to produce precipitins but did cause a delayed allergic reaction.

LITERATURE

- Amersbach: Ziegler's Beiträge, 1909, xlvi, 341.
Brown: Jour. Amer. Med. Assoc., 1934, cii, 1293.
Bruck, C.: Ergeb. d. allg. Path., 1912, xvii, 134 (literature).
Haberman and Isrealoff: ibid., 1934, ciii, 18.
Jadassohn: { Handbuch der Geschlechtskrankheiten, 1910, i; 1912, ii, pp. Ehrmann and others: } 1-612. (These papers are excellent but very prolix.)
Lindau: Acta Pathol., Scandinavica, 1924, i, 263.
Miller and Boor: Jour. Exp. Med., 1934, lix, 63, 75.
Pearce, L.: Jour. Exp. Med., 1915, xxi, 289.
Thayer: Amer. Jour. Med. Sci., 1905, lxxx, 751. Johns Hopkins Hosp. Bull., 1922, xxiii, 361.
Wätjen: Ziegler's Beiträge, 1914, lix, 418.

CHAPTER XXIX

TYPES OF INJURY.—BACTERIAL DISEASE (Continued)

Diphtherial infection: Diphtheria of respiratory tract. General effects upon the heart, kidneys, etc. Paralysis.

Tetanus infection: Mode of occurrence and mechanism of distribution of the toxin. Botulism.

DIPHTHERIAL INFECTION

THE diphtheria bacillus is, as is well known, an organism which produces its wide-spread disturbances in the body by the agency of a soluble poison. In this respect it is paralleled by the tetanus bacillus, but by few, if any, other organisms. It can, however, in growing at the point from which it diffuses its toxin, produce a considerable local lesion, a power which is less striking in the case of the tetanus bacillus.

Diphtheria is perhaps most commonly a disease of children and young people, and it is doubtless possible that infection from one person to another may occur when association is intimate. Indeed, some healthy persons have been found to be carriers of virulent bacilli in their mouths and throats, and these may be the cause of its epidemic occurrence. But the explosive outbreak of epidemics of diphtheria over considerable areas is characteristic, and several of them have been traced to the contamination of milk or ice cream from infected milkmen or others who work in large public dairies (Howard, McCoy).

The organisms may become localized in the throat, producing characteristic lesions on the mucosa of the fauces, the uvula, the tonsils, the pharynx or larynx, often extending into the trachea and even deep into the smaller bronchi. Similar lesions occur in the nose, rarely in the ear, more often in the vulva and vagina, and sometimes in the skin, especially in connection with maceration of the epidermis or skin lesions, which prepare the way, or with ulcers and wounds. Spitz has collected instances in which the diphtheritic membrane was found in the oesophagus and stomach. Since the character of the local lesion is essentially the same everywhere, a description of the more common form in the throat will suffice.

A few days after the bacteria lodge in the mucosa, that is, after the lapse of enough time to allow them to grow and gather their forces, redness of the whole lining of the throat appears, with soreness, difficulty in swallowing, and evidences of an acute illness—fever, leucocytosis, etc. White or yellowish-white flakes appear on the reddened surface at one point or other, and spread. It is seen that the confluent patches thus form a slightly elevated, dull, opaque, membrane-like layer, which is pretty tenaciously adherent to the underlying tissue. This can be peeled off, but leaves a raw surface which oozes blood, and upon which a new false membrane quickly forms. In other places the pseudomembrane

may be less adherent, and this is likely to be the case within the larynx and trachea, where it sometimes forms a complete lining, stretching for a long way (Fig. 299). Evidence of this looser connection is seen in the frequency with which children cough up the whole lining, or at least large areas of it. The reasons for the closer adherence of the false membrane to the mucosa of the pharynx and mouth than to that of the larynx and trachea must be discussed later.



Fig. 299.—Diphtheritic membrane extending far down into the trachea. The tonsils are slightly swollen.

While this is the ordinary type of local lesion, the diphtheria bacilli may produce much milder inflammation of a more catarrhal character, or, on the other hand, especially when there is a mixed infection and virulent streptococci add their effects, there may be the most destructive affection of tonsils, fauces, and larynx, with deep necrosis and sloughing of the tissues, together with the most violent inflammatory reaction, and with great oedema of the surrounding parts.

Occlusion of the respiratory tract, either by the great swelling produced as just described, or more commonly by the accumulation and folding together of the false membranes, can cause death by asphyxia. Indeed, in spite of tracheotomy, deaths from this cause were frequent. O'Dwyer's method of intubation went far to save children from this evil, and the timely administration of antitoxin has practically cleared away the danger.

Pathological Anatomy of the Lesion.—The diphtheria bacillus is *one* of the many agencies which can produce a diphtheritic inflammation. It has been remarked that it may also produce milder forms, but even alone it is able to produce this most severe form.

It may be repeated, however, that many strong alkalies or acids or salts of heavy metals, such as mercury, can produce typical diphtheritic forms of inflammation, just as many bacteria can. In other words, the term diphtheritic is used in a purely anatomical sense, to describe the nature of the lesion and not its *aetiology*.

The lesion consists in an effective destruction of some of the superficial cells of the mucosa, which, under the influence of these bacilli, undergo necrosis and coagulation. The destruction of the overlying cells starts and favors the pouring-out of a coagulable fluid, which permeates them and spreads on the surface. The formation of fibrin through the coagulation of this fluid not only upon the surface, but everywhere in and among the dead cells, establishes the false membrane. Leucocytes appear in great numbers and there is some haemorrhage. Thus the first false membrane to appear is composed of the vaguely outlined coagulated bodies of the dead cells, buried in a feltwork of fibrin, together with many leucocytes. If this is torn off, the next membrane which forms to replace it will consist chiefly of fibrin and leucocytes, unless the growth of bacteria at the base of this fresh ulcer causes more necrotic tissue to become incorporated into the new membrane. Where the necrosis is wide-spread, the false membrane will be found firmly attached by a broad base. In the trachea (Fig. 300) and bronchi the membrane is found to be attached only at the points where the epithelial cells are necrotic and the basement membrane is destroyed. Through such places it exudes on the surface, becoming confluent over the intervening intact epithelium in a series of arcades. Beneath these arcades much of the epithelium may remain intact and serve to regenerate cells to repair the gaps after the disease is over.

The old discussion as to whether a diphtheritic membrane was to be regarded as formed by a fibrinoid degeneration of the superficial cells of the tissue, and not by fibrin from the blood, raged violently for a long time among such men as Orth and Marchand, on one side, and Neumann and his supporters, on the other. A historical review is given by Gaylord (Jour. Exp. Med., 1898, iii, 1). Even yet there are echoes of this in the acrimonious paper of Dietrich in criticism of Sudsuki (Ziegler's Beiträge, 1901, xxix, 562; xxx, 414). It seems clear enough that most of the fibrin must come from exuded plasma, but that necrotic cells embedded in it may become indistinguishable and add to the bulk of the mass. Fibrin formed through and through their dead bodies would still give its characteristic staining reaction.

Sequelæ.—While the mechanical effects of such a membrane are often serious, the more remote sequels of the infection are even more important. Bronchopneumonia is a common one, and is probably due in most cases to accompanying streptococci which pass into the bronchi.

The other things result from the diffusion of the strong toxin from the place where the bacilli are growing, into the circulating blood.

Death may take place in the height of the intoxication, evidently from its direct action upon the heart and circulatory system. In the

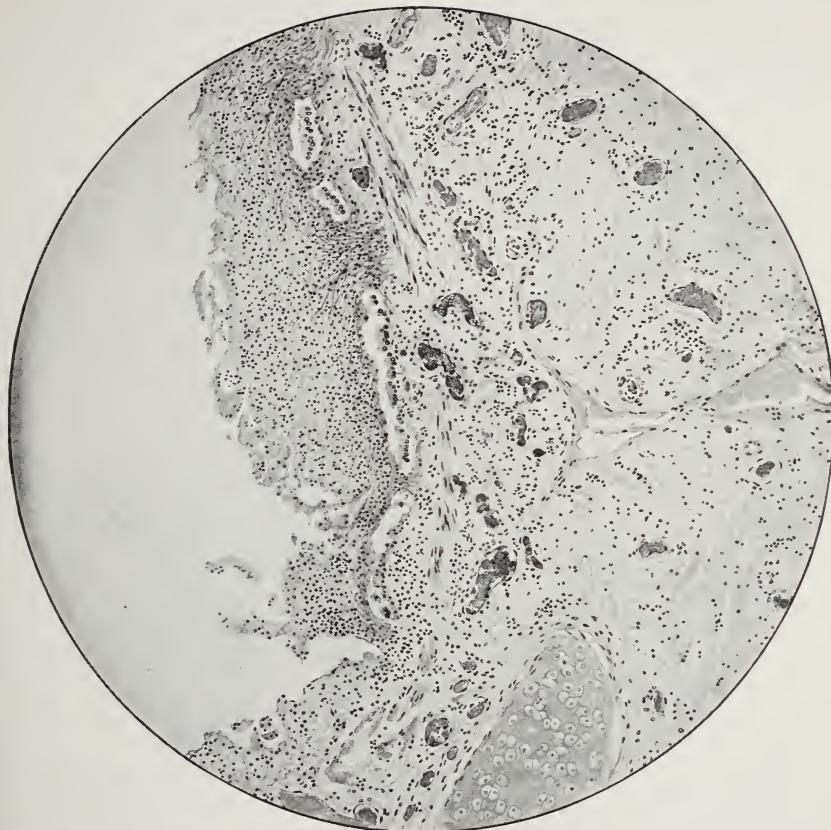


Fig. 300.—Diphtheritic membrane in a bronchus. Acute laryngeal and bronchial diphtheria. The exudate has the arrangement in arcades.

heart itself in such cases no gross changes are to be seen, and, indeed, the microscopical changes, cloudy swelling, fat infiltration, and fragmentation of the heart muscle do not offer convincing evidence of the cause of death. As has been mentioned elsewhere, Pässler and Romberg held the opinion that the effect of the poison was chiefly upon the vaso-motor control of the blood-vessels, allowing them to relax so that circulation failed. I was able to confirm this by artificially maintaining the blood-pressure in the brain and coronary arteries, upon which life

was greatly prolonged. But it seemed clear that the heart itself was also injured, since it would not beat quite so long as a normal heart. It is even more difficult to explain the gradual or sudden weakening of the action of the heart, with increased pulse-rate and altered rhythm, which may occur after or during convalescence. It is generally ascribed to myocardial degeneration, sometimes to derangement of the nerves which control the heart. Löw describes slight alterations of the conducting bundle of His in such cases, but is unwilling to claim this as the cause of the heart failure.

Albuminuria is common in diphtheria, and the kidneys show acute and subacute changes in most fatal cases. These rarely have the character of a glomerulonephritis, but are more commonly instances of acute interstitial nephritis.

The lesions in other organs are essentially those of any acute infection, except that the changes in the adrenals are likely to be more intense, resulting in haemorrhages and cellular degenerations.

Paralysis of motor and to less extent of sensory nerves is dependent upon degenerative and destructive changes in the nerves themselves, as well as in the nerve-cells. The axones disintegrate, and the myeline sheaths lose their homogeneous character, fatty globules which stain with osmic acid appearing in their place. The nerves which supply the palate and larynx, those of the extrinsic muscles of the eye and of the muscles of accommodation, suffer especially. Paresis or definite or temporary paralysis of the muscles of the extremities occur, but are less common. Guillain and Laroche find that the toxin is fixed in the gray matter of the central nervous system apparently in combination with the phosphorized lipoids of the brain, and Walshe, in a review of the localization of the poison, brings evidence to show that while paresis of the muscles of accommodation and generalized peripheral neuritis are probably due to a haematogenous intoxication of the nervous system, there are distinct local paralyses corresponding with the site of the diphtheritic infection and apparently resulting from the transportation of the toxin along the lymphatic channels in the nerves to their centres in the spinal cord or medulla. Hence the paralysis is of central origin, but naturally distributed according to the source of the toxin.

Skin lesions in the height of the infection are usually in the form of an erythematous rash, but petechiae and extensive purpuric haemorrhages sometimes appear in the severest cases.

The toxin produces in those who recover a certain immunity and this may be artificially imitated by the injection of a small dose of the toxin or of a modified toxin or toxoid. The susceptible person shows a positive Schick reaction—in response to the inoculation in the skin—while the immune have a negative Schick reaction.

Such immune persons may still be carriers of live bacilli and hence a menace to the susceptible. Unless in an antidiphtheria campaign a very large percentage are immunized, the diphtheria rate is likely to be maintained by these carriers. Some strains of the bacillus, especially one known as *C. gravis*, seem far more virulent than others.

LITERATURE

- Behring: Zeit. f. Hygiene u. Infektionskr., 1892, xii, 1-58.
Etris: Jour. Infect. Dis., 1934, lv, 220.
Löw: Ziegler's Beiträge, 1910, xlvi, 1.
Nuttal and Smith, Graham: Bacteriology of Diphtheria, Cambridge, 1908.
Oertel: Pathogenese der epidemischen Diphtherie, Leipzig, 1887. Deut. Arch. f. klin. Med., 1887-8, xlvi, 511.
Park, W. H.: Amer. Jour. Publ. Health, 1933, xxiii, 600; Lancet, 1935, i, 170, 228.
Walshe, F. M. R.: Medical Science, 1924, ix, 267.
Welch: Johns Hopkins Hosp. Bull., 1892, iii, 17; 1895, vi, 97. Amer. Jour. Med. Sci., 1894, n. s., cviii, 437.

The most comprehensive discussion of diphtheria, including a review of all the experimental studies, is found in the publication of the British Medical Research Council: Diphtheria, Its Bacteriology, Pathology, and Immunology, London, 1923.

TETANUS INFECTION

Tetanus, well described by Hippocrates and Aretaeus, has only recently been recognized as an infectious disease. Nicolaier, in 1884, and Rosenbach, in 1886, saw the bacillus, but Kitasato isolated and cultivated it, and the work of Behring and Kitasato upon the toxin and antitoxin in the case of this bacillus and that of diphtheria is the foundation of serum therapy.

This, like diphtheria, is essentially an intoxication, since the bacteria grow only at the site of inoculation, usually in a wound into which dirt has been forced, and there produce a soluble toxin, which is diffused throughout the body. A certain latent period elapses after the infection before the symptoms appear, and the longer this lasts, the less serious are the effects. Those cases in which the incubation period is only four days are almost sure to end fatally. The effect of the poison is to produce extension and extreme rigidity of the extremities, often preceded by clenching of the jaw (hence lockjaw) and stiffness of the neck, and followed by violent contractions of the muscles of the back, such as to throw the body into a rigid backward curve (opisthotonus). When the muscles of respiration are involved, death ensues, or it may result from exhaustion. Reflex or spontaneous convulsions of great violence may occur. At autopsy no lesions are found which are characteristic of the disease. It is true that Goldscheider and Flatau, Nissl, and others, have found swelling and fragmentation of the tigroid bodies of the motor ganglion-cells and shrinkage with deep staining of the nuclei, but this condition is found under many other circumstances and is by no means specific. Tetanus must then be regarded as a functional disturbance produced by the toxin. Exactly the same phenomena can be produced in animals by the injection of the bacteria-free toxin, which is an extremely virulent poison.

In the pathogenesis of tetanus the greatest interest lies in the point of action of the poison and its mode of distribution. It is observed that there may be a local rigidity of the muscles in the neighborhood of the point of infection (local tetanus), but that while this may sometimes be the only symptom, it usually leads to a similar rigidity of the opposite extremity, and finally to an involvement of the whole body (ascending tetanus). Another form, beginning with clenching of the jaw and stiff-

ness of the neck, quickly spreads to all the extremities (universal or descending tetanus), while a third form is that in which convulsions form a striking feature.

It was shown by Meyer and Ransom that the toxin travels from the point of inoculation up the nerves to the central nervous system, although it is also diffused to some extent by the blood and lymphatics. In the case of the local tetanus, which is less striking in man than in experimental animals, there arose some question as to the possibility of its being due to a direct effect of the toxin upon the muscles, but the experiments of Permin show clearly that if the nerve be cut shortly after the injection of the toxin, no such local/rigidity appears. But the rigidity persists if the section of the nerve be performed after it is well established, probably owing to secondary changes of unknown character in the muscles themselves. Similarly, Meyer and Ransom showed that the injection of antitoxin into the nerve above the point of inoculation would block and neutralize the toxin. Further, since it might be supposed that diffusion by the blood-stream could bring the poison to the ganglion-cells of the cord, Permin has shown by experiment that if antitoxin be injected first, so as to neutralize the poison carried by the blood, a distinct local tetanus can be produced by a small dose of toxin injected into the muscles. The poison passes along the nerves rapidly, probably in the axis-cylinders, since destruction of the perineurium does not halt it, and reaches the corresponding ganglion-cells of the anterior horn. If it is limited in quantity so as to affect only this group, a local tetanus will appear. Otherwise it can spread to affect the whole spinal cord and brain, and rigidity of the muscles over the whole body follows.

In other cases in which the toxin gains more ready entrance to the blood-stream, or in which it is injected into the vein in an animal, the universal or descending type appears.

The question as to the type of nerve which conducts the poison seems not yet settled,* nor whether the anterior horn cells become spontaneously active in sending impulses to the muscles, or only excessively irritable and responsive to sensory impulses, to which they act as in reflexes. Permin showed that, by cutting all the posterior roots on one side and injecting toxin into both legs, one produces local tetanus only on the intact side, while the leg from which no sensory impulses reach the cord, remains relaxed.

Teale and Embleton from many ingenious experiments conclude that although the toxin ascends to the central nervous system by way of the axis-cylinders, it also travels by way of the perineural lymphatics and is delayed if these be blocked. The toxin does not pass from the capillaries to the tissue of the central nervous system, nor from the choroid plexus to the cerebrospinal fluid, and is blocked from reaching the cord along the afferent nerves by the posterior root ganglia. The antitoxin, they find, does not pass to the central nervous system by the way of the

* Nevertheless, Meyer and Ransom produced only pain and greatly increased reflex excitability to pain by injecting the toxin into the spinal cord or posterior roots (*tetanus dolorosus*), while injection into peripheral sensory nerves was without result. They therefore think the motor nerves the paths of conduction of the poison.

blood, axis-cylinders or lymphatic channels, and acts only by combining with circulating toxin, preventing it from reaching the central nervous system, although that which has already reached the cord and brain is unaffected.

In the case of the convulsive attacks it seems that the impulses come from the brain itself, which in those cases has been affected by the poison. They can be prevented by the removal of the motor cortex in animals, and can be produced in their most extreme form in other animals by injecting the toxin into the brain or into the eye, whence it quickly passes into the brain. Tetanus is thus ordinarily the effect of the toxin upon the spinal cord, the convulsive features being due to its spread into the brain.

The enormous importance of this disease, especially in the late war, where wounds were contaminated with the highly manured soil, in which the bacilli were abundant, has led to great efforts to counteract the poison. Antitoxin, so useful in guarding against the poison, and so active in neutralizing it in the blood, cannot follow it from the circulation into the nervous system. Therefore, unless it be injected into the nervous tissue, it is relatively valueless. As stated, it will block the passage of toxin along the nerve if injected into the substance of the nerve, but it must remain difficult to diffuse it into the substance of the cord and brain in more advanced cases. The mortality remains high, although certain narcotics are useful in stopping the flow of impulses from the ganglion-cells.

Since all this was written, Dr. Abel with his associates has been continuously at work on the mode of action of the tetanus toxin and in many points is in disaccord with these results. He finds that the toxin is not carried along the nerves, either by the axis-cylinders, the perineurial lymphatics, or the tissue spaces of the nerves. No toxin is found in the nerve proximal to a point of inoculation and toxin directly injected into the nerve produces no local tetanus in the area of distribution of that nerve. The perineurial lymphatics would not carry toxin to the brain but empty, of course, finally into the blood-stream. It is by way of the blood-stream that the toxin reaches the central nervous system. Local tetanus can be produced by injecting small doses of the toxin directly into the muscle. The action of the toxin on the central nervous system has not been further studied.

LITERATURE

- Abel, J. J., and others: Science, 1934, lxxix, 63, 121; Bull. Johns Hopkins Hosp., 1935, lvi, 84, 317.
Behring and Kitasato: Dtsch. med. Woch., 1890, xvi, 1113.
Flatau: Flatau, Jacobsohn, and Minor, Path. Anat. des Nervensystems, Berlin, 1904, i, 1290.
Kitasato: Zeitschr. f. Hyg., 1889, vii, 225.
Meyer and Ransom: Arch. f. exp. Pathol., 1903, xl, 369.
Permin: Mittb. a. d. Grenzgeb. d. Med. u. Chir., 1913-14, xxvii, 1.
Rosenau and Anderson: Bull. No. 43, Hyg. Lab., U. S. Pub. Health and Mar. Hosp. Serv. (Gives good review of the history of tetanus.)
Teale and Embleton: Jour. Path. and Bact., 1919, xxiii, 50.

BOTULISM

For a long time it has been known that the eating of spoiled sausages, preserved meat, etc., might produce a fatal illness. This was especially common in Württemberg in the last century, but is now recognized everywhere, and spoiled canned fruits and vegetables have also proved to be the cause. Van Ermengem cultivated a large Gram-positive anaërobic spore-bearing and gas-producing bacillus from spoiled ham in one such group poisoning, and this has proved since to be concerned in the later outbreaks. It was called *Bacillus botulinus*, or *Clostridium botulinum*, and is evidently capable of producing a powerful toxin for which an antitoxin can be made. As shown by Dickson, who has devoted himself to the study of this affection, the imperfect methods of home canning often allow this organism to develop in such things as canned beans, asparagus, fruits, etc., and these, if not boiled again before eating, convey the disease even when partaken of in minimal amounts. Chickens and other animals are also susceptible. The illness is essentially an affection of the nervous system with ophthalmoplegias, difficulties of deglutition and speech, and respiratory failure, and fatal results are very common.

The studies of the pathogenesis of the disease are, however, entirely unsatisfactory. Ophüls and Dickson report multiple small thrombi in the vessels of the brain, but give no information about the presence of the bacilli or their localization. It seems clear that the disease is caused not by the growth of the organisms in the body, but by the extremely powerful toxin which has been formed by them during their growth in the infected foodstuffs. The toxin is readily absorbed from the intestine, in which it differs from the tetanus toxin, and can be demonstrated in the circulating blood. It appears to be neutralized by the tissue of the central nervous system. No clear information is available as to its exact mode of entry into the nervous system nor as to its point of attack. Cowdry, from negative histological examinations of the central nervous systems in animals, tends to the opinion that the site of action may be in the peripheral nerve terminals. A comprehensive study is found in the Hygienic Laboratory Bulletin, No. 136, by I. A. Bengston, 1924.

LITERATURE

Cowdry and Nicholson: Jour. Exp. Med., 1924, xxxix, 827.

Dickson: Monograph of Rockefeller Institute, 1918, No. 8; Jour. Exp. Med., 1923, xxxvii, 711.

Geiger, Dickson, and Meyer: Public Health Bulletin, No. 127, 1922 (Epidemiology).

Van Ermengem: Z. f. Hyg. u. Infektionskr., 1897, xxvi, 1.

CHAPTER XXX

TYPES OF INJURY.—BACTERIAL DISEASE (Continued)

Asiatic cholera: Intestinal lesions. General intoxication.

Bubonic plague: Transmission. Bubonic type. Pneumonic type.

Glanders: Acute and chronic forms.

Anthrax: Infection through skin, digestive tract, lungs.

SEVERAL other types of bacterial infection must be considered here, some of them infections of enormous importance at certain times, when they rage as epidemics, or in tropical countries, where they exist constantly as endemic plagues, but described here only in outline.

ASIATIC CHOLERA

An epidemic disease spreading with the course of human travel, and occurring either in groups of cases or suddenly affecting a whole community. It is largely dependent upon infection of water supply or of food, and hence the rapidity of its spread in cities where the drinking-water comes from an infected source, as was the case in the Hamburg epidemic. It is endemic in India, and is the cause of hundreds of thousands of deaths every year in that country.

Taken into the stomach and intestines, the spirillum of Koch requires forty-eight hours or more to develop to a sufficient extent to cause the symptoms. Then the disease proceeds with extreme violence. There are several forms, in the mildest of which there is intense diarrhoea, which may pass off in a few days. In the so-called choleric, there are diarrhoea, vomiting, and extreme prostration. These conditions may pass into the more severe form, in which, with great desiccation of the tissues, there are painful muscular cramps, cold sweats, stagnation of the cutaneous circulation, delirium, and collapse. In others the patient passes into coma and dies.

Anuria, which may persist until death, is in many cases a most prominent feature, and is accompanied by acidosis. This is largely due to the extreme dehydration of all the tissues which leaves no water for excretion by the kidneys, and a very rational treatment which is in general use consists in the continuous infusion of salt solution in a slow stream into a vein.

The following impressions of the pathological anatomy are copied from notes made in Manila at a time when I had an opportunity to perform a large number of autopsies in cases of cholera during an epidemic of considerable severity. When the body is brought warm to autopsy, rigor mortis appears during the autopsy and often draws the arms and legs into a cramped position. In cases which have lain several hours there is usually the most extreme rigidity. The face is not distorted, but the eyelids are drawn up so as to expose the uprolled eyes.

The arms and legs are like iron and it requires one's full strength to break down such rigor. The pectoral muscles are hard and offer a wooden resistance to the knife. The hands and feet are blue and shriveled and shrunken in the most curious manner. The skin over the balls of the fingers is wrinkled and in some cases almost hornlike and transparent. The same change is visible over the palms of the hands and soles of the feet. Elsewhere the skin is very inelastic and pasty, and when pinched up takes a long time to smooth down. The blood which oozes from the heart and blood-vessels is viscid and very deep red, almost black. In this state of extreme concentration it seems to coagulate less firmly than normal.

The organs in general seem almost normal, and it is as though one were performing a series of autopsies on the normal victims of some railway disaster. The peritoneum contains no free fluid; even in the recesses and fossæ there is usually not a drop. The peritoneal surfaces are dull and dry and are no longer slippery; when quickly pulled apart they sometimes adhere a little and draw out minute threads of viscid fluid. The small intestines are usually distended with fluid and gas, and are of a dull grayish rose color, showing injected blood-vessels. They are relaxed and tend to lie flat. The colon and parietal peritoneum contrast rather sharply with this on account of their relatively normal pearly white color.

The pleural cavities, like the peritoneum, are dry, but the pericardium contains a little fluid. The thymus is enlarged in nearly every case. In children it is especially bulky, reaching 10 to 12 grams, and extending downward as a thick mass. Even in adults the organ lies over half the pericardium and may measure 10 cm. in length. This persistence of the thymus is especially striking and probably accords with the lymphoid swelling in the intestine. The heart shows no changes in anything except the presence of many ecchymoses in the epicardium and in the endocardium, especially in the papillary muscles and trabeculæ of the left ventricle. In marked contrast with the extreme rigidity of the body muscles the myocardium is rather soft, opaque, and grayish-brown and in its inner layers more yellowish. In the lungs there was in two or three cases a patchy lobular pneumonia, and in as many more distinct œdema. But in most instances there was no characteristic alteration. The spleen is not enlarged or, indeed, changed in any particular from normal. In no case was there found anything which could be described as an acute splenic tumor. The liver too is practically normal; the lobules are distinct and easily outlined and are not dull or cloudy looking. There were several cases, however, in which the liver seemed drier than normal and was very dark grayish red. The bile ducts seem normal and the gall-bladder is full of green bile which usually contains the cholera spirilla. It is said to show a definite cholecystitis at times, with turbid fluid and reddened mucosa, but I saw no such cases. The pancreas shows no gross abnormality. The stomach is usually empty and its mucosa pale. The duodenum begins at once to show the characteristic lesions of cholera and these continue throughout the small and large intestine.

The contents of the small intestine vary greatly; they are, as a rule, fluid, but not quite watery, for there is a viscidity due partly to the admixture of mucus. The fluid is like thin barley soup, and turbid. When the intestine is opened the fluid pours out with radiating shreds of gray mucus which are readily washed off the mucosa. Toward the lower ileum it often becomes tinged rose color, but this by no means always so, and it may continue like thin gruel through the whole colon. "Rice water" must be a poor descriptive phrase, for the stools seem more viscid, turbid, and mucoid than that could be. Microscopically the contents of the upper ileum show myriads of bacteria and thick masses of desquamated epithelium with few or no leucocytes. The bacteria are of many kinds, large stout bacilli, long rods both coarse and thin, minute thin bacilli, but rather few spirilla. They can be found after rather long search, but, of course, grow out abundantly on selective media. The epithelial cells seem to be partly digested and few of them will take a nuclear stain. They are often to be found in sheets.

The mucosa is lax, smooth and slippery, and spreads out easily as though half decomposed. It is not swollen as in oedema, but seems to be easily permeated by the fluid, and not to hold it back. When washed it shows the individual villi as tiny opaque grayish-white threads. The mucosa has a certain opacity, about as intense as that of wet white tissue paper. It allows the red of the injected submucosa to show through as a rose color veiled by the gauzy wet mucosa. Lower in the intestine there may be many minute haemorrhages so fine as to give a pale red color to the mucosa in the neighborhood of the Peyer's patches and solitary nodules. In the lower ileum these lymphoid structures become swollen and prominent, not to the degree seen in typhoid fever or marked status lymphaticus, but still enough to make them quite conspicuous. There is no ulceration, although there may be haemorrhages of small extent. A frequent phenomenon is the appearance of a grayish-green opaque spot in the centre of each solitary nodule and each unit of the agminated patch. In a few cases the haemorrhage is more intense, and in one case the whole mucosa was deep blood red with only a few patches of normal color. Occasionally there are, in protracted cases, patches of diphtheritic exudate.

The mucosa of the colon is almost exactly like that of the small intestine. It is pale, lax, moist, and rather white and opaque. In some cases there are many sharply outlined haemorrhages. The mucosa of the appendix is similarly altered, although to a slighter degree. The contents of the colon are like those of the ileum in most cases, but it must be remembered that there are some in which death occurs before diarrhoea appears, and in these cases of *cholera sicca* the colon contains formed faeces.

The adrenals show nothing abnormal. The kidneys when not modified by old changes are practically normal in their general appearance. The capsule strips off smoothly, leaving a pale yellowish-gray and rose-colored surface. The size and consistence are normal. On section the striations of the cortex and glomeruli are normal in arrangement and the only abnormality consists in a slight opacity and yellow hue in the

labyrinthine portions. Even in cases in which there was anuria for days before death I was able to see little more than this blotchy yellow opacity in the bands which contain the convoluted tubules. In other cases the kidney was found dry and dull looking, dark grayish-red, pasty, and inelastic.

The urinary bladder is always empty or, at most, contains a few drops of thick, viscid, turbid yellow urine. The bone-marrow is soft, fatty, and often shows patches of dark red. The brain and cord show no obvious changes.

Microscopically examined, the wall of the intestine shows an almost complete loss of the epithelium from the mucosa. Only in the depths of the crypts is any left, and the villi project quite uncovered. Their limiting membrane is still continuous, but the cells which fill them at their tops are all necrotic. The lymphoid nodules are swollen and show many fragmented cells in their central portions, but there is no ulceration. The mesenteric lymph-nodes nearly always present wide areas of necrosis which occupy the position of the sinuses. The kidneys, in accordance with their naked-eye appearance, are undisturbed in their anatomical arrangement, and there is no inflammatory reaction, but in the severer cases there are profound destructive changes in the epithelial cells of the convoluted tubules. Even in the less advanced, certain tubules are partly lined by cells which are swollen and contain large hyaline droplets, but in those which have passed through several days of anuria the convoluted tubules are choked throughout their whole course with masses of necrotic cells. No constant changes can be made out in the spleen and liver in this series of cases, although, as stated, some authors have observed, apparently in cases which survive for some time, an acute cholecystitis and even an extensive cholangitis.

Great differences of opinion prevail as to the exact nature of the infection in cholera, especially with regard to the distribution of the organisms in the body. I found difficulty in distinguishing the spirilla in the mass of miscellaneous bacteria in the intestinal contents, while Schöbl and others speak of that fluid as a pure culture of cholera vibrios. Most authors state that the specific organisms are confined to the intestinal tract, and that the violent symptoms are due to the absorption of toxic materials, but Colonel Greig has found patches of bronchopneumonia loaded with the spirilla and has cultivated them also from the spleen. He therefore naturally regards the cholecystitis and cholangitis, and even the mere infection of the bile of the gall-bladder, as due to circulation of the bacteria in the blood, rather than to wandering from the intestine by way of the gall-duct. The necrosis of the mesenteric glands which occurred so often in our series would suggest an escape of the organisms by way of the lymphatics. The necrosis of the renal epithelium has the appearance of a toxic process, especially since the cholera vibrios have been so rarely found in the urine, although so carefully searched for. But so far cultures from the circulating blood have been negative.

The great frequency of infection of the bile is of much importance, since it is the basis of the persistence of the organisms in the excreta

of convalescents, just as in typhoid fever, although probably these persons do not remain infected for nearly so long a time. The stools have been found to contain the spirilla for forty to ninety days after recovery, but Kulescha had one case in whose bile-duets they were found ten months after the onset of the disease.

LITERATURE

- Crowell: Philippine Jour. Science, 1914, ix, 361.
Fahr, Th.: Ergebni. d. allg. Path., 1909, xxiii, 1.
Goodpasture: Philippine Jour. Science, 1923, xxii, 413.
Greig: Indian Jour. Med. Research, 1914, i, 67.
Heiser and Ernst: Wood's Ref. Handb. Med. Sci., New York, 1917, viii, 552.
Koch, R.: Arb. a. d. Kais. Gesundheitsamte, 1887, iii.
Krause and Rumpf: Handb. d. Tropenkrankheiten, Mense, 1914, iii, 242.
Schöbl: Philippine Jour. Science, 1915, x, 11.

BUBONIC PLAGUE

The plague is another affection endemic in certain countries, where it is essentially a disease of rats and other rodents, but spreading with the transportation of infected materials or rats to other countries. It has occurred with the same virulence in winter weather in Manchuria as in the heat of India or Africa.

Plague is caused by the *Bacillus pestis*, discovered by Yersin and Kitasato, an organism of extraordinary virulence, capable of causing infection from the slightest inoculation, and producing a highly mortal disease, in which it becomes distributed in enormous quantities through the body. Infection can occur through the skin, through the respiratory tract, and, possibly, though this is unimportant, through the digestive tract. By far the most common are infections through the skin, either through wounds (Dürck describes infection from a rat-bite) or through the bites of infected fleas. The rather rare cases of primary plague pneumonia are often caused by the inhalation of bacilli carried in fine droplets of sputum exhaled by another person with plague pneumonia. In the great Manchurian epidemic of 1910-11 Strong tells me the cases were nearly all of the pneumonic type and were uniformly fatal. He and his assistant escaped infection by wearing thick masks of cotton.

By far the greater number of the cases in ordinary plague are not of the pneumonic type, but are characterized by buboes or suppurations of the inguinal, axillary, and other lymph-glands. In these the infection is probably caused by the bites of fleas which have infected themselves from plague-stricken rats. C. J. Martin has shown me the plugs of plague bacilli which form in the proventriculus of the flea, preventing the access of any blood to its stomach. Such a flea, constantly hungry, will bite again and again, each time transferring plague bacilli to its victims.

Bubonic Type.—After a short incubation period painful swellings appear in the groin. In one case in which I performed the autopsy recently in Rangoon, there was no swelling of externally visible glands, but those about the brim of the pelvis and in the retroperitoneal region

were greatly enlarged. In the early stage these glands are swollen and sprinkled with haemorrhages. The lymph-sinuses are packed with phagocytic cells which contain the bacilli in numbers. Necrosis follows quickly and becomes extensive, and is associated with much haemorrhage and outpouring of leucocytes. Dürck thinks it largely due to circulatory obstruction. The whole centre of the gland breaks down into an abscess cavity and may be discharged. Metastases of the bacilli



Fig. 301.—Pneumonic plague. The exudate and congestion are such as are described for the stage of engorgement in ordinary pneumonia. Great quantities of bacteria in the tissues, especially in the lymphatics of the bronchial walls.

occur to the next glands, and shortly to the lungs and other organs. In the lungs foci of necrosis of the tissue with suppuration are produced by this embolism, and the same is true for the liver. There is a great swelling and softening of the spleen with grayish opacity, caused by the new formation of cells, which Dürck thinks are endothelial cells from the sinuses. Abscesses occur there also. In the kidneys there may be definite focal necroses, abscess-like in appearance, with many bacilli, or more commonly an acute haemorrhagic nephritis with necrosis and

desquamation of the epithelial cells, both in the glomerular capsules and tubules.

On the whole, the appearance is that of a fulminant general septicaemia, with the lodgment of enormous numbers of bacilli in any or all of the organs, and their transportation in quantities in the lymph and circulating blood.

Pneumonic Form.—In the bubonic form there may be found, in some cases, lobular consolidation of the lung, sometimes discrete, more often confluent. This is, in fact, the commoner type of pneumonia found in such epidemics as that of Manchuria, but Strong emphasizes the fact that the somewhat hypothetical stage of engorgement, always described for the pneumococcus pneumonia, is really the commonest phenomenon in these cases, since the affected persons die before actual hepatization can be produced (Fig. 301). He describes lobar consolidation also, in which, however, only a small part of the lung was ever found in the stage of gray hepatization, another part in that of red hepatization, while the greater part was in the stage of engorgement. Even in the gray stage there is little fibrin, while in the more usual stage of engorgement there are hardly any leucocytes, although the alveoli are filled with bacteria and fluid and desquamated epithelium, and the capillaries are greatly distended.

In the other organs there were found evidences of an intense general septicæmia, with cloudy swelling and haemorrhages, but usually no such embolic lesions as described for the more slowly advancing bubonic form.

LITERATURE

Albrecht and Ghon: Beulenpest im Bombay, Wien, 1898–1900.

Dürck: Ziegler's Beiträge, 1904, Suppl. vi.

Strong: Science, 1935, lxxii, 307.

Strong and Teague: Philippine Jour. Science, 1912, vii, 129, 137.

GLANDERS

Primarily a disease of horses, mules, etc., infection with the *Bacillus mallei* may occur in those who handle horses or who are exposed in some way to contagion from them. In a few cases fatal infections have occurred in persons working in laboratories with cultures of the organism.

In horses the disease is largely an affection of the nasal and respiratory tracts, and frequently assumes a chronic course. Nodules appear in the nasal mucosa, especially upon the septum, which are quite firm at first, but later present a necrotic centre and develop into ulcers, which heal with extensive scar formation, recognizable by its curious stellate arrangement. Affections of the trachea and lungs, of the intestines, lymph-glands, spleen, etc., are also found in these animals (Kitt).

In man the formation of necrotizing or pustular eruptions in the nose has been described, and in such cases the destructive action of the bacilli leads before long to the ulceration and perforation of the septum of the nose, partial destruction of the turbinate bones, or even of the palate. More common are infections through the skin, which give rise to deep indurated swellings which persist until incised, or until they burst spon-

taneously, setting free a thick, stringy pus. Such abscesses heal very slowly, and usually a sinus persists for a long time. In other cases serpiginous ulcers are formed in the skin which extend in one or other direction, leaving behind a partly healed or scarred area. Most of the cases have presented deep muscular abscesses which evacuate the same thick pus and are slow to heal. At times the bone is attacked, and in many instances there have been necrosis and final perforation of the bones of the skull. Multiple embolic lesions in which necrotic or caseous

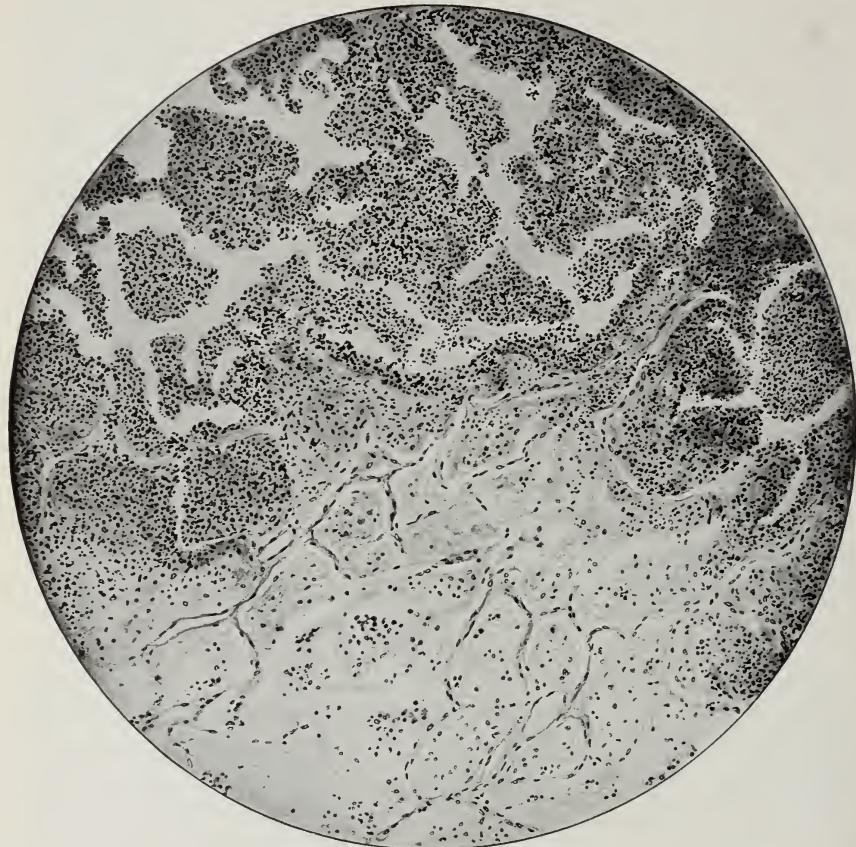


Fig. 302.—Glanders. Focus of lobular pneumonia with abscess-like destruction of tissue and organization of adjacent exudate.

material is formed and surrounded by a dense granulation tissue are found in various situations in the body. Pulmonary lesions are especially frequent, and assume various forms. In one case which I studied in Professor Marchand's laboratory the man had been accidentally infected by thrusting the needle of a syringe full of a culture of *Bacillus mallei* into his thumb. Two months later he died with what appeared to be a diffuse tuberculous pneumonia. In these lesions, however, there were found the bacilli in pure culture, and microscopically

the changes were quite unlike those of tuberculosis. Instead (Fig. 302), there were foci of necrosis with débris of cells and tissue closely coagulated together, but without nuclear stain, surrounded by a zone of fragmented nuclei, and this in turn by a thick infiltration of leucocytes. The adjacent lung tissue was the seat of an organizing pneumonia, and there was extensive filling of alveoli with large mononuclear cells, as in caseous pneumonia. In this case there was nothing of the formation of nodules with giant-cells which has been so generally described in the lesions of glanders. Especially in the foci in the nasal mucosa, but also in glanders lesions elsewhere, there is said to be an extensive new formation of epithelioid cells and even of giant-cells which gives the lesions something of the character of a tubercle. As Duval points out, this occurs only with bacilli of relatively low virulence and in the more chronic cases. Otherwise the necrosis of the tissue is quickly produced and the surrounding granulation tissue is less characteristic.

LITERATURE

Kitt, Th.: Path. Anat. d. Hausthiere, 1901, ii, 138, etc.

MacCallum: Ziegler's Beiträge, 1902, xxxi, 440.

Robins, G. D.: Studies from the Royal Victoria Hosp., Montreal, 1906, ii, No. 1.

Wright, J. H.: Jour. Exp. Med., 1896, i, 577.

ANTHRAX

A disease which affects cows, sheep, and other herbivorous animals is caused by infection with the well-known *Bacillus anthracis*, and is transmitted to man through contact with the sick animals, or through handling their infected hides. In certain industries which have to do with hides (tanning, etc.) or with hair or wool in the making of mattresses, paper, etc., infection may occur, sometimes almost in epidemic form (wool-sorter's disease, Hadernkrankheit).

Cattle are infected especially in pastures which are subject to inundation, but a field once infected may remain so for a long time, and the infection be added to by the excretions of the cattle themselves, or by soiling of the ground with the remains of cattle which have died or been slaughtered and buried there. Naturally, chances for infection occur in the stalls where such cattle are kept.

In these animals the disease may be very acute, killing within a few hours, or there may develop definite carbuncles or more diffuse oedema in the skin or in the intestinal tract. At autopsy there is found a general septicæmia—the blood-vessels are full of the bacilli, and the internal lesions in general are ecchymoses, acute splenic tumor, cloudy swelling of liver and kidneys, etc., such as might be found in other acute infections.

In man the portal of entry may be through the skin, the digestive tract, or the lungs. In the case of the skin some slight abrasion is usually the point of entrance, although it has been shown experimentally that anthrax bacilli rubbed on the intact skin can pass through the hair-follicles. During the war there were several cases in which the infection was traced to the use of shaving brushes made of hair from infected animals. A small painful red nodule appears, resembling a flea-bite, and

rapidly enlarges and shows a greenish, necrotic centre, induration and reddening of the surrounding tissue, with blisters filled with yellowish or bluish fluid. This phlegmonous infiltration of the skin and subcutaneous tissue spreads quickly, and the central part dries up into a leather-like crust under which the tissue is necrotic and loaded with anthrax bacilli. Such a carbuncle is at least evidence of a certain resistance, although from it the bacilli may spread in quantities into the blood. There is another type in which, instead of a localized carbuncle, a wide-spread œdema of the skin and underlying tissue appears, with myriads of bacilli. This indicates a poorer ability to resist, and passes on to a more surely fatal outcome. In the more resistant cases the leucocytosis is high and phagocytosis is active, but in some the bacilli surround themselves



Fig. 303.—Anthrax meningitis.

with thick capsules, and are then not readily taken up by the leucocytes. It is thought that the formation of such capsules is an indication that the bacilli are gaining the upper hand in the struggle, and the prognosis is correspondingly bad. The neighboring lymph-glands become swollen and haemorrhagic, and thence the infection becomes generalized.

In the persons who work with hair, hides, and wool, inhalation of the dust which bears the anthrax spores produces a singularly fatal form of the disease, which is primarily a lobular or lobar pneumonia, distinguishable only by the recognition of the bacilli from other types of pneumonia. Eppinger has described many cases in which he found lesions chiefly in the thoracic viscera; the pleural and pericardial surfaces were covered with a fibrinopurulent or hemorrhagic exudate, and the lungs were partly consolidated. A lobular or confluent hepatization of the lungs with exu-

date of a soft or hæmorrhagic character was found, and microscopically the alveoli, as well as the lymphatics and tissue crevices, were loaded with bacilli. Neighboring lymph-glands were greatly enlarged and hæmorrhagic, and elsewhere there were the changes of a general septicæmia. Risel described in this connection great hæmorrhagic infiltration of the mediastinal tissues, as well as of the bronchial lymph-glands. In persons who have swallowed infected meat or milk there arise intestinal carbuncles, just as in cattle. These are usually single, but may be multiple, and occur most commonly in the jejunum. The lesion seems to begin in the depths of the mucosa, or in the submucosa, and appears as a red, pea-sized to plum-sized swelling, which is made up of oedematous tissue loaded with bacilli and leucocytes. The whole adjacent mucosa becomes infiltrated, and the carbuncle itself ulcerates deeply. The mesenteric glands swell and are hæmorrhagic.

In all these cases there are evidences of the most intense acute general infection. Probably in no other disease do such quantities of bacteria appear in the circulating blood. So extensively do they fill the capillaries that it has even been suggested that in this disease the symptoms may be due to that obstruction. The bacilli can be recognized by staining a single drop of the circulating blood. The spleen becomes greatly swollen and soft and turgid with dark blood. Indeed, it is from this dark color and incoagulability of the blood, which give the spleen such a peculiar appearance, that the disease derives its various names (Milzbrand, charbon, anthrax). Cloudy swelling of the liver and kidneys is constant, but there may also be necrosis and disintegration of the cells in these organs.

Hæmorrhagic meningitis appears to be not uncommon, and in one of Risel's cases it formed the most striking feature. There were in the nasal mucosa ulcerated nodules extending into the submucosa, and from these a hæmorrhagic cellular exudate rich in bacilli could be traced along the lymphatic sheaths of the olfactory nerves to the brain.

Figure 303 illustrates the meningeal lesions from a recent case which we studied.

LITERATURE

- Eppinger: Die Hadernkrankheit, Jena, 1894.
Herzog: Ziegler's Beiträge, 1915, ix, 513.
Koch, W.: Deutsche Chirurgie, 1881, Lief 9.
Koranyi: Nothnagel's Handb., 1897, Bd. v, Th. v, Abt. i.
Risel: Zeit. f. Hygiene, 1903, xlvi, 381.
Salmon and Smith: United States Department of Agriculture, Bureau Animal Industry, Circular 71, 1094.

UNDULANT FEVER—BRUCELLOSIS

This disease, long known to be prevalent in Malta and therefore known as Malta fever, was studied by Bruce who discovered the bacterial cause in 1887. This organism, since named *Brucella melitensis*, is contained in the goat's milk so generally consumed there. It was found that goats are not the only animals that may be infected and later Bang described an organism derived from cases of infectious abortion in cattle. This organism which, as Theobald Smith has shown, may occur also in

hogs, is now called *Brucella abortus*. It seems to be widely distributed in America and other countries, and many cases of undulant fever differing slightly from that in Malta have been recognized. They occur chiefly in persons who come into close contact with cattle or hogs, or who drink unboiled milk from infected animals.

There are now recognized *Brucella melitensis*, *abortus* and *suis*, so closely related, however, as to be distinguished with difficulty. The destructive diseases produced in goats, cattle, and hogs respectively by these organisms are of great economic importance, not only in this country but nearly everywhere in the world. Sheep, fowls and other animals seem also susceptible. Infection is transmitted to man in a far greater number of cases than formerly suspected, not only in those who drink unboiled, infected milk but especially in veterinarians and farmers and butchers who come directly into contact with the infected animals. Up to the present so few fatal cases have occurred in human beings that the nature of the lesions produced in their tissues is not well known. Wohlwill describes nodular focal accumulations of cells of the "reticuloendothelial system" with many eosinophiles which he regards as infectious granulomata. These occur in many organs throughout the body and perhaps especially in spleen and lymph nodes and to a less extent in the liver. Cases of meningeal infection have been reported and other cases in which bones were involved. The evidence of actual production of abortion in women by this infection requires confirmation. In cattle the infection of the endometrium and placental areas is well known. The disease is recognized by culture of the organisms from the circulating blood in which they sometimes remain after symptoms have disappeared, also by allergic reactions and by complement deviation.

The literature on this subject is colossal but not very satisfying. There are many reviews of which those of Sharp and of Giltner are among the best and the recent book of Huddleson gives an excellent summary of the situation, especially from the veterinary and laboratory side.

LITERATURE

- Bang: Jour. Comp. Path. and Therap., 1897, x, 125.
Bruce: Practitioner, 1887, xxxix, 161; 1888, xl, 241.
Evans, A. C.: Hygienic Laboratory Bulletin 143, 1925.
Giltner: Brucellosis, Memoir Michigan State College, 1934.
Huddleson: Brucella infections. N. Y. Commonwealth Fund, 1934.
Laun and Heide: Ztschr. f. Hyg. u. Infektionskr., 1934, cxvi, 315.
Sharp: Arch. Path., 1934, xviii, 72.
Smith, Theobald: Medicine, 1929, viii, 193.
Wohlwill: Virch. Arch., 1932, cclxxxvi, 141.

TULARÆMIA

Tularæmia, named by Francis for Tulare County in California, is a disease primarily of rabbits occurring in epizootics, and transmitted to man and probably to the rabbits, too, by the bite of the deer-fly, *Chrysops discalis*, or of such ticks as *Dermacentor andersoni*, and others. Bed-bugs can transmit it but for man infection is probably most often due to direct introduction of the bacilli through cuts or scratches while



Fig. 304.—Tularæmia. Areas of consolidation in the lung with necrosis.



Fig. 305.—Tularæmia. Multiple necroses in the liver.

skinning rabbits. The disease is contracted very easily and in one laboratory every worker was infected.

It develops rapidly with fever, extreme illness, swelling of the lymph nodes, beginning with those draining the necrotizing ulcer which forms

at the point of entrance of the organism. Recovery with a certain immunity is usual but about 3 per cent of the cases are fatal.

The infective agent is a small Gram-negative non-motile aërobic organism which can be cultivated on media containing coagulated egg-

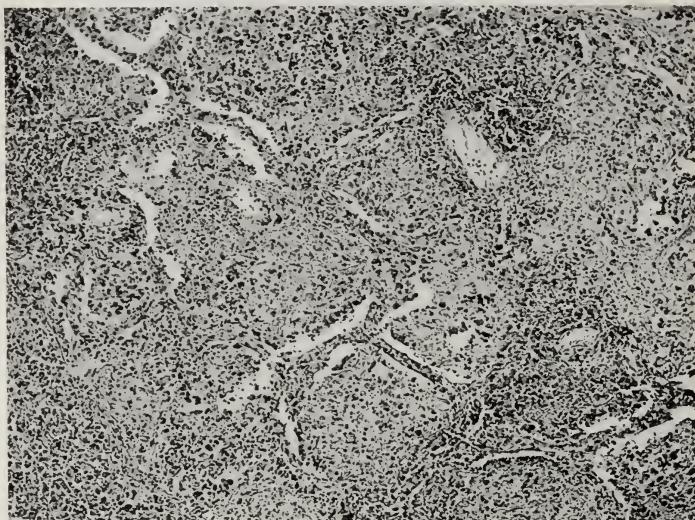


Fig. 306.—Tularæmia. Pneumonic consolidation of the lung with necrosis.

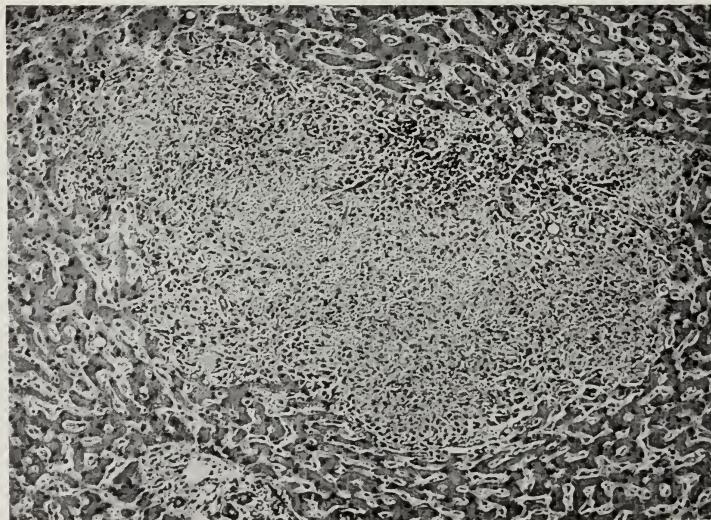


Fig. 306A.—Tularæmia. Focal necrosis in the liver.

yolk or on blood dextrose agar, better with a piece of fresh tissue. It appears in bacillary, coccoid or bipolar forms and is stained easily in smears but has rarely been demonstrated in stained sections of tissue.

The lesions are found especially in the swollen lymph nodes, in the

liver, spleen and lungs and are essentially similar wherever they occur. Beginning apparently with necrosis and the accumulation of phagocytic cells, they soon show a marginal arrangement of epithelioid cells and rarely any giant cells.

In four cases which we have studied recently, the liver was found thickly studded with such nodules as shown in Fig. 305. Most impressive, however, is the confluent lobular pneumonia with an appearance almost like that of caseous tuberculous pneumonia, in three of the four cases (Fig. 304). The character of the lesions is shown in Figs. 306, 306A.

The disease can be recognized by agglutination tests after it has progressed for a week or more. Foshay has recommended the use of immunized goat serum.

LITERATURE

- Francis, E.: Public Health Bulletin, 1922, 130; Jour. Amer. Med. Assoc., 1922, lxxviii, 1015. Arch. Path., 1927, iii, 577; Medicine, 1928, vii, 411.
Goodpasture and House: Amer. Jour. Path., 1928, iv, 213.
Gundry and Warner: Ann. Int. Med., 1934, vii, 837.
Kavanaugh: Arch. Int. Med., 1935, lv, 61.
McCoy and Chapin: Public Health Bulletin, 1912, liii.
Permar and MacLachlan: Ann. Int. Med., 1931, v, 687.
Simpson: Arch. Path., 1928, vi, 553; Jour. Lab. and Clin. Med., 1930, xv, 311;
Illinois Med. Jour., 1931, lx, 207.

CHAPTER XXXI

TYPES OF INJURY.—BACTERIAL DISEASE (Continued)

Typhoid infection: General relations. Intestinal, lymphatic, splenic, and other lesions. Necroses in various organs. Affections of circulatory, respiratory, and nervous system.

Paratyphoid infection: Relation to typhoid and enteritis infection. Acute gastro-enteritis, accessory lesions.

Dysentery: Various organisms concerned. Intestinal lesions.

Pyocyaneus infection. Localization of necroses.

TYPHOID INFECTIONS

INFECTION with the *Bacillus typhosus* ordinarily produces characteristic lesions only in man, although Greenbaum has succeeded experimentally in setting up similar effects in the organs of chimpanzees by inoculation. In the smaller laboratory animals a general septicæmia may follow infection, but there are none of the destructive anatomical changes observed in man.

In man, although attention has long been concentrated upon the more local manifestations, there occurs a general septicæmia in which the bacilli are readily demonstrated in the blood in the earlier days of the disease, less readily or not at all in the later stages. While in most cases the local alterations of the intestines are most striking, they may be completely absent, so that it seems that the less conspicuous changes due to the general distribution of the bacilli are more constant and characteristic features.

The bacilli gain entrance by way of the digestive tract, being introduced with drinking-water, vegetables grown on infected ground or watered with infected water, and infected milk and other food into which the bacilli may have been introduced in the process of preparation. Even ice and oysters seem to have been the source of infection in epidemics. Flies may carry the bacilli from exposed fæces, etc., to food. Since persons who have recovered from typhoid fever may harbor the bacteria in bile, urine, and fæces for many years, they become a menace to others, and especially when they act as cooks the danger of their transferring the bacilli to food is very great. Thus a recent epidemic in the Sloan Hospital was traced to a cook who was a typhoid-bacillus carrier. Another, reported in the Journal of the American Medical Association in 1915, was traced in the same way to the cook who prepared a large panful of spaghetti, even though it was cooked in another place and not again touched by her. It was shown that in the spaghetti, which had stood overnight, there had been a great growth of bacilli, which in the cooking were scarcely warmed in the centre of the mass.

Typhoid fever is essentially a disease of unsanitary conditions of life, and disappears in proportion as the food and water supplies are kept clean. But the introduction and perfection of the method of vaccination

against typhoid infection by Wright and Russell has gone far toward obliterating the disease altogether. When the troops were called together in the camps during the war, some such plague of typhoid fever as occurred at the time of the Spanish War might have been expected. But vaccination of every recruit was compulsory, and there was no typhoid. It is one of the few great triumphs of preventive medicine, but it is not all powerful, for overwhelming doses of bacilli will still produce the disease. Although the wards of the hospital used to be filled with these



Fig. 307.—Typhoid fever with swelling and beginning ulceration of Peyer's patches.

cases, they are rare now, and the only autopsy we have seen in the last year was in the case of a cleaner in a laboratory who must have swallowed a culture.

Infection with the *Bacillus typhosus* produces in man a protracted febrile disease, which begins usually one or two weeks after infection and lasts for five or six weeks or more. There are localized changes in the intestines, especially in the lymphoid structures, in the abdominal lymph-glands, the spleen, and bone-marrow. There is a general cloudy

swelling of the organs, with wide-spread focal necroses, and other less constant lesions.

Intestinal Lesions.—In the first week of the disease the lymphoid nodules of the intestines, including, of course, the Peyer's patches, become swollen and stand up above the surrounding mucosa (Fig. 307). This may be caused partly by hyperæmia, but is chiefly due to an increase in the numbers of lymphoid and other cells. The change is most evident in those Peyer's patches and solitary nodules in the lower part of the ileum, becoming less marked, and finally fading away toward the upper part of the intestine. In the colon the degree of swelling varies greatly—sometimes it is imperceptible; in other cases it is extreme and overshadows the slighter changes in the ileum. On gross inspection it appears that this swelling is sharply limited to the lymphoid structures, which thus become very conspicuous and prominent, but it may be concluded, both from the microscopical examination in this stage and from the later ulceration, that the alteration in the tissue extends beyond their limits. There is a catarrhal inflammation of the rest of the mucosa, which may be evident as a moderate hyperæmia, but is often inconspicuous.

Later, in the second week in most cases, the superficial parts of the swollen Peyer's patches and nodules lose their reddish-gray color and the velvety smoothness of their surface, and in smaller or larger areas become opaque and dry looking, and in these areas become stained a brownish-green from the intestinal contents. This is the formation of the slough, which is an expression of the partial necrosis of the swollen patch. Sometimes the change progresses rapidly and goes deep, involving all but the margin of the patch. In the nodules the necrotic slough appears as a little, rough, greenish plug embedded in the top, and surrounded by the hyperæmic margin. From the outside the Peyer's patches can be recognized, as a rule, by their darker color and by the injection of the subserous blood-vessels, but, as a rule, the solitary nodules scarcely show through at this stage.

Not all the swollen Peyer's patches or solitary nodules advance to this stage. Indeed, in every case at autopsy it is usual to find some, perhaps even the majority, which have proceeded no further than the swelling, as far as the unaided eye can see. It is quite common to find the advanced change only in those situated rather low in the intestine, near the ileocecal valve, although it is quite true that there are other cases in which all the lymphoid areas throughout the greater part of the ileum have run the whole gamut of changes. In persons who recover and in whom these swollen lymphoid structures which have not progressed to necrosis return to normal, there must be a process of resolution somewhat analogous to that in pneumonia. Still later other changes occur in those Peyer's patches which present necrotic areas. The greenish mass retracts a little from the edge and loosens all around its margin. The crevice goes deeper toward the middle (Fig. 308), and soon the whole slough is dislodged and falls into the lumen of the intestines, leaving an excavation or ulcer of corresponding depth (Fig. 309). If the slough is completely removed, it leaves a clean ulcer, the bottom of which is

usually formed by the muscular layers of the wall, which show plainly the parallel arrangement of their fibres. Sometimes the ulcer is more shallow, and then its floor is part of the infiltrated submucosa—at other times it is deeper and may even extend quite through to the subserous tissue, in which case complete perforation is likely to occur. One may find such ulcers on the point of perforation with only a thin, easily torn film of the necrotic wall remaining. From the outside this appears as an opaque, greenish-gray patch surrounded by a dark haemorrhagic zone.

It has already been said that the ulcer need not excavate the whole of the swollen patch. One frequently finds several small and rather deep



Fig. 308.



Fig. 309.

Fig. 308.—Typhoid fever. Swollen Peyer's patches with beginning separation of the slough.

Fig. 309.—Typhoid ulcers after the discharge of most of the necrotic tissue.

ulcers in one Peyer's patch, separated from one another by partitions of still living tissue. On the other hand, the ulceration may extend quite beyond the margin of the lymphoid tissue, so as to correspond no longer with the original form, and in the neighborhood of the ileocecal valve it is common to find neighboring ulcers confluent to such a degree that only small islands of mucosa are left. Higher up it is usual to find the ulcers more limited to the outlines of the Peyer's patches and solitary nodules. Quite similar processes take place in the colon and in the vermi-

form appendix, and it is not uncommon to have a perforation in the base of an ulcer in the latter situation. Since these perforations occur rapidly without time for any adhesions to form between the intestinal loop and other tissues, a general peritonitis is the common result. Naturally, in this respect perforations in the free moving ileum are more serious and likely to be fatal than those in the appendix, where localizing agencies are more available.

In many cases there is bleeding from the ulcerated intestinal wall, the blood escaping with the stools sometimes in such quantities that the patient dies from its loss. It is rare that one can find any vessel which can be shown to have been the source of the haemorrhage.

After the ulcer is cleaned of its slough, healing begins by the formation of a layer of granulation tissue in the base, soon followed by the growth of a single smooth layer of epithelium across its surface. The depression into which this epithelium must grow is before long made up to its original level by the new formation of lymphoid tissue, and it becomes impossible to tell where the ulcer had been. No great scar formation occurs, and there seems never to be a stricture of the intestine due to the healing of a typhoid ulcer.

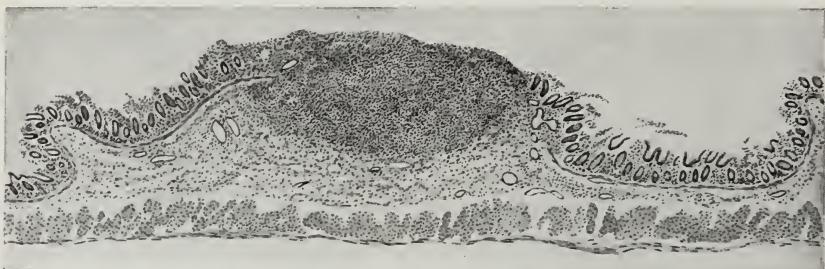


Fig. 310.—Typhoid fever. Beginning swelling of a lymph-nodule in small intestine.

The nature of these lesions is rather different from any of the effects of bacterial invasion met with so far, and is to be understood only in the light of the general effect of the typhoid bacillus upon the body. The bacteria hitherto studied have been found to produce a reaction on the part of the bone-marrow, which liberates into the circulating blood great numbers of polymorphonuclear leucocytes. Such a leucocytosis fitted well with the mechanism of ordinary inflammation, and even though we recognized the presence of many mononuclear wandering cells in all stages, and especially in the more chronic forms of inflammation, the polymorphonuclear neutrophiles dominated the scene in fresh inflammations. In typhoid fever there is no such leucocytosis—the total number of leucocytes per cubic millimetre is rather decreased, and the lymphocytes become relatively numerous. Even in the presence of secondary infections, which in normal persons produce a leucocytosis, the bone-marrow seems incapable of responding actively, and there is only a halting leucocytosis.

In the typhoid lesions the bacilli are found—indeed, they are carried everywhere in the circulating blood, but their presence rather repels the

polymorphonuclears. Nor is it possible, as in the case of the staphylococcus, to demonstrate the bacilli as the central point about which the lesion is concentrated. Instead, one finds clumps of bacilli in the tissues without any striking reaction about them, and elsewhere foci of coagulative necrosis, with few or no bacilli.

In the earliest stages of medullary swelling (Fig. 310) the Peyer's patches and solitary nodules show an increase of the lymphoid cells, which become scattered into the adjacent mucosa and into the submucosa underneath. But the lymphocytes, many of which seem to have emigrated from the blood-vessels, are soon rendered less conspicuous, and separated by the appearance of great numbers of large pale cells with rather pale vesicular nuclei. It is about these cells, which occur in all typhoid lesions, that violent discussion has raged, especially with regard to their origin. They are most actively phagocytic, and engulf the injured lymphocytes until soon the latter are found only in groups, while the large cells, each of which may contain two or three bodies of lymphocytes, occupy most of the field.

Hoffmann and Billroth described these cells and noted their phagocytic capacity. Mallory decides that, since they behave like endothelial cells, they are endothelial cells, and without further ado calls them endothelial cells throughout. Marchand, more cautious, thinks that they may be partly derived from the reticulum cells, partly from the endothelium of the lymphatics. Saltykow thinks that he can trace them from the endothelial cells of the lymph sinuses, but finds them mixed in the sinuses with lymphoid cells of various types. It is a matter most difficult to decide by the fallible methods of tracing transitions, and especially difficult in this case, since it is so rare a piece of fortune to be able to study the typhoid lesions in their earliest stages.

The cells seem to be mobile not only because they are phagocytic, but because they are found in abundance far in the tissue of the submucosa, away from the reticulum of the lymphoid tissue and from the lymphatic channels. They are not peculiar to typhoid fever, but occur in identical form in tuberculosis and other affections.

It seems, indeed, that they are indistinguishable from other large mononuclear wandering cells, and that the conception of the lesions in typhoid fever becomes far simpler if we look upon them as a form of reaction in which the wandering cells which come into the neighborhood of the bacilli are the various types of wandering mononuclear cells instead of polynuclear leucocytes. That some endothelial cells can act as phagocytes is unquestionable, but that the whole reaction to the presence of the typhoid bacilli should be ascribed to endothelial cells makes typhoid fever a disease without an analogue. While it is usually stated that in the spleen the endothelial cells of the venous sinuses are in typhoid fever, as in other conditions, actively engaged in phagocytosis, it is not so clear in other situations, such as the substance of the lymphoid tissue or the submucosa of the intestine, that the phagocytic cells are derived from the endothelium. Confusion arises perhaps from the persistence of the idea that all crevices in the tissues are lined, if only incompletely, with endothelial cells. It is my belief, on the contrary, that endothelial cells are not thus scattered everywhere, but that they form the specialized lining of closed blood-channels and lymphatic channels. The lymph-sinuses of the lymph-gland in connection with the lymphatic trunk are lined with continuous endothelium, but these cells are not found everywhere among the elements of the lymphoid tissue. This specific position, as the lining tissue of channels, is even more clearly seen in such tissue as the submucosa, where it is not confused by the great mass of lymphoid cells. How such lining cells could disperse themselves in such quantities and wander everywhere through the tissue without completely disorganizing the blood- and lymph-channels is not clear. This is, after all, the same question which confronts us

everywhere as to the origin of the mononuclear phagocytic wandering cells, although it is generally believed that in the embryo they arise from the vascular endothelium at least in part and later wander in the tissues. Whether this origin is everywhere



Fig. 311.—Edge of swollen patch in early stage of typhoid fever. The large phagocytic cells are accumulated in the submucosa, and there are two lymphatic channels distended with them. In the detail some of these phagocytes are shown with their content of injured lymphocytes.

possible in adult life remains a problem. Instead, therefore, of calling them endothelial cells, I prefer to speak of the large, phagocytic cells briefly as macrophages, and to regard them as members of the familiar, if much misunderstood, group of



Fig. 312.—Typhoid fever. Margin of swollen and slightly ulcerated Peyer's patch.



Fig. 313.—Typhoid fever. Later stage, with superficial slough and beginning ulceration.

mononuclear wandering cells which are present in some stage of their development and wandering career everywhere through the tissues, and are especially ready to swallow up injured cells and fragments of cellular débris.

The accumulation of the wandering cells, and especially of the pale macrophages, goes far to obliterate the architecture of the Peyer's patch and convert it into a continuous mass of cells. On the surface various bacteria are found. Some of these may invade the interior, but this is especially true of the typhoid bacilli, which are found in clumps in the

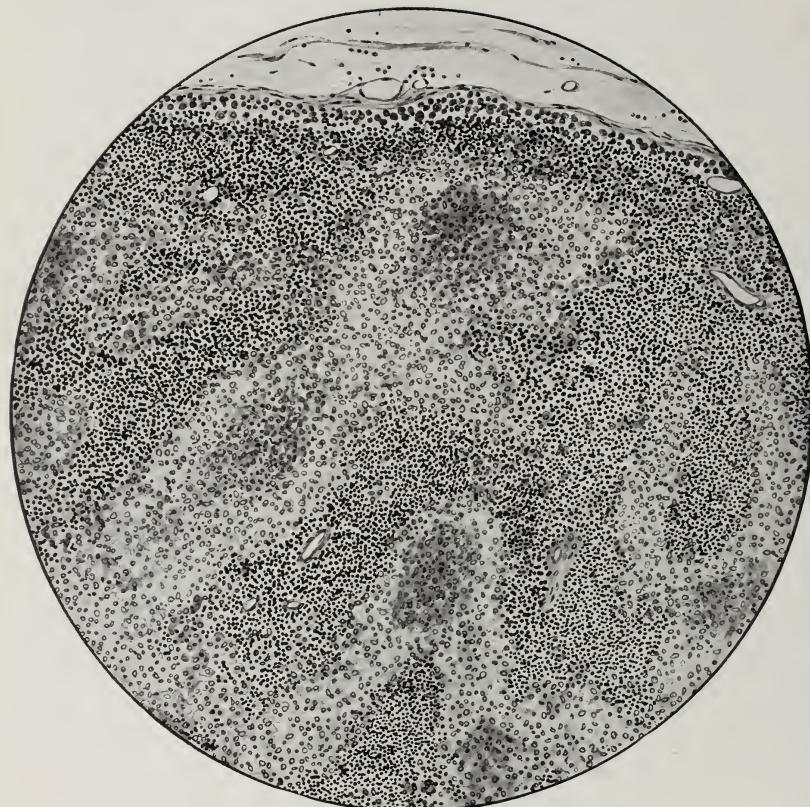


Fig. 314.—Mesenteric lymph-node in typhoid fever. The sinuses are filled with large mononuclear cells, among which are necrotic clumps.

tissue. Foci of coagulative necrosis appear irregularly, and not in any especial relation with the bacilli, and becoming confluent, form the slough (Fig. 313). There is no leucocytic reaction to the presence of these patches of dead tissue—a zone of fragmented nuclei may mark them out. Some authors have thought them due to the diffusion of a poison produced by the bacilli; others ascribe them to anaemia produced (Orth) by compression of the blood-vessels or (Mallory) by thrombosis of the small arterioles and venules. Mallory describes many such thrombosed vessels, the thrombus being caused sometimes by the clumping of in-

jured endothelial cells within the vessel, at other times by the lifting-up of the lining endothelium by cells and fibrin accumulated beneath it.

At this stage, when the necrosis becomes confluent, nearly all the cells of the compact mass, even at a distance from the necrosis, show signs of degeneration and disintegration. Doubtless many macrophages burdened with lymphocytes and other materials fall into fragments, which are swallowed in their turn by other phagocytic cells.

The lymphatic channels are often packed with cells, which they transport to the sinuses of the nearest lymph-gland. The stroma of the neigh-



Fig. 315.—Acute splenic tumor in typhoid fever. The splenic pulp shows great accumulations of blood with phagocytic cells containing red corpuscles.

boring mucosa presents changes almost exactly like those in the lymphoid nodules and in the submucosa, through the muscle, and in the subserous tissue one finds the fixed tissue elements spread apart by the abundant wandering cells.

Lymphatic Glands.—The mesenteric lymph-glands become greatly swollen, soft, and often haemorrhagic. The retroperitoneal glands take some slight part in this, but the glands most affected are those which drain the most involved part of the intestine (Fig. 314). Bacilli are scattered in their sinuses and tissues. The lymph-cords show exactly

the same changes as are seen in the Peyer patches. The sinuses are enormously widened and packed with cells, which are mostly macrophages, although there are many lymphocytes. Probably most of these cells are swept into this situation from the intestinal lesions, but some may appear in the gland itself. Necroses quite like those described are found beginning in the mass of cells which fills the sinus, and extending thence to the lymph-cords. Sometimes nearly the whole gland becomes necrotic. From the glands great quantities of the large cells and others can be swept on into the thoracic duct, and thus into the subclavian vein. In one instance (Verh. Dtsch. Path. Gesellsch., 1903, ix) I found them transported in this way in such quantities as to plug many branches of the pulmonary artery.

The Spleen.—The acute splenic tumor, which is very constant in typhoid fever, differs from that found in other infections in the extreme abundance of red corpuscles, both loose in the splenic pulp and engulfed in numbers by large phagocytic cells (Fig. 315). The presence of these "red corpuscle-carrying cells" is, of course, the result of the profuse scattering of red corpuscles out of the venules into the pulp. Most of them correspond to the macrophages seen elsewhere. There are relatively few nucleated cells in such a pulp, and if the haemoglobin is washed out by fixation of the piece of spleen in alcohol, the tissue looks rarefied under the microscope. Necroses occur in the splenic pulp, exactly as they do in the lymph-glands and Peyer's patches. The result of these changes is the great enlargement of the spleen, which sometimes weighs 900 grams. The organ becomes extremely soft, and may rupture during life, with alarming or fatal haemorrhage. At autopsy it is usually like a semifluid mass of deep-red color, and on section the relatively unchanged Malpighian bodies are scarcely to be seen through the overflowing splenic pulp. In other cases the splenic pulp may contain many more macrophages than are shown in the drawing.

Blood and Bone-marrow.—The blood contains bacilli through most of the course of the disease. The leucocytes are low, with usually a relative increase of the mononuclear cells. Platelets are decreased in number. In the course of the disease, especially in its later stages, there may arise a severe anaemia. The bone-marrow responds to the infection by the production of abundant lymphoid cells and others resembling plasma cells, but the formation of granulated myelocytes, the forerunners of the neutrophile leucocytes, appears to be in abeyance. Everywhere through the marrow there are found the macrophages, which show here, as in the Peyer's patches, a great avidity for the injured bodies of other cells. Necroses occur, just as they do in the spleen and the lymphoid apparatus (Longcope).

Liver and Gall-bladder.—The liver is always swollen, and on section appears dull, opaque, and inelastic. It forms a typical example of cloudy swelling, and microscopically the cells present the changes characteristic of that condition. Occasionally in the fresh-cut surface, or through the capsule, one can see minute, opaque, yellowish spots, which sometimes reach a diameter of 1 to 2 mm. These are focal necroses, which are constantly present in the liver in this disease, although they are usually

so small as to be scarcely made out with certainty with the naked eye. Mallory describes two types—one produced in the lymphoid tissue, which occurs in the so-called portal spaces, and which shows changes identical with those in the Peyer's patches; the other occurring anywhere within the lobule, and involving the destruction of a group of liver-cells. The first type must be uncommon or very inconspicuous. The second is the type found in every typhoid liver. The foci consist of compact masses of distorted and fragmented cells, bound together with fibrin, and pretty sharply marked out from the surrounding tissue. Mallory regards these foci as anaemic areas caused by the plugging of the capillaries of the liver by macrophages which have been swept in with the portal blood. These large cells lodging in the capillaries, soon become surrounded by thrombi,



Fig. 316.—Typhoid fever. Beginning focal necrosis in liver; accumulation of wandering cells with little evident injury of liver-cells.

which continue the occlusion. Fränkel and others have thought the necroses due rather to the direct action of the toxin upon the liver-cells, with secondary invasion of wandering cells.

It has always been difficult to believe that the occlusion of the capillaries, even if it occur on all sides of such a minute mass of tissue, should cause the death of the liver-cells in these tiny areas, since they might receive enough nutrition from the adjacent capillaries. In a series of dogs we have injected corn-starch in suspension so as to plug a great many capillaries, but without producing necroses, except perhaps in one case, where the capillaries became distended into great spaces filled with the granules and the liver-cells were compressed and displaced. Even then it was scarcely possible to demonstrate actual necrosis of the cells.

Something analogous to this seems to occur in the typhoid liver, in which, in the necrotic and coagulated patches, one does not find many actual necrotic liver-cells. We have had an opportunity to study the beginning of the lesions in the liver of a man who had been ill only a few days, and in whom the autopsy was performed one hour after death, and it becomes perfectly clear that these foci are not primarily areas of necrosis of the liver-cells at all, but accumulations of the large mono-nuclear cells swept in by the portal stream, which distend the capillaries to a huge size and push aside the liver-cells (Fig. 316). Even in the middle of such a mass, that is, between two such distended capillaries, the liver-cells are found to be alive. It is possible that they may be



Fig. 317.—Typhoid fever. Foci in liver in which the areas are occupied by phagocytic cells, the liver-cells having been displaced or destroyed.

so included as to be involved in the necrosis, but most of them are pushed aside, and the necrosis, when it appears, is essentially the degeneration and disintegration of a mass of macrophages which has packed itself into the widened capillaries at a point in the liver tissue from which the liver-cells have been for the most part dislodged, and has there become matted together by fibrin. When the areas become larger by the constant accumulation of the cells floating in the blood, it is no longer possible to determine how they were formed, but from the early stages one may convince oneself that the coagulative necrosis is primarily an affair of the wandering cells, and that the liver-cells are only accidentally involved in the mass.

Rarely large necroses or abscess-like foci occur in the liver.

The gall-bladder may become infected with the bacilli, probably by way of the bile-duets, either from the intestines or from the liver, although it is perfectly possible that they might arrive there by the blood-stream. They may cause no trouble, but may remain and multiply there for many years. Such persons are among the typhoid carriers mentioned above. Occasionally there are attacks of pain in the region of the gall-bladder during the fever, but more frequent are the cases of acute or chronic cholecystitis occurring some time after recovery. In Hunner's case eighteen years had elapsed since the attack of typhoid fever. The exudate is sometimes purulent, but more commonly mucoid, and is usually associated with gall-stones. Cushing was able to cultivate the *Bacillus typhosus* from the centres of the gall-stones, as well as from the bile, and thought that agglutinated bacilli might constitute the nucleus upon which gall-stones could form. The evidence in this question has been discussed elsewhere (Chapter XX).

Kidneys and Bladder.—The kidneys show a cloudy swelling of the cortex comparable to that of the liver. œdema with great pallor is sometimes observed. Actual acute nephritis with exudative changes is, in my experience, rare. The bacilli pass through the kidney evidently through lesions of some sort, and appear in the urine. Although the bladder and ureters are not commonly affected, catarrhal or diphtheritic cystitis may occur. The urine continues to show the presence of bacilli for a long time in some cases.

Respiratory Organs.—Lobar and lobular pneumonia may accompany typhoid fever, the former rarely, the latter as a common terminal affection. Lobar pneumonia caused by the *Bacillus typhosus* is of a peculiarly haemorrhagic character. Usually the pneumococcus is the causative agent when this complication occurs, and there may be a combined septicaemia with both organisms (Robinson). In the bronchopneumonia the typhoid bacillus may cause the lesions, and appear in the sputum, but probably in most cases other organisms are concerned.

In the pharynx and larynx there is sometimes an extensive diphtheritic and haemorrhagic inflammation in a late stage of the disease.

Circulatory Apparatus.—The heart muscle is soft and flabby and opaque, and may contain a little fat. Endocarditis is uncommon, but has been described, the vegetations containing the bacilli. There are instances in which the peripheral arteries, especially the arteries of the brain, have been occluded by thrombi. In other cases thrombosis of brachial or femoral arteries has led to gangrene. Thayer has examined the arteries in many cases after typhoid fever, and finds, in rather a high percentage, evidences of beginning arteriosclerosis. This is, however, not peculiar to this infection.

Thrombosis of the veins is far more common than that of the arteries. It occurs usually in the left femoral and saphenous veins, and causes the extremely painful swelling of the leg which has long been known as "milk-leg," or *phlegmasia alba dolens*. With the organization of the clot and its recanalization, together with the development of collateral chan-

nels, the œdema disappears and the leg can again be used. Other veins may also be affected.

Muscles.—A wide-spread hyaline degeneration of the substance of the muscle-fibres, first described by Zenker, is often found, especially in the abdominal muscles and in the muscles of the thigh. (See Fig. 46.) The muscle-fibres lose their striations, and are divided into irregular, formless clumps within the sarcolemma. Rupture of such injured muscles gives rise to gross haemorrhages, and if one observes a great haemorrhage within the sheath of the rectus abdominis, suspicion is at once directed to a typhoid infection, although the condition is not peculiar to typhoid.

Bones and Joints.—After convalescence, or even many years later, there sometimes arise painful, abscess-like swellings over the ribs or the tibiae, or, indeed, over any bone. Incision allows the escape of a thick, stringy, purulent fluid, and it is found that an abscess cavity extends down through the periosteum or into the bone. The periosteum is greatly thickened and uplifted from the bone, and there may be necrosis and sequestration of part of the bone. Mixed infections occur, but the typhoid bacillus is found and may cause these changes alone. Such infections are very persistent, and unless thoroughly cleaned out, fail to heal. Typhoid arthritis occurs, but is very rare.

Skin.—Prominent among the changes in the skin is the roseola or typhoid rash. Slightly raised, flat, rose-colored spots appear early, and are an evidence of the diffuse septicaemic character of the disease. The bacilli have been cultivated from these rose spots, and Fränkel, in sections, found branched colonies of the bacilli in what he thought were the lymph-vessels of the papillæ. Purpuric spots, diffuse erythema, etc., may also occur. Furunculosis, so common in the later stages, is due to a secondary staphylococcus infection.

Nervous System.—The disease has its name from the stuporous conditions produced by the infection. Nevertheless, actual cerebral changes, recognizable anatomically, are rare. I have described one case of purulent leptomeningitis due to the *Bacillus typhosus* alone, and Cole has collected many others from the literature. The exudate resembles that in the epidemic cerebrospinal form, but is richer still in macrophages which contain the débris of cells. Here it seemed especially clear that these large cells are to be regarded as part of the army of mononuclear wandering phagocytes. Local and multiple neuritis occurs, but is not serious, and quickly disappears in convalescence.

Genital Organs.—Typhoid bacilli have been cultivated from the uterus in cases in which typhoid fever occurred during pregnancy. Lesions of the placenta of haemorrhagic type give one explanation for the transmission of the bacilli to the foetus, but it seems that this may occur without obvious placental changes. Lynch shows that the effect is a foetal septicaemia, and that the child dies *in utero* or soon after birth. Mastitis is a rare sequel of typhoid fever. McCrae has recorded three cases.

In rare cases orchitis follows convalescence and may lead to indurative atrophy or abscess formation.

Parotitis.—Owing to the prolonged illness and the stuporous condition, the mouths of these patients become foul unless continually cleansed. Parotitis may arise by extension of infection along the duct, or by lodgment of bacilli carried there by the blood. Suppuration may destroy much of the gland and extend into the adjacent tissue or into the neck. In these cases there is commonly a mixed infection.

LITERATURE

Louis, P. Ch. A.: *Fièvre typhoïde*, Paris, 1829.

General.—Brouardel and Thoinot: *La Fièvre Typhoïde*, Paris, 1905.

Curschmann: *Nothnagel, Spec. Path. u. Ther.*, 1902, Bd. iii, Th. 1.

Gay: *Typhoid Fever*, New York, 1918.

Hoffmann: *Veränderungen der Organe beim abdominal Typhus*, Leipzig, 1869.

Mallory: *Jour. Exp. Med.*, 1898, iii, 611.

Osler: *Principles and Practice of Medicine*, New York, Sixth Edition, 1905. "Studies in Typhoid Fever," *Johns Hopkins Hosp. Reports*, 1895, v; 1902, x.

Posselt: *Ergebn. d. allg. Path.*, 1912, xvi, 184.

Typhoid Septicæmia.—Cole: *Johns Hopkins Hosp. Bull.*, 1901, xii, 203.

Lartigau: *New York Med. Jour.*, 1900, lxxi, 944.

Rüdiger: *Trans. Chicago Path. Society*, 1903, v, 187.

Roseola.—E. Fränkel: *Zeit. f. Hygiene*, 1900, xxxiv, 482.

Typhoid Cholecystitis.—Cushing: *Johns Hopkins Hosp. Bull.*, 1898, ix, 91, 257.

Hunner: *Ibid.*, 1899, x, 163.

Placental Transmission.—Lynch: *Johns Hopkins Hosp. Reports*, x, 283.

Typhoid Meningitis.—Cole and MacCallum: *Johns Hopkins Hosp. Reports*, 1904, xii, 411.

Bone Lesions.—Parsons: *Johns Hopkins Hosp. Reports*, 1895, v, 417.

Miscellaneous.—Longcope: *Centralbl. f. Bakt. u. Paras.*, Abt. i, 1905, xxxvii, Ref. 23.

Mason, A. L.: *Boston Med. and Surg. Jour.*, 1897, cxxxvi, 449, 468.

McCrae: *Johns Hopkins Hosp. Reports*, 1902, xiii, 20.

Robinson: *Bull. Ayer Clinical Labt.*, 1906, iii, 96.

Vaccination.—Russell: *Mil. Surgeon*, 1909, xxiv, 479.

SALMONELLA (PARATYPHOID) INFECTIONS

In discussing the effects of poisons upon the tissues reference was made to the outbreaks of severe gastro-intestinal disturbances produced by the eating of infected or partly decomposed meat, and it was then shown that such epidemics of what seems to be a form of poisoning are really commonly due to infection with some member of that group of bacilli, of which the *Bacillus enteritidis* of Gärtnér is the type. These are somewhat allied to the *Bacillus typhosus*, and it has been more recently recognized that there are at least two types of bacilli which are not only members of this family, but produce at times a disease practically indistinguishable from a mild attack of typhoid fever. These are the paratyphoid bacilli A and B, of which A is an acid producer, B an alkali producer. Of these, the latter occurs far more frequently and is so like the *Bacillus enteritidis* of Gärtnér as to be most easily distinguished by the agglutination reactions. They were first described in America by Gwyn.

The infection occurs by the gastro-intestinal tract, probably from

eating from an animal infected before slaughtering, meat which, upon standing, has become far richer in bacilli, but epidemics with fatal outcome have arisen from the infection of other foods, including milk products and pastry.

Many cases have been studied at autopsy, particularly those occurring during the war, and Suzuki could recognize a group in which intestinal lesions quite like those of typhoid fever were found, as well as another with nodular or nodular ulcerative type of enteritis. Further, there were some with slight catarrhal inflammation of the intestine, but most often the lymphoid structures were notably involved, and histologically these changes were quite like those seen in typhoid fever. The swelling of lymph-nodes and spleen was variable, but they too showed lesions resembling those of typhoid histologically even to the abundant phagocytosis of red corpuscles and the scattered necroses. In the liver necroses occur, and in the gall-bladder the bacteria are found with or without inflammatory lesions of the mucosa. So, too, in the pelvis of the kidney, the bladder, and the seminal vesicles there are lesions associated with the bacilli which seem to persist longest in gall-bladder and seminal vesicles. In general, the paratyphoid bacillus possesses a greater power to produce inflammatory lesions than the typhoid bacillus, and abscesses in lung, spleen, gall-bladder wall, etc., were not uncommon. Sometimes the disease appeared in the form of a septicæmia with a roseola-like rash.

In most cases, however, the course is mild and brief, but some of the complications, especially cystitis and pyelitis, may persist for a long time with discharge of the bacilli.

Erdheim has studied especially the paratyphoid A infections and gives analyses of a large number of cases, but without anatomical studies.

More recently much attention has been given to the study of this whole group of organisms which, including the old hog cholera bacillus of Salmon and Smith, the typhoid bacillus of Eberth, and the paratyphoid bacilli of Gwyn, as well as Gärtner's bacillus, is now spoken of under the name *Salmonella*. A detailed study with classification of the *Salmonella* group is that of Kauffmann.

The *Salmonella cholerae suis*, or hog cholera bacillus, which in the early days we thought to be the cause of hog cholera, not realizing the necessary association with a virus which is now known, is often spoken of as *Bacillus suipestifer*, and human infections with this organism, under whatever name it is known, are not uncommon. Kuttner and Zepp have studied a number of such cases and have found intestinal changes with purpura and occasionally arthritis and osteomyelitis. Gärtner's bacillus has been found in several cases to produce meningitis, sometimes without definite intestinal lesions and in these the portal of entry was obscure. It is impossible here to enter into the serological relations of these organisms or to discuss their toxin production. Boivin, Topley and others were able to extract a toxin from *B. aertrycke* which could be used to immunize against the living bacilli.

LITERATURE

- Erdheim, J.: Virch. Arch., 1916, ccxxii, 87.
 Gwyn: Johns Hopkins Hosp. Bull., 1898, ix, 54.
 Harvey, A. M.: *Salmonella* *suipestifer* infections, Review. In press.
 Kauffmann: Ergebni. d. Hyg., Bakt., Immunitätsforsch., u. Exp. Therap., 1934, xv, 219.
 Kuttner and Zepp: Bull. Johns Hopkins Hosp., 1932, li, 373; Jour. Amer. Med. Assoc., 1933, ci, 269.
 Pick, L.: Med. Klin., 1925, xxi, 1458; Berlin klin. Woch., 1918, Nr. 28.
 Stevenson and Wells: Lancet, 1933, ii, 1084.
 Suzuki, S.: Virch. Arch., 1924, ccl, 685.

DYSENTERY INFECTIONS

The bacilli responsible for the causation of the endemic and epidemic dysentery which prevails so widely in the tropics and in occasional epidemics in temperate zones were recognized by the aid of the agglutination reaction with the patient's serum. Four types, differing in this agglutination and in certain biological characters, are recognized, and known as the Shiga, Flexner, Y type of His and Russel, and the type of Strong. Of these, the Shiga type seems to be most widely disseminated, and produces a distinct toxin. The Flexner type has only a very slight power of toxin production.

Epidemics arise in the rainy season, especially where there are sudden variations of temperature, and in the hot seasons in more temperate zones. The bacilli are disseminated by people who have partially or completely recovered from a previous attack, but still carry and discharge the organism. They are distributed in drinking-water, in food, by direct and indirect contact, by flies, dust, etc. The unsanitary mode of life in many parts of the tropics and in many cities favors their rapid spread.

The disease is chiefly an infection of the colon, although the lower part of the ileum may also be involved. It begins with the hyperæmia of the mucosa and the secretion of abundant slimy, clear, mucoid fluid, which is later streaked with blood. The swollen mucosa shows points and streaks of haemorrhage, and soon there appear chaff-like, opaque flecks on the crests of the folds (Fig. 318). Even at this stage, when these flecks indicate the death of the surface of the mucosa, resolution or healing may take place, but usually the diphtheritic character of the lesion becomes more evident and progresses to ulceration. The more prominent parts of all the folds become covered with a thick, dull layer of exudate, which constitutes a false membrane and is continuous with the densely coagulated dead layer of mucosa (Fig. 319). All around, haemorrhage and an intense inflammatory reaction with oedema appear. With the sloughing off of this layer irregular ulcers are left. These vary in size and depth, and while sometimes quite large sheets of dead and coagulated mucosa and exudate escape with the stools, at other times the ulcers are more localized, but penetrate deeper into the submucosa, the musculature, or even the subserous tissues (Fig. 320). Perforations occur, but are rare. The presence of this process excites the most violent diarrhoea, with tenesmus and the passage of liquid, mucoid,

and blood-tinged stools. So constant is the passage of fluid stools, and so violent the continual straining, that the patient becomes exhausted. Vomiting may begin; the skin is covered with sweat; the voice hoarse and eyes sunken, and the whole condition cholera-like. Such patients may die in collapse. If the attack is not fatal, there may be relapses from time to time, lasting over a long period, and finally the disease settles into a milder chronic process. The ulcers heal by the formation



Fig. 318.—Dysentery. Diphtheritic and haemorrhagic inflammation of the intestine involving the crests of the folds of the mucosa. The pseudomembrane is still adherent, and there is extensive haemorrhage beneath it.

of granulation tissue, over which a smooth layer of epithelium grows without the new formation of glands. Much scar tissue develops in the gut wall in the base of such ulcers, and contracts so as to constrict or kink the intestine. Very narrow strictures may be formed thus. The ulcers are irregular in extent and outline, and are often confluent, leaving islands of mucosa which stand out above the new epithelium as pedunculated polypoid masses. In one case which I saw there were long

bridges of mucosa which had been undermined and which, in some places, having broken away at one end, hung in the intestine like long pendulous polypi.

Even in the acute disease the other organs are not much changed; there is no septicaemia, and therefore there are no cutaneous changes.



Fig. 319.—Acute diphtheritic and haemorrhagic dysentery. Colon of a child, showing abundant pseudomembrane on the crests of the folds of the mucosa.

There is no acute splenic tumor and no pronounced cloudy swelling of the viscera. The bacilli are found in the swollen mesenteric glands and also in the spleen and liver, but not elsewhere. Painful joint changes are not uncommon, consisting in effusions into the joints, especially those of the foot, knee, and hip. When the pain and swelling subside

in one joint, another may become affected, and with each there is a rise in temperature. They recover their normal condition without any inflammatory residue. Transient paralyses, which sometimes involve muscular atrophy, also occur.

In children in summer epidemics it has been shown by Bassett and Duval, Knox and Wollstein, that the Shiga bacillus is the causative

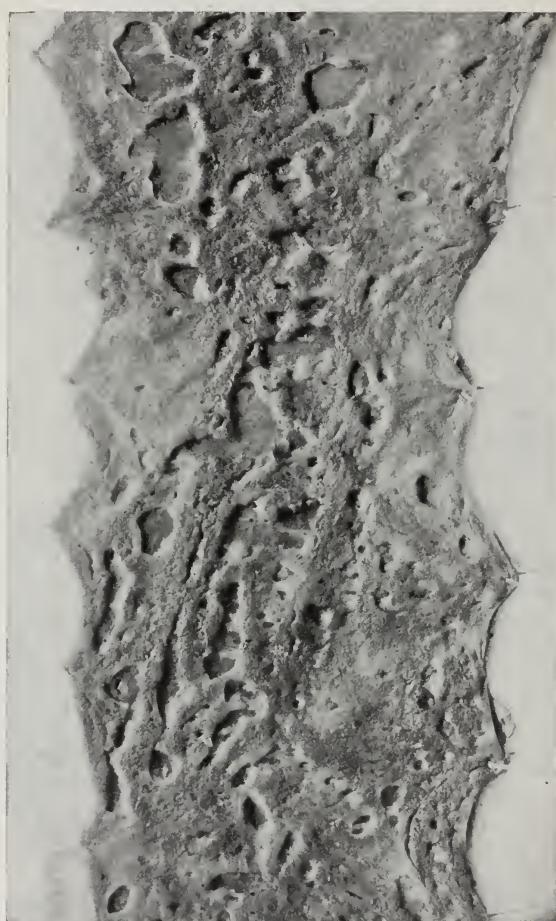


Fig. 320.—Dysentery in a child. Extensive ulceration of the colon, which involved also the ileum to a less extent.

agent of the dysentery, which is practically identical with that of adults, and in which the mortality is high. It has long been known that in asylums and prisons outbreaks of dysentery were due to some such infection, doubtless introduced, as we now appreciate, by a bacillus carrier. Kruse spoke of this as pseudodysentery, which was unfortunate, since it has been shown that these cases were due to the Shiga bacillus (Vedder and Duval).

As stated, the blood of dysentery patients acquires, after eight to ten days, the power of agglutinating bacilli of the same type. But the serum of those infected with the Shiga type agglutinates only the Shiga bacillus except in very concentrated form, while the serum of those suffering from infection with the Flexner type will agglutinate both in considerable dilution. The Shiga bacillus produces a strong toxin which has long been known to cause in rabbits not only a severe intestinal lesion with haemorrhages but also paralysis. This is well described and illustrated by Doerr in his monograph on the toxin. Clinicians have recognized the occurrence of postdysenteric paralyses in human beings, and have ascribed them to some form of neuritis, but Dopter has shown that in rabbits at least the paralyses are due to definite lesions in the gray matter of the central nervous system. Olitzky and Kligler have recently restudied the toxin, and have found that there may be distinguished an exotoxin which is heat labile, and which attacks the nervous tissues, and an endotoxin which is more stable and which is responsible for the intestinal lesions. Antitoxins can be produced for each of these, and are specific.

Shiga suggests a division of these related organisms into three groups, (1) dysentery, including Shiga; (2) metadysentery, including Flexner, Strong and His-Russel, and (3) paradysentery, including the Sonne form. The first group is toxic and forms no indol nor splits mannite, the second produces no toxin, the immune serum is antibacillary instead of antitoxic, as in the first group; it splits mannite and forms indol. The third group is evidently less virulent, it coagulates milk and forms no indol. The term *Shigella* seems to be applied to all now, and in recent years the prevalence of the Sonne type as the cause of mild epidemics affecting especially children, has been made clear.

Transmission by carriers, by flies and through lack of cleanliness in preparation of food is especially important.

LITERATURE

- Burnet: Brit. Jour. Exp. Path., 1934, xv, 354.
Doerr: Das Dysenterietoxin, Jena, 1907.
Duval and Bassett: American Medicine, 1902, iv, 417.
Felsen and Osofsky: Jour. Amer. Med. Assoc., 1934, ciii, 966.
Flexner: Bull. Johns Hopkins Hosp., 1900, xi, 231. Trans. Cong. Amer. Phys. and Surg., 1900, v, 61. Studies of Diarrheal Diseases of Infancy, New York, 1904.
Olitzky and Kligler: Jour. Exp. Med., 1920, xxxi, 19.
Shiga: Centralbl. f. Bakt. u. Paras., 1898, Abt. 1, xxiii, 599. *Ibid.*, 1898, xxiv, 817. *Ibid.*, 1933, cxxx, 1.
Sonne: Ctbl. f. Bakt., 1915, lxxv, 408; lxxvi, 65.
Soule and Heyman: Jour. Trop. Med. and Hyg., 1933, xxxvi, 281.
Vedder and Duval: Jour. Exp. Med., 1901-05, vi, 181.

PYOCYANEUS INFECTIONS

The Bacillus pyocyaneus can produce a most intense and often widespread infection, generally in children, entering the body through the skin, mucosæ, middle ear or otherwise. The lesions in the skin

are areas of necrosis with haemorrhage and vesicle formation, known as ecthyma gangrenosum. Those in the conjunctiva, tonsils, pharynx, trachea, and bronchi are similar areas of necrosis with great numbers of bacilli and surrounded by haemorrhage. Throughout the intestinal tract and most frequently in the appendix, these foci of necrosis with yellow opaque centre and deep red margin, are conspicuous. Here, as in the kidneys, and sometimes in the meninges, the lesions show especially the localization of the bacilli in the walls of the blood-vessels, causing thrombosis and anaemic necrosis extended by the action of the bacilli. A fatal septicaemia is usual. We have had two cases recently in which most of these features were accentuated and the infection is apparently of not infrequent occurrence.

LITERATURE

Bezi: Ziegler's Beiträge, 1933, xcii, 41.

Epstein and Grossman: Amer. Jour. Dis. Child., 1933, xlvi, 132.

Fraenkel, E.: Ztschr. f. Hyg. u. Infektionskr., 1917, lxxxiv, 369.

CHAPTER XXXII

TYPES OF INJURY.—BACTERIAL DISEASE (Continued)

Leprosy: Nodular and anaesthetic forms. The bacillus and transmission. Lesions of the internal organs. Affections of nerves and their sequelæ.

LEPROSY

KNOWN in detail in ancient times as a contagious disease of destructive character and quite incurable, leprosy has spread over practically all the countries of the world, and lepers are now, as in the time of Moses, objects of horror and aversion.

The disease is the result of infection with the Bacillus lepræ, discovered by Hansen in 1874, and is a slowly developing affection, of extreme chronicity, in which nearly all the tissues become invaded by the bacilli. It occurs in at least two main forms, although there are many combinations and modifications of these types. One is the tubercular or nodular leprosy, in which the skin, especially in the exposed parts, is lifted up over firm nodules, which in time break through and ulcerate. The other is the so-called anaesthetic leprosy, in which, without much change in the skin, disease of the nerves leads to a loss of sensation, which is followed by trophic changes in the extremities and by mutilations from unnoticed injuries. The lepers live for a long time and become fearfully deformed, dying finally from the disease itself, or from some intercurrent affection.

Since writing this chapter the first time I have had the opportunity of visiting many leper colonies in the South Sea Islands, the East Indies, the West Indies, and in South America, and have had occasion to perform some autopsies in advanced cases. The affection is far more prevalent than we are accustomed to think it, and on account of its disabling character and the isolation it enforces is one of the most tragic of all diseases.

The mode of transmission is not really known, although various statements are made with an air of authority. Mere contact with those suffering from the disease is probably sufficient if prolonged enough because so many bacilli are discharged from the nose and from open ulcerations, but we must hasten to add that the Catholic Sisters and others who spend their lives in nursing and caring for these patients, are practically never infected. No doubt they are well aware of the risk and are very careful, but they do not avoid contact with the sick. There is no good evidence that leprosy is inherited, even when both parents are lepers, and there are many examples of the contrary. But when the children are left to live with their mothers in the leper colony they frequently develop the disease. Of four such children in a colony visited last summer, three showed large circinate skin lesions, while the other was clean. Some statistics seem to show that transmission is not

Not hereditary
Long catenary
Early & anti



Fig. 321.—Nodular or tubercular leprosy showing lesions especially on face and hands (Jamaica).



Fig. 322.—Tubercular leprosy involving face, hands, and body. Note the keratitis with opacity in the left cornea (Tahiti).

so frequent between husband and wife as might reasonably be expected, and that among relatives cases are found most often in brothers and sisters. Nevertheless it has always been thought that sexual intercourse plays a very great part in the spread of the infection. Every sort of biting insect has been investigated in the hope that one of them might be found responsible for the carrying of the bacilli, but so far with negative results. It is, of course, largely on account of the fact that the incubation period of the disease may last over months or years that the difficulty of determining the manner of transmission is so great.

The two forms mentioned above are seldom quite distinct, and it is only recently, in Jamaica, that I have seen a considerable number of cases of the pure anaesthetic form, with practically no changes in the skin, but with mutilation of the hands and feet from which fingers and toes had disappeared so that only stumps were left. The tubercular

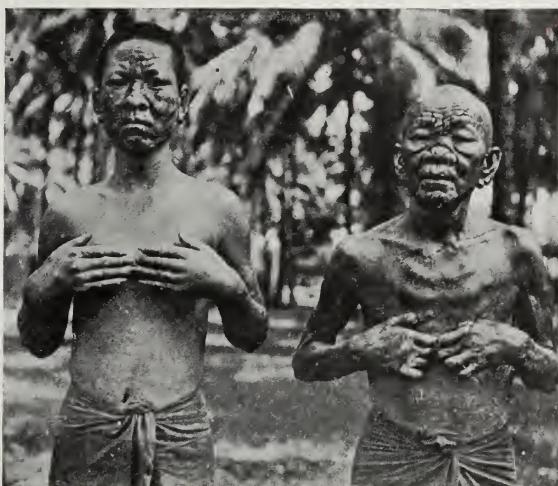


Fig. 323.—Tubercular leprosy, showing advanced lesions of face and hands (Kuala Lumpur).

form is almost always found to show anaesthesia and the nerves are thickened into cords and are found at autopsy to be densely embedded in the peculiar tissue which is so characteristic of all the lesions.

It would be difficult to describe all the atypical forms of skin lesion found in leprosy, and yet the average advanced case presents an almost monotonously uniform appearance (Figs. 321, 322, 323, 324, 325). The disease begins insidiously, sometimes with a febrile illness which passes off, to be followed some time later by the appearance of a reddened elevated patch somewhere upon the body, or by the partial depigmentation of patches of the skin. There is really no basis, however, for the expression "white as a leper," for they show no patches or scars which would impress one as white. Leucoderma from other causes is common though, and has, no doubt, given rise to this idea. The nodules or elevated patches become more numerous and affect especially the

face, hands, and feet, although they are also frequently enough found on the trunk when not covered with clothing. The eyebrows and eyelashes fall out, and there appears a diffuse thickening of the brows, the upper parts of the cheeks, the alæ of the nostrils, and the edges of the ears. The lobes of the ears are often especially enlarged and are soft, so that they swing about as the man walks. Later in all these positions the thickening takes the form of rough nodules which throw the skin up into great folds and eminences. Tumor-like masses form, especially on the alæ of the nose, and spread out laterally. The cartilage of the nose often becomes destroyed so that the nose is telescoped into itself in such a way that the nostrils open forward. By this time the lesions elsewhere are also far advanced and usually several fingers have been lost.



Fig. 324.—Leprosy in young people with destruction of fingers, keratitis, great swelling of ears, etc. (Tahiti).

Even early in the disease there are ulcerative changes in the mucosa of the nose, and diagnosis often rests upon finding the bacilli in scrapings from this ulcerated mucosa. Later many of the nodules in the skin break open and fail thereafter to heal for a long time, discharging quantities of bacilli with the exudate from the ulcer. The most disfiguring losses of substance may occur in this way in the tissues of the face and even in the bones underneath, so that sometimes no recognizable face is left. In the case of the fingers it is not always the advance of the strictly leprous lesions that produces the mutilation, for secondary infections are very common. They begin in the form of a panaritium or felon, and infection extends rapidly along the tendon sheaths, so that amputation must be performed, if at all, at a point far above that which is obviously diseased.

The conjunctivæ and corneæ are frequently the seat of leprous lesions which spread across and produce opacity, and with healing leave the eye quite blind.

The bacilli, which are acid fast and resemble closely the tubercle bacillus, are present in the lesions in enormous numbers. They are in such relation to the pathological changes that there can be little doubt that they are the actual cause of the disease, although the other postulates for the proof of the aetiological relation of an organism to a disease have not been very satisfactorily carried out.

The lesions are all based on the formation of a specific sort of granulation tissue which is composed of a loose network of branching connective-tissue cells, rich in blood-vessels and especially in wide lymphatics. It is infiltrated with mononuclear wandering cells of many



Fig. 325.—Anæsthetic leprosy. Mutilation of hands and feet without lesions of face (Bali).

forms and sizes, all of which appear, however, to belong to one series. Many of these attain the size of giant-cells and are provided with several nuclei. All of the wandering cells are loaded with globules of fat. Such tissue occurs in discrete lobules beneath the skin or in the internal organs, which when stained with Sudan, appear as solid red masses. Some of the cells become so swollen with fat as to lose all recognizable cell structure, and in these large fat globules which are sometimes surrounded by several cells there is a mass of bluish staining granules which become apparent after the fat has been dissolved out. It does not appear that bacilli accumulate in such globules. All the cells are thus vacuolated, as seen in preparations from which the fat has been dissolved out, and much has been written on the foamy cell, characteristic of leprosy. All of these cells are phagocytic, and may contain

bacilli, but it is chiefly in the swollen endothelial cells of the lymphatics and blood-vessels that they are heaped up in red staining masses. In other cases we have found the bacilli so numerous that almost every wandering cell contained them. Leucocytes play very little part in the infiltration, but necrosis of the tissue occurs frequently, and in those areas there are many fragmented nuclei and some leucocytes.

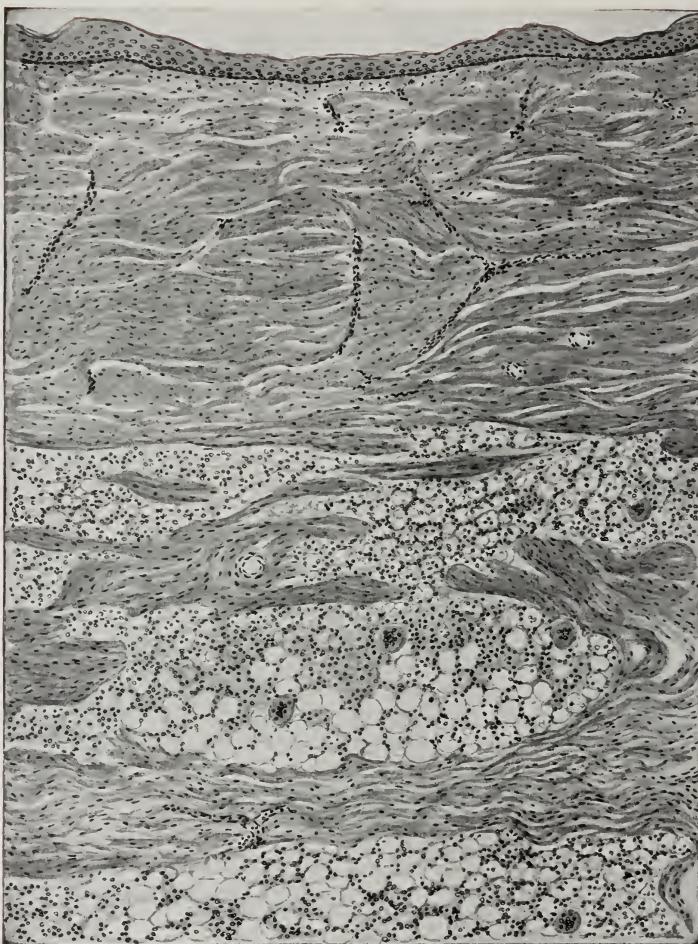


Fig. 326.—Leprosy. The section through a lepromatous nodule of the skin shows the obliteration of papillæ and the accumulation of giant-cells, which are loaded with bacilli in the deeper tissues.

In the nodules on the body surface the overlying epithelium is stretched out in a smooth layer so that the papillæ are obliterated (Fig. 326), and the tissue beneath is hyaline and almost devoid of nuclei for a short distance. After it breaks down the ulcer persists for a long time, but is usually filled up at length by a dense scar. The mucose



Fig. 327.—Leprosy. Focal accumulation of lepra cells in the liver. These cells contain many bacilli.

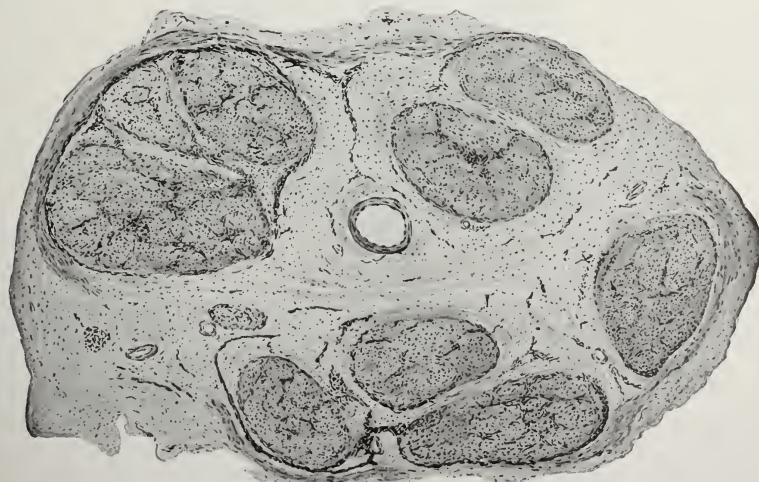


Fig. 328.—Lepromatous neuritis with much scar formation about the nerve-bundles.

of the nose and nasal sinuses are affected in exactly the same way, and ulcerations on a basis of the same sort of tissue are found throughout the pharynx, larynx, and trachea. Some authors have described lepromous lesions of the lungs which were hardly distinguishable from tuberculosis, but in the cases which I have studied it was really tuberculosis, which seems to be a common secondary infection in leprosy.

In the liver and spleen there are scattered everywhere minute foci of tissue made up of the same network with vacuolated or fat-holding



Fig. 329.—Atrophy and distortion of the bones of the foot in leprosy (Harbitz).

cells as seen elsewhere. These miliary lepromata (Fig. 327) which contain bacilli are quite conspicuous in a microscopical section, although they cannot be seen with the naked eye. Lesions of the intestines have been described, but must be rare. In the lymph-nodes the lepromous granulation tissue is found to occupy the margins of the lymph cords, leaving the sinuses fairly free. In the testicle the tubules are spread apart by the same tissue, loaded with bacilli, and the tubules are reduced to hyaline strands. In the bones there may exist a kind of lepromous osteomyelitis, with lesions analogous to those of the skin, but

this is much less important than the changes in the bones associated with the affection of the nerves and with the secondary infections.

Leprous neuritis or perineuritis is one of the most constant features of the disease, and the disturbances of sensation which result are often the first to arouse suspicion of its existence. It is by no means limited to the anaesthetic form, but is found in the tuberculous and mixed forms. The nerves of the arm and the more superficial ones in the leg may be felt through the skin as thick stiff cords, which at autopsy are found to show the nerve bundles spread apart and embedded in tissue of the type described above (Fig. 328). Bacilli are scattered in this tissue, but also make their way into the medullary sheaths of the individual fibres. The fibres degenerate and sensation is lost long before any motor disturbances appear. The lesion of the nerve is usually only in patches along the course, but the bacilli may be found not only there, but sometimes in the ganglion cells of the root ganglia and in the spinal cord and brain.

Most striking are the atrophies of the bones of the extremities which result from this interruption of the nerves which causes the phalanges to shrink and the bones to fuse into thin, pointed remnants of bone, attached to the metacarpals or metatarsals. These, in their turn, may atrophy and become disarranged, so that finally the hand or foot, further cramped by contractures, assumes the most distorted, claw-like appearance (Fig. 329). Harbitz, in describing these, has pointed out the fact that this is a process of mutilation not necessarily associated with ulceration and inflammation. Indeed, the most disfiguring mutilations arise from the insensibility of the hands and feet, which makes it possible for these patients to suffer from burns or other injuries without drawing away or protecting themselves. Nevertheless, it seems probable, from Harbitz's pictures, that most of these deformed extremities are the most direct result of loss of nerve impulses.

Barrera and Chavarria have recently described, either in the course of chronic leprosy or in the very beginning of the disease, acute febrile attacks accompanied by an exanthem which may take the form of reddish macules or of tender spherical or flattened nodules of small size in the depths of the skin. Such outbreaks last only a short time, are associated with a discharge of bacilli from all excretory channels, and either result in some improvement in the general condition, or, in weakened patients, lead to death. The exact significance of such attacks has yet to be made clear.

LITERATURE

Babes: Histologie der Lepra, Berlin, 1898.

Clifford, Sir Hugh: Daughter of the Muhammadans, in the Further Side of Silence, 1917.

Duval: Jour. Infectious Diseases, 1912, xi, 116.

Harbitz: Arch. Int. Med., 1910, vi, 147.

Kedrowski: Arch. f. Derm. u. Syphilis, 1914, cxx, 267.

Sakurane: Ziegler's Beiträge, 1902, xxxii, 563.

Sokolowsky: Virch. Arch., 1900, clx, 521.

Sticker: Handb. d. Tropenkrankheiten, Mense, 1914, iii, 1.

Uhlenhuth and Westphal: Centralbl. f. Bakt. u. Paras., 1901, xxix, Abt. i, 233.

v. Klingmuller: Die Lepra, Handb. d. Haut- u. Geschlechtskr., 1930, x, 2.

CHAPTER XXXIII

TYPES OF INJURY.—BACTERIAL DISEASE (Continued).— TUBERCULOSIS

Tuberculosis: Aetiology. Distribution and transportation of bacilli. Modes of infection. Immunity and hypersensitization. Effects of the tubercle bacillus on the tissues. Relation of resistance and immunity to the form of lesions. Distribution of bacilli in the body. Acute miliary tuberculosis.

TUBERCULOSIS

Aetiology.—The disease tuberculosis was known in practically all its forms long before its cause was discovered. Since it is of universal distribution and causes the death of more persons than any other disease, it has always been earnestly studied as far as was possible with the available means. Several epochs stand out in this study, although it must be confessed that we are still far from a complete understanding of the disease, and other epochs are still to come. Laënnec knew that pulmonary consumption was in some way the same disease as that in which the organs were sprinkled with small gray tubercles; Villemin proved it by inoculating caseous material into animals and producing tubercles, but it was not until 1882 that R. Koch discovered the bacillus. Then, since it was shown to be the common cause of all the different manifestations of the disease, there should have been no further dispute between the supporters of the duality or of the unity of tuberculosis. Nevertheless, this went on for years. Koch made the further discovery that a protein material which he called tuberculin could be extracted from the bacilli. For a time he maintained that this could be used as a curative or, at least, as a protective therapeutic agent and, of course, the whole world was stirred by this. But it proved a vain hope, and tuberculin became known only as a material which could be used for diagnosis, since it is harmless when injected into normal persons, but stirs up a febrile reaction in those already infected with tuberculosis. Koch also observed that injection of tuberculin caused a flare up of activity in the tuberculous lesions already present, and, what was more important, that injection of live bacilli in an animal already tuberculous had something of the same effect. He saw that the course of infection by these live bacilli themselves was quite different in an animal already tuberculous from what it would be in an animal which had never been infected, but he made no further use of this observation.

In 1898 Theobald Smith proved that all tubercle bacilli were not alike and that there were easily recognizable differences between the bovine type obtained from the common tuberculous lesions in cattle and the human type. Others later recognized avian, reptilian, and even piscine types, which are probably still more remote from the human

type. The bovine bacillus is shorter and stouter than the human form and grows less easily upon artificial media. In acid glycerin bouillon it tends to produce an alkaline reaction, while the human type only accentuates the acid reaction. But most definite of all is the far greater virulence of the bovine type, since it infects rabbits easily, is rather often found producing fatal tuberculosis in man, and readily infects cattle. The human type, on the contrary, while readily causing tuberculous lesions in guinea-pigs and man, will hardly infect rabbits and may be injected with impunity into cattle. Indeed, it is used as a harmless organism still possessed of the family characteristics to immunize cattle against the bovine form. The tuberculin produced from these two forms is probably identical. There has been some question as to whether the human type is not merely an attenuated bovine type through long passage in human beings, but all observations and experiments, such as passage through monkeys, show that this is unlikely, and that the types maintain their identity.

In 1901 Koch went so far in an address in London as to say that there was so little in common between the tubercle bacilli of cattle and that of man that precautions against infection from milk might safely be omitted. The weight of his authority was so great as to insure the acceptance of any statement he might make, and for a second time the whole world was stirred. But since even then fatal cases of human tuberculosis due to the bovine type of bacillus were known, practically all other experienced workers, including von Behring and Theobald Smith, immediately attacked and disproved Koch's assertion, to avert the danger which would follow neglect of the measures then in use to prevent the consumption of infected milk.

Distribution and Transportation of Tubercle Bacilli.—Nothing is known as to any life or development of the bacilli apart from the animal body, so that as sources of infection we must look to infected animals. It is true that the tubercle bacilli can remain alive for a long time even when dried up in sputum or in dust, and probably even longer when kept moist. But exposure to bright sunlight quickly kills them, whether moist or dried, so that it seems probable that street dust is of little importance in transmitting the disease.

Bacilli in this disease are discharged in quantities from the bodies of infected animals because they are abundant in the softened material set free from ulcerations in the lungs, intestines, or urinary bladder. When there are tuberculous sinuses draining from some internal focus the discharges from these canals carry abundant bacilli. But they are also set free with milk from cows which have tuberculosis of the udder. Therefore, not only milk but butter and even cheese may contain them. They are expectorated by consumptives in the sputum, but according to Flügge and his students, they are also sent forth suspended in a spray of fine droplets with the breath of such a person, especially when he coughs or sneezes or talks loudly. Lange, however, finds that this type of droplet infection is much less important than the inhalation of dust from dried sputum which may be deposited on handkerchiefs, bed clothing, or carpet.

Since the organism is so tenacious of life and so abundantly evacuated from the bodies of those infected, there is small wonder that tuberculosis is so wide-spread. It was not, however, until recent years that we had any idea of the extraordinary prevalence of this infection, although the extent to which actual illness resulted was well enough known. This is primarily because in most people the infection is quickly overcome and never progresses beyond the formation of a tiny focus of destruction of tissue which ends in a scar or in a calcified nodule.

Two methods have been employed, however, to discover how widespread infection has been: one, the search for the traces of tuberculous lesions in all bodies at autopsy, the other, the application of the tuberculin test to large numbers of persons in a community. The results are astounding, for while they agree almost precisely, they show that the percentage of all persons examined and found to show evidence of having been infected with the bacilli, increases from about 15 in the first decade, through 30 to 60 in the second, to 99 in the sixth and seventh. Such are the statistics of Nägeli, in Zürich, and Burekhardt, in Dresden, from autopsy material, while Nothmann, in Düsseldorf, and Hamburger and Monti, in Vienna, found by the tuberculin test in children a steady rise from the second year to 90 to 100 per cent. in the fourteenth year. These figures are from large cities in the central European countries where tuberculosis is notoriously common, and are taken from the proletariat of these cities, in whom no doubt infection occurs more readily than in the classes which live in a more cleanly way. Hillenberg has shown that practically the same condition exists in the country in Germany, but still it seems possible that in other less densely populated lands where people are not so crowded infection may be less inevitable.

Two things are argued from this: first, that in spite of almost universal infection, relatively few develop progressive tuberculosis, and second, that those who do develop tuberculosis in later life must in many cases have been infected before as children.

Modes of Infection.—The determination of the mode of entrance of the tubercle bacilli into the body is of prime importance and, of course, every possibility has been minutely canvassed. It would seem that the tubercle bacillus which produces such characteristic lesions should leave a plain trace behind it, and usually it does so. Nevertheless there is little that is certain in the explanation offered for the commoner forms of invasion. The rarer forms are clear enough—for example, when in a ritual circumcision, a tuberculous individual officiating, applies his mouth to the bleeding prepuce of the infant, it is easy to understand the subsequent appearance of tuberculous lesions there and in the inguinal glands.

But infection through the skin or genitalia is relatively unimportant. It is true that tubercles may form upon the hands of pathologists, butchers, and others who expose their skin directly to infectious material, but such infections are usually self-limited, perhaps because such persons have become immunized, and seldom give rise to pulmonary or other wide-spread tuberculosis.

The great portals of entry are clearly the respiratory and intestinal tracts, and a little consideration of the distribution of the bacilli will convince one that the common sources of infection are to be found in intimate contact with consumptives and in the swallowing of infected milk and milk products. All sources of bacilli other than the exhalations and sputum of consumptives and the milk from tuberculous cows seem remote and rarely to be regarded as important.

Congenital transmission of the infection has been much discussed, but there is little evidence to show that it can occur. Schmorl has found that placental tuberculosis is not uncommon and it is conceivable that bacilli might in this way reach the body of the foetus.

Most cases of tuberculous infection are to be regarded as due to either aspiration or swallowing of the bacilli. There is no difficulty in believing that dust laden with bacilli could be inhaled deep into the lung, and possibly could be drawn deeper into the lung than the spray or droplets of Flügge. Coal dust and other recognizable dusts are breathed into the furthest alveoli in this way, and while part of it is wafted back by the bronchial epithelium, much of the rest is lodged in phagocytic cells and carried back through the lymphatics to the bronchial nodes. The same path must be followed by the tubercle bacilli and, indeed, Heymann and others have settled this question conclusively by exposing guinea-pigs to inhalation of dust or spray laden with tubercle bacilli, killing them at short intervals. Tubercle bacilli were found in the most distant bronchioles and alveoli both by staining them in sections and by inoculating those portions of the lungs into other guinea-pigs.

The demonstration of Ghon, and more recently by ourselves, in most cases of tuberculosis of the lungs in children, of an old primary lesion in the extreme periphery of the lung, followed by lymphatic transportation to the bronchial nodes, is to be explained only in this way. The later rupture of the caseous node into a bronchus, flooding that lobe of the lung with bacilli and establishing a fresh tuberculosis, is very easily understood. In later life it is usually less easy to trace the course of the infection, chiefly because it is resisted and distorted by efforts at healing.

The infection of the upper respiratory tract has, of course, been studied, but the lesions of nasal sinuses, tonsils, larynx, trachea, and cervical lymph-nodes have rather the character of secondary infections and it is not easy to maintain that they precede the infection of the lung.

While keeping a perfectly receptive attitude toward the proof for the origin of pulmonary tuberculosis through transport of the bacilli to the lungs by way of the lymphatics or the blood-vessels, I think we must still accept as valid, in most cases, the old explanation of the direct aspiration of the bacilli into the bronchioles.

With regard to the discussion of these possibilities the student should read the papers of Opie, Baldwin and Gardner, and of Ghon.

As far as concerns the other great portal of entry, the alimentary tract, there need be little difficulty in accepting the possibility of the

safe passage through the gastric juice with its disinfecting hydrochloric acid, of such resistant and wax-bound organisms as the tubercle bacilli. At least it appears that they do reach the intestine in persons with advanced pulmonary tuberculosis who must swallow much of their sputum.



Fig. 330.—Acute miliary tuberculosis of lung. Small tubercles of several sizes scattered through the lung.

In these cases, however, it may well be that temporary disturbances of gastric secretion make the passage of the bacilli easy.

Von Behring points out the fact that in the very young infant the ferment-secreting glands of the digestive tract are little developed and the epithelial lining not yet a serious obstacle to the passage, unchanged, of any foreign protein. Antitoxin can be administered effectively by

mouth. In these infants, therefore, he thought it possible that there might be rapid absorption of tubercle bacilli, which leave no trace behind.

Rössle, Calmette, Ravenel, Orth, and others find a rapid general spread of such bacteria throughout the body, lodging in lymphoid tissues everywhere, and sometimes (Bartel) producing no visible lesions whatever. All argue that tubercle bacilli brought into contact with any mucosa are readily absorbed without leaving a destructive lesion to mark the place of entrance.

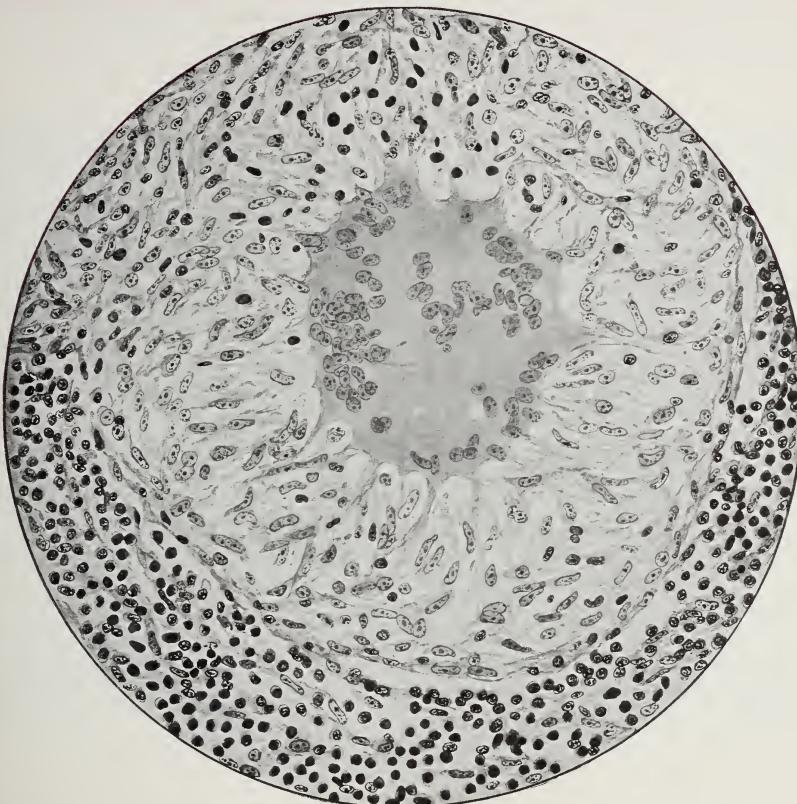


Fig. 331.—A single tubercle, rather sharply outlined, with a giant-cell sending protoplasmic processes among the epithelioid cells.

With regard to the mode of entrance of those bacilli which cause pulmonary phthisis in adults there has been much discussion. Some authors, as von Behring, thought that they might be absorbed through the intestine in infancy and give rise later to pulmonary disease as an auto-infection. Others regarded the primary lesion in the lung in children with lymph-node involvement as the source of the more extensive adult form of the disease, although this would require a latent period of years. But Opie and many others feel that it is far more probable that there occurs another inhalation of bacilli from outside, so that

the phthisis of adults begins as a new infection although its course is doubtless influenced by the immunity conferred by the former infection.

Effects of the Tubercle Bacillus on the Tissues.—We have long known that the bacilli can produce minute nodules in the tissues on the one hand, and acute inflammatory exudates on the other. In both cases progressive necrosis and coagulation of the product is common, but reabsorption of the exudate or even of the early stages of the nodule is possible, and healing processes with encapsulation and scarring even after extensive necrosis and loss of tissue form an every-day occurrence. The reasons for the occurrence of each type of lesion are still being eagerly studied.

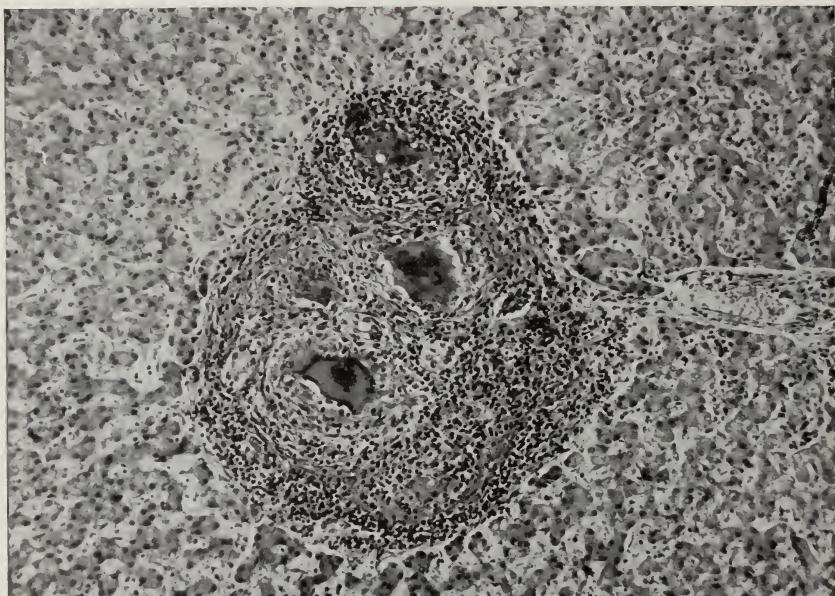


Fig. 332.—A group of minute tubercles in the liver showing giant- and epithelioid cells and marginal lymphoid cells.

Tubercles.—Most commonly on reaching the tissue the bacilli produce minute, translucent, grayish nodules, which, from being supposed to be of about the size of millet-seeds, were called *miliary tubercles* (Fig. 330). We now know, however, that those were really little groups of tubercles, and that a single tubercle is a great deal smaller and scarcely visible to the naked eye. The tendency to grouping and coalescence is very strong, and such a mass, instead of being round, is really lobulated or mulberry shaped. While the tubercles are very fresh and young they remain translucent, but very soon they show a spot of yellowish opacity in the centre.

Microscopically, a fresh tubercle is a roughly concentric mass of cells, pretty sharply marked off from the surrounding tissue (Fig. 331).

These cells, clustered around a central area, are sometimes arranged in laminae, but are usually attached to one another in less orderly fashion to form a pale staining tissue. They have elongated vesicular nuclei, with little chromatin and a faintly outlined cell-body, which is irregular in form and branches to connect itself with its neighbors. These are the cells commonly known as epithelioid cells, which form the most constant feature of the tubercle. Often, but not always, the central part of the mass is occupied by a giant-cell, a large mass of protoplasm containing a great number of nuclei which are usually arranged around its periphery or at the opposite poles (Figs. 331 and 332).

This protoplasmic mass also gives off processes which ramify among those of the epithelioid cells. In the marginal portion of the tubercle one usually finds numbers of mononuclear wandering cells of the

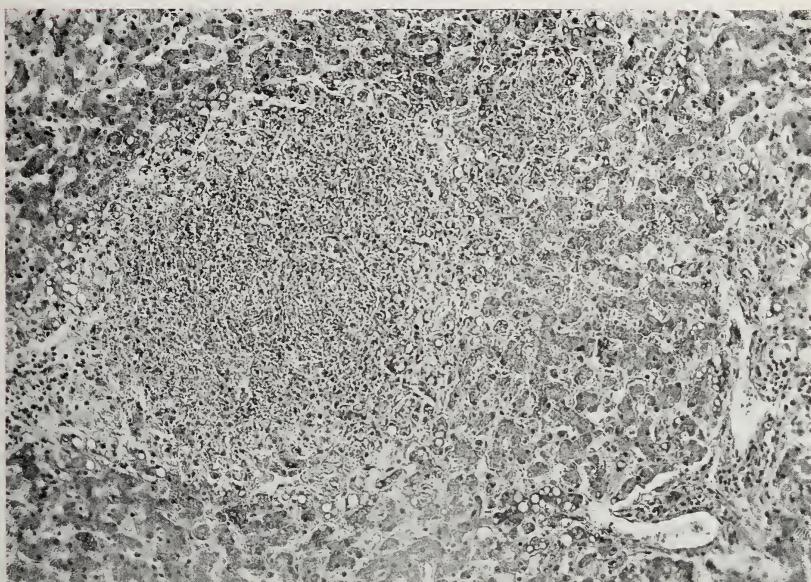


Fig. 333.—Soft tubercle in the liver. This is the response to the lodgment of great numbers of bacilli and is a collection of mononuclear phagocytic cells.

lymphoid type. The whole is supported by a newly formed framework or reticulum, which can be demonstrated by digesting away the cells. Usually, too, there can be shown to exist a delicate network of fibrin.

Tubercle bacilli may be found in the body of the giant-cell or lying in or between the epithelioid cells. But there is absolutely no provision for a blood-supply in such nodules, and those capillaries which were present at that point before are found to be obliterated, so that if an organ studded with tubercles be injected through the artery with blue gelatin, each tubercle will stand out as a white nodule against the blue background. This can have nothing to do with the central necrosis which is so common in these nodules.

The epithelioid cells become distorted, their nuclei elongated and

twisted, so that they lie radially and for a time take a deep stain (Fig. 336). Then, beginning sometimes in the giant-cell and involving the whole centre of the nodule, there occurs a complete disintegration of the cells, which melt together into a formless mass.

Occasionally we are able to see another type of minute tuberculous lesion which seems to result when the bacilli are brought to the tissues in greater numbers and the reaction is more intense and rapid. Then, instead of a compact nodule of characteristic epithelioid cells, there is a loose collection of clearly outlined mononuclear phagocytic cells of rather large size (macrophages) together with a number of lymphoid



Fig. 334.—Conglomerated tubercles composed chiefly of epithelioid cells.

cells. In the liver such a collection distends a sinus, pushing aside the liver-cells, and among the cells that make up the mass there are to be seen numerous tubercle bacilli—a condition very different from that in the compact tubercle with its giant-cell, where it is difficult to find one bacillus. Such foci, long recognized by French authors, we are accustomed to call, for lack of a better term, soft tubercles to distinguish them from the more compact or hard tubercles. Neerosis is particularly prompt in such areas, so that it is difficult to find those in which all the cells are well preserved and there is as yet no evidence of coagulation (Fig. 333).

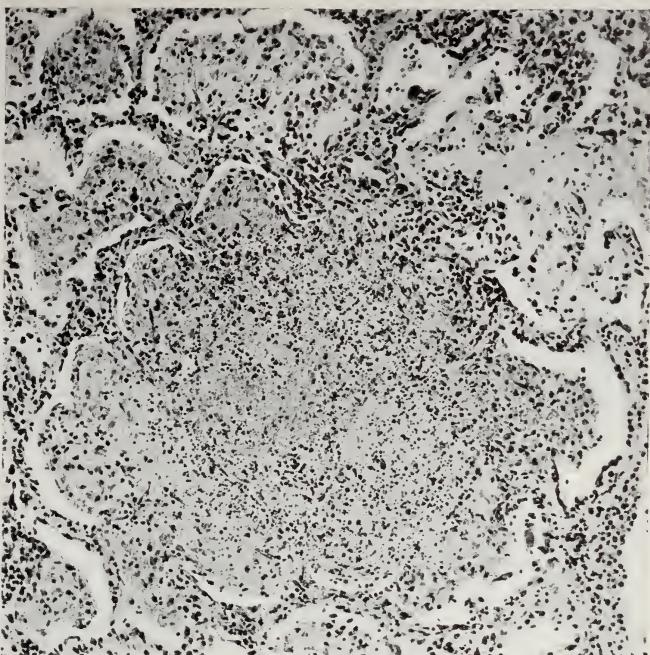


Fig. 335.—One of many minute areas of caseous pneumonia which might readily be mistaken for a miliary tubercle when the lung is examined by the naked eye.

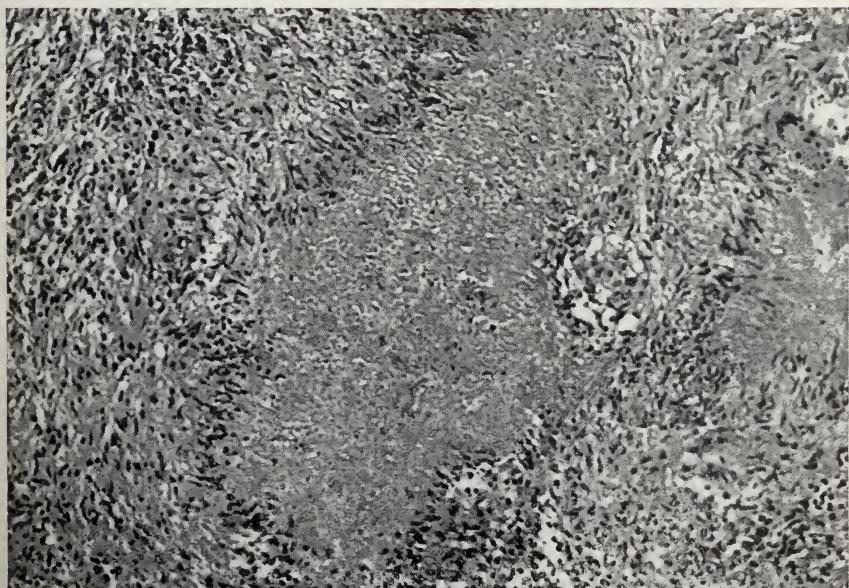


Fig. 336.—Rather older tubercles with beginning central degeneration and radial arrangement of the epithelioid cells.

Doubtless identical with this process is the acute inflammatory type of tuberculosis best represented by the caseous tuberculous pneumonia of Fraenkel and Troje (Fig. 338), in which areas of the lung are solidi-



Fig. 337.—Large tubercles in the spleen.

fied by an exudate of large mononuclear phagocytic cells and lymphoid cells, often with some admixture of polymorphonuclear leucocytes and with a network of fibrin. These areas are sometimes accompanied by

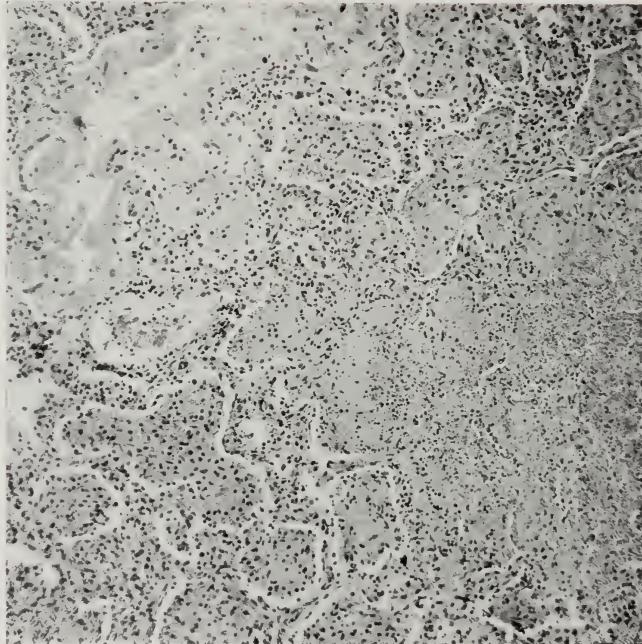


Fig. 338.—Margin of an area of caseous pneumonia. Some alveoli are filled with macrophages, others, with their walls, are merged in a necrotic mass.

a viscid glutinous fluid exudate in the adjacent alveoli giving a characteristic gray translucence. The consolidated areas are loaded with swarms of tubercle bacilli and quickly undergo coagulative necrosis or

caseation which involves the walls of alveoli, bronchi, and blood-vessels in complete destruction, although for a time their faint outlines may be recognizable. Similarly, in the pericardium, pleura, and peritoneum, we may encounter an inflammatory exudate with abundant fluid and a great outpouring of cells of the types described, together with a coagulum of fibrin. In florid tuberculous meningitis when great numbers of bacilli are present, as is usually the case, the exudate has the same character.

Efforts directed toward healing are surprisingly successful and most elderly persons carry about with them the scars that follow an infection



Fig. 339.—Primary tuberculous infection with secondary lesion in lymph-node healed and calcified. Adult lung.

which has been overcome. There may remain a chalky or stony nodule in the lung or in a lymph-node (Fig. 339), or, more commonly, only a thin slightly depressed pearly scar over the apex of the lung (Fig. 352).

When the bacilli reaching the tissue are few in number and resistance is already developed, the epithelioid cells which cluster about them may, after their destruction, wander away and leave no trace. But even when definite tubercles have formed and have begun to show

a central necrosis, the bacilli may be killed and the nodule become first hyaline and then replaced by a scar. And in such processes as caseous pneumonia it is not long before abortive tubercles appear in the margin of the caseous area and are soon associated with new connective tissue formation which may extend outward so as to build a wall about the area. That this is dependent upon a relative prevailing of the protective activity and a destruction of bacilli, and that in the changing fortunes of the conflict it may be encroached upon or destroyed is evident in any chronic pulmonary tuberculosis. So too, in relation with tuberculous lesions of long standing elsewhere, the barricading action of granulation tissue in the attempt to heal is familiar. There is noth-



Fig. 340.—Tuberculous granulation tissue.

ing specific about tuberculous granulation tissue (Fig. 340) except that it remains infected with tubercle bacilli which form tubercles in it and cause its caseation, exactly as they do with other tissue. It is perhaps best seen in the constantly frustrated attempt to form adhesions in tuberculous pericarditis, or in the walls of a sinus leading down to a tuberculous bone which carries to the opening in the skin a constant discharge of infected material.

There has been long discussion as to the origin of the cells concerned in the tuberculous processes, and especially of the epithelioid and giant-cells. Every conceivable origin has been claimed for them, endothelium, connective tissue, even epithelium, and finally the so-called histiocytes, or reticulo-endothelial elements to which the Kupffer cells of the sinuses

of the liver and the large mononuclear phagocytes belong. Vital staining, known to mark out so definitely these macrophages, has shown clearly that they are the cells chiefly concerned. The soft tubercles show them plainly, the epithelioid cells can readily be traced to the same origin and show the same staining, and so do the giant-cells, which are evidently the result of coalescence of several epithelioid cells or of their inordinate growth with division of the nucleus only. This, clearly stated long ago by Miller, is conclusively demonstrated by the work of Lewis, Willis, and Lewis and of Sabin and her co-workers by the use of vital stains and the methods of tissue culture, employed by them and by Maximow.

Orth long ago pointed out the same peculiar characters in the large cells found in the alveoli of the lung in caseous pneumonia, although they had always been thought to be desquamated alveolar epithelium. With regard to the epithelioid cells of the tubercle, Baumgarten always maintained their origin from fixed tissue, probably from endothelium. The French have regarded them as wandering cells. Wechsberg thought that the first effect of the lodgment of the bacilli is the destruction of a few adjacent cells, responded to by an inwarding of polymorphonuclear leucocytes, but that this process is soon masked by the development of the epithelioid cells. Wallgren and Fieandt emphasized the importance of the lymphoid cells and mononuclear phagocytes, but the latter thought the epithelioid and giant-cells formed later from fibroblasts. Evans, Bowman, and Winternitz stained animals vitally and injected tubercle bacilli into the portal vein. They thought the giant-cell derived from the Kupffer cells the epithelioid cells arising from endothelium. Rich and Prommas found that while it is true that the Kupffer cells take up the bacilli, become multinuclear, and divide greatly, they are usually killed and disintegrated before the final giant-cells appear. They hold firmly to the conclusion that epithelioid cells and giant-cells are formed from the wandering macrophages which are so clearly seen in the softer forms of tubercles and so readily shade off into the more elongated forms in slightly older collections in the same tissue. It remains difficult to understand the appearance of a reticulum in these nodules and the firm cohesion of the cells into a dense tissue.

LITERATURE

- Baumgarten: Ueber Tuberkel und Tuberkulose, Berlin, 1885.
Evans, Bowman, and Winternitz: Jour. Exp. Med., 1914, xix, 283.
Lewis, Willis, and Lewis: Johns Hopkins Hosp. Bull., 1925, xxxvi, 175.
Long, Vorwald, and Donaldson: Arch. Path., 1931, xii, 956.
Maximow: Jour. Infect. Dis., 1924, xxiv, 549; 1925, xxxvii, 418.
Miller: Jour. Path. and Bact., 1904, x, 1.
Vorwald: Amer. Rev. Tuberc., 1932, xxv, 74.
Wallgren: Arb. a. d. path. Inst., Helsingfors, 1911, iii, 139.
Wechsberg: Ziegler's Beiträge, 1901, xxix, 203.

Virulence, Immunity, Allergy and Dosage in Relation to the Form of Lesions.—Koch, as stated above, had observed that the progress of tuberculous infection in animals which had suffered a previous infection was different from that in fresh uninfected animals, but he pursued the

subject no further. Römer repeated the experiment, being careful to measure the dosage of tubercle bacilli precisely, and found that the first infection of a normal animal produces tubercles which, if the dose is small and the organisms feebly virulent, may be completely healed, but otherwise may progress so as to produce a wide-spread and fatal tuberculosis.

If now, after the preliminary inoculation has been survived a time, fresh, uninfected guinea-pigs and these tuberculous guinea-pigs be inoculated, side by side, with a constant, small, measured dose of virulent tubercle bacilli by injecting the bacilli into the skin itself, it is found that the normal guinea-pigs proceed to die with extensive tuberculosis of the organs and with a tuberculous ulcer at the point of inoculation while the lesions in the organs of those already tuberculous are not much increased, and the point of inoculation, although for a time intensely inflamed and necrotic, heals up completely. It is evident that the previous infection affords a fairly satisfactory protection against a reinfection, provided the dose in the second inoculation is not too great.

Krause and Peters repeated this work and found that in the first few days nothing is to be seen at the point of inoculation in the normal animals, while there arises quickly in the previously infected ones a redness and swelling which, when the dose is small, fades away in a day or two. This is the allergic reaction and if the dose is larger it may proceed to necrosis and ulceration, the bacilli being held, as Krause and Willis found, at the point of inoculation. Tubercles also develop and the two processes may overlap, but in a short time the ulcer heals and the tubercles disappear and there is no special change in whatever internal lesions there were from the first infection. On the other hand in the normal animals there is little reaction and but slight limitation of the bacilli to the point of inoculation; these are carried throughout the body and tuberculous lesions develop in the internal organs as well as in the skin where they were introduced. They develop more slowly than in the previously infected animals and there is no allergic inflammation, but they progress with ulceration, sometimes until the death of the animal.

Nichols found that normal animals upon subcutaneous injection of tubercle bacilli developed numerous tubercles in the lungs, while the previously immunized animals, after going through an acute haemorrhagic, inflammatory process, with tubercle formation, survived for a long time with encapsulated and fibroid caseous areas in the lungs. Paterson found that injection of bacilli into the pleura produced no obvious change in normal rabbits, although the bacilli were quickly absorbed and set up tubercles in the lungs and other organs. In immunized rabbits, in contrast with this, there was an immediate outpouring of bloody exudate which filled the pleura, but healing processes followed, and these animals survived the others by a long time. Soper found the same contrast in the liver. Injection of bacilli into the portal vein produces the progressive tubercles in normal animals; in the sensitized immune animal the tubercles are formed more rapidly, and the lesion is apparently more serious, but after two or three weeks it begins to heal and disappear, so that these animals long survive the others.

With this preliminary information we must consider various factors which are important in determining the outcome of infection with the tubercle bacillus. These are the virulence of the organism, the resistance of the host, the allergic reaction, and the number and concentration of the bacilli concerned.

Virulence must be regarded primarily as the ability of the organism to gain a foothold and grow in the tissue of the host. This seems to be a question of age-long adaptation for certain types can grow in the tissues of certain animals and not in others. Thus the bovine type is virulent for human beings, rabbits, and guinea-pigs, while the human type will infect and maintain itself in guinea-pigs, but not in rabbits or cows. The human being has probably nothing to fear from infection with the types that live in reptiles or fishes, although even the timothy bacillus, which also has a lipoid covering, can remain alive for a short time in animal tissues and stir the formation of tubercle-like nodules which soon disappear as the bacillus dies out.

Resistance Resist-
ance Living bacilli growing in the tissue stir the production of resistance or immunity, and there must be some element in the presence of the live bacillus which is lacking, or remaining only in traces in dead bacilli, for injection of dead bacilli rouses a much less potent immunity and tuberculin, the extracted protein of the bacillus, none. Calmette contends that non-virulent bacilli that persist only a short time confer a lasting immunity, and thousands of children in France have been given such a protective inoculation. No one has, as yet, been able to demonstrate in the tubercle bacillus the production of any poisonous substance, and yet infection with the living bacillus rouses a power of resistance to the growth of the organism, the power of agglutinating them and making them adhere to the tissue at their point of entrance, and of killing them by the aid of phagocytes which digest their remains.

Allergy arises also in the course of infection, but it can be produced equally well by the injection of dead bacilli or tuberculin and its rôle is extremely important. The student should especially read the papers of Rich in which all the experimental evidence and the conflicting ideas are discussed. He has shown that allergy is quite distinct from immunity or resistance and not necessary for its development. Indeed, in spite of our long cherished feeling that any reaction developed universally throughout the ages toward the introduction of a foreign agent must be essentially protective and beneficial, allergy seems to be, in certain instances such as infection with the tubercle bacillus, distinctly harmful. He shows that allergy can be annulled by desensitization without loss of immunity, and that it is probably due to an antibody accumulated upon the surfaces of cells which in contact with the antigenic protein forms a poison that kills the cell. Thus the necrosis or caseation of tissue in the allergic animal where the bacilli lodge is almost entirely due to the allergic reaction.

Allerg-

jmr

The number of bacilli which reach the tissue at any one time and their clumping or concentration is of extreme importance, for while a single bacillus produces little reaction and is treated in one way, a great mass of bacilli lodged in one place produces entirely different

effects and different reactions. Single or scattered bacilli produce no obvious destruction of the tissue cells and are quickly surrounded by an encapsulating tubercle, or even killed and removed. No allergic reaction is aroused, even in highly allergic animals. On the contrary in previously uninfected animals, a large number of virulent bacilli in one place causes an acute outpouring of leucocytes and mononuclear phagocytes. Of course in animals which have already been infected and have developed a high grade of allergy the lodgment of such numbers of bacilli is immediately followed by a necrotizing allergic reaction upon the death of some of the bacilli and the liberation of their protein. It is in this way that "soft tubercles" and other rapidly caseating lesions are produced. Naturally, except in experimental animals, such intro-



Fig. 341.—Edge of a fresh area of caseous and gelatinous pneumonia. Note the numerous large cells in the less affected alveoli.

duction of large numbers of bacilli into the tissues is practically invariably a late occurrence in persons already infected and in whom destructive lesions are progressing.

It is clear, therefore, that these several factors are always concerned in the development of any tuberculous lesion; virulence, resistance, allergy and dosage, and in each instance and in every lesion their relative importance must be weighed.

Attempts to analyze the bacillus have been numerous and it is known that the lipoid material which coats the organism will, upon injection, set up the formation of tubercle-like nodules, while the proteins and carbohydrates extracted from the body of the bacillus will not. The most recent papers on this are from Sabin and her co-workers.

LITERATURE

- Baldwin: Harvey Lectures, 1914-15, Series X, 154.
- Baldwin and Gardner: Amer. Rev. Tuberculosis, 1921, v, 429.
- Calmette: Presse Médicale, 1924, Nr. 53; 1925, Nr. 49.
- Flügge: XIV Hygien. Kongr., 1907, ii, 42.
- Gerlach: Hyperergische Entzündung, Basel, 1923; Verh. Dtsch. Path. Gesellsch., 1925, xx, 272.
- Ghon and Roman: Sitzb. d. k. Akad. d. Wiss. in Wien, Math. naturw. Kl., 1913, cxxii, 1.
- Ghon and Pototschnig: Beitr. z. Klin. d. Tub., 1919, xl, 87; xli, 103.
- Huebschmann: Münch. med. Woch., 1921, Nr. 43.
- Huebschmann and Arnold: Virch. Arch., 1924, cclxix, 165.
- Koch: Mitt. a. d. kais. Gesundheitsamte, 1884, ii, 1. Berl. klin. Woch., 1882, xix, 221.
- Krause: Amer. Rev. Tuberculosis, 1919, iii, 1; 1920, iv, 558.
- Krause and Peters: Römer's reaction, Amer. Rev. Tuberculosis, 1920, iv, 551.
- Krause and Willis: Trans. Nat. Tuberculosis Assoc., 1924, xx, 277; Amer. Rev. Tuberculosis, 1926, xiv, 197, 316.
- Lange: Beiträge z. Klinik d. Tuberk., 1920, lxv, 278.
- Marchand: Münch. med. Woch., 1922, Nrs. 1 and 2.
- Maximow: Jour. Infect. Dis., 1924, xxxiv, 549.
- McJunkin: Tuberculin Sensitiveness from Filtrates, Jour. Exp. Med., 1921, xxxiii, 751.
- Neufeld: Harvey Lectures, 1928, xxii, 27.
- Nichols: Med. News, 1905, lxxxvii, 638.
- Opie: Tubercle, Oct., 1925; Amer. Rev. Tuberculosis, 1922, vi, 525; 1924, x, 249; Jour. Exp. Med., 1924, xxxix, 659; Jour. Immunology, 1924, ix, 231; Trans. Nat. Tuberculosis Assoc., 1925, xxi, 362.
- Orth: Sitzb. d. k. Preuss. Akad. d. Wiss., 1913, iii, 51.
- Paterson: Amer. Rev. Tuberculosis, 1917, i, 353.
- Rich: Arch. Int. Med., 1929, xlvi, 691. Johns Hopkins Hosp. Bull., 1930, xlvii, 189; 1932, I, 115. Transactions 3rd Internat. Pediatric Cong., Acta Pædiatrica, 1933, xvi, 1.
- Rich and McCordock: Johns Hopkins Hosp. Bull., 1929, xlii, 273.
- Römer and Joseph: Brauer's Beitr. zur Klinik der Tuberkulose, 1910, xvii, 281-427.
- Rössle: Verhandl. d. deutsch. path. Gesellsch., 1923, xix, 18.
- Smith, Th.: Jour. Exp. Med., 1898, iii, 451. Jour. Med. Research, 1905, xiii, 253; 1907, xvi, 435. Trans. Massachusetts Med. Soc., 1907. Harvey Soc., 1906.
- Soper: Amer. Rev. Tuberculosis, 1917, i, 385.
- Trudeau: New York Med. Jour., 1903, lxxviii, 105.
- von Behring: Deutsch. Med. Woch., 1903, xxix, 689.
- Willis: Amer. Rev. Tuberculosis, 1925, xi, 173.

Distribution of Bacilli in the Body.—The modes of entry of the bacilli have already been considered, and we are now concerned with the escape of the organisms from an established lesion and their transportation to other parts of the body. It is because we can generally trace this by the trail left behind in the case of tuberculosis that it has always aroused interest, although in other infections in which it is equally important it may be difficult to follow the path taken by the bacteria because the traces of their passage are confused or indefinite.

Even though it has so far been impossible to demonstrate the existence of any toxin in the most virulent tubercle bacilli, there is something in their invasion of the body which results in a degree of immunity which cannot be adequately produced by the inoculation of dead bacilli, and which contrasts still more sharply with the result of injecting tuber-

culin which produces no immunity whatever. Nevertheless, both dead bacilli and tuberculin rouse an intense allergic hypersensitization. One of the striking effects of immunity is the fixation of the bacilli at the point of inoculation as shown by Krause and Willis. Rich in discussing this has, by experiment, proven that the fixation is not due to the inflammation of the allergic reaction but is quite as definite in an immunized animal in which allergy has been abolished by desensitization. It is, as he shows, due to adhesion of the bacilli to the tissues and to agglutination which constitute prominent features of the actual immunity.



Fig. 342.—Tubercle formed in a small venule. This one has an endothelial covering, but many of the softer type can be seen actually discharging bacilli into the blood.

Therefore, it is possible to understand the differences in the distribution of bacilli in normal and immune animals. In previously uninfected animals the bacilli quickly spread from the point of entrance, throughout the body and give rise to progressive lesions wherever they lodge. In immune animals they are held clumped and adherent to the tissues with which they first come in contact. Gradually some escape and are carried perhaps to the lymph-nodes draining that area. It is for this reason that in infants and children abundant bacilli are carried from the first point of infection in the lung to the bronchial lymph-nodes at the hilum and produce extensive caseation. In later life, except in the few persons who have never been infected before, such as natives of

remote, unpeopled districts who have never been exposed to infection and who, when they do come into contact with tuberculous infection, develop the child's type, the immunity remaining from a former infection restrains the passage of bacilli to the lymph-nodes even in advanced pulmonary tuberculosis, so that they do not become caseous. They show occasional tubercles and hyaline areas but are not conspicuously enlarged.

In some cases it is possible to find a gross rupture of bacillus-laden material into some channel or cavity in the body which readily explains



Fig. 343.—Caseous tubercle developed in the wall of a pulmonary vein, and separated from the blood by a partly organized thrombus.

the spread of the infection, while in other cases the paths of distribution are only to be discovered with the aid of the microscope. Of the first it is obvious that when a tuberculous cavity is formed in the lung, connected as it invariably is with the wide open ends of several eroded bronchi, it is inevitable that great numbers of bacilli should be coughed up through the trachea and aspirated into bronchi going to other parts of the lung or to the other lung. It is particularly striking when, as so often happens in children, a caseous, softened lymph-node breaks into a bronchus and spills its contents into it. Then that lobe of the lung is flooded with bacilli and becomes quickly the seat of a tuberculous pneu-

monia. The swallowing of tuberculous sputum with infection of the intestinal wall is another obvious mode of distribution of the bacilli.

Even more interesting are those instances in which a tuberculous focus, often a caseous lymph-node, extends so as to penetrate and empty its contents into such a serous cavity as the pericardium or pleura or peritoneum, or into a ventricle of the brain. The opportunity for a sudden intense infection of the whole cavity is evident. It occasionally happens that one may demonstrate the same evacuation of liquid caseous material with bacilli into a vein, and then, of course, the bacteria are distributed over the whole course of the blood-stream—at least from that point to the next capillary bed. Thus the invasion of a systemic vein or the thoracic duct pours the bacilli first into the capillaries of the lung while the invasion of a pulmonary vein endangers all the other tissues of the body. Of course, in both cases some bacilli may pass through the capillaries.

Less conspicuous but very effective in distributing tubercle bacilli through the tissues are the minute involvements of the walls of tiny venules and of lymphatics (Fig. 342). In the case of the small veins, as Rich points out, it is extremely common to find in microscopical sections caseous lesions actually in their walls and exposed to the still circulating blood in such a way as to scatter a few bacilli at intervals into the blood-stream (Fig. 343). There must be many cases in which this progresses from numerous venules so as to set up very large numbers of tubercles in the other organs. In the case of the lymphatics the same thing prevails. The lymphatic channels seem to be the natural means of transportation of the bacilli, and from any tuberculous lesion we confidently expect to find evidences of the passage of bacilli by this path to the next draining lymph-node, from which after producing a caseating lesion many more may be transferred to the succeeding nodes. The lymphatic channels themselves are commonly obstructed here and there by tubercles developed in their walls so that they become distended and beaded with accumulated lymph. When the thoracic duct is invaded or when caseating tubercles form in its lining wall it serves readily to discharge bacilli into the large veins and thus into the heart.

Acute Miliary Tuberculosis.—Acute miliary tuberculosis is a term which has long been used for the wide-spread production of minute tubercles all through the organs. There has been much discussion of the exact mechanism of this distribution and Weigert especially insisted that it must be due to the sudden rupture into a vein of a caseous mass laden with virulent bacilli, so that the organisms would be carried throughout the body and lodged in capillaries everywhere. He, with Schmorl and others, has diligently searched with scissors and has demonstrated such a rupture in a very great proportion of the cases, especially in pulmonary veins, but also in systemic veins when they lay in contact with a destructive caseous lesion. The orifice is soon closed by the deposit of a protective covering of thrombus material on the exposed surface but one could easily believe that the discharge of bacilli might be repeated. It is, however, not necessarily possible to find a grossly evident rupture into a vein for, as Rich suggests, it is quite possible that a continuous entrance of bacilli from the invaded walls of many minute veins may have the same effect though these would be more readily and quickly obstructed. Nor is the single, momentary invasion made evident by the appearance of the tubercles for as a glance at Fig. 330 (which was made without any thought of this point) will show, the tubercles are of various ages and sizes.

Benda and others point out that caseous lesions may develop on the endothelial lining of a vessel and liberate bacilli upon becoming caseous. This is true in the case of the thoracic duct which comes to be lined with caseous, ulcerating

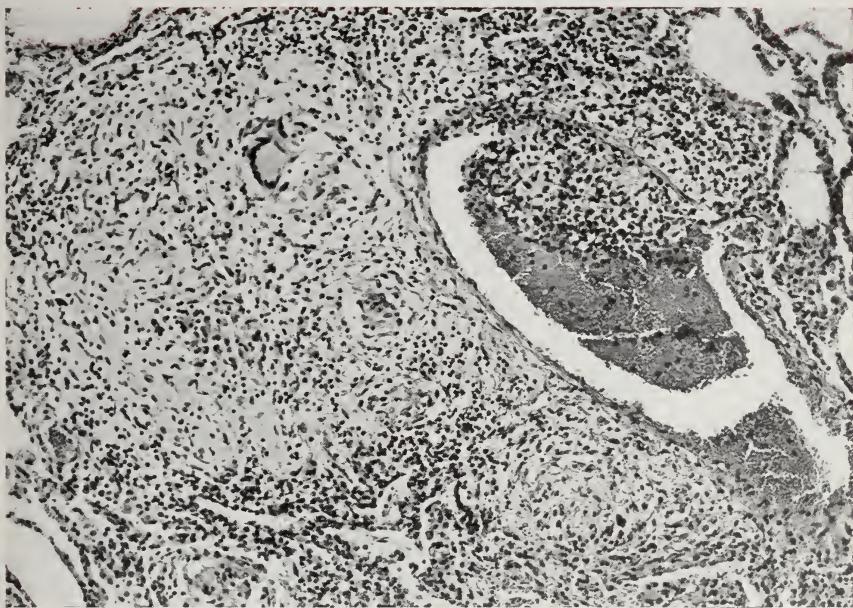


Fig. 344.—Tubercle extending into the lumen of a pulmonary venule.

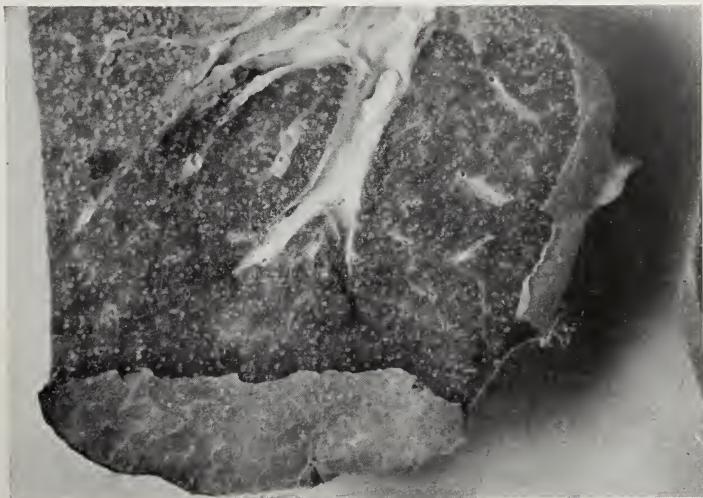


Fig. 345.—Caseous mass projecting into pulmonary vein. Miliary tuberculosis.

areas from which bacilli pass into the blood-stream. Rarely one may find caseous lesions in the heart discharging bacilli into the blood. Intimal tubercles and erosions in the aorta and smaller arteries are uncommon, but as Rich points out such tubercles

as are shown in Figs. 344 and 345 may be due to the lodgment of bacilli on the endothelium of the vessel rather than to extension of a caseous mass from outside.

The tubercles formed by this wholesale distribution appear practically in those tissues and with the frequency with which any particles injected into the blood-stream are lodged. Thus, as Brickner found, the lungs, spleen, liver, and bone-marrow retain the greater part of the carbon particles injected into a vein while such tissues as voluntary muscle, skin, and brain show hardly any.

The tubercles are scattered profusely in the spleen, liver, and lungs and are beautifully seen with the ophthalmoscope in the choroid of the living patient. Even in the pancreas, thyroid, muscle, and skin, which seem very little prone to develop tubercles, they are found at times.

CHAPTER XXXIV

TYPES OF INJURY.—BACTERIAL DISEASE.—TUBERCULOSIS (Continued)

Tuberculosis of lungs in children and adults. Tuberculosis of digestive tract, serous surfaces, lymph-nodes, genito-urinary tract, nervous system, skin, bones, and joints.

THE fact that, apart from the acute miliary form, tuberculosis is commonly a localized affection, makes it possible to refer to the lesions produced according to their situation. It will be seen, however, that, regardless of the organ involved, the same general characters are maintained.

Tuberculosis of the Upper Respiratory Tract.—The mucosa of the nose and pharynx may become infected by the breathing-in of bacilli, but probably more often by the direct introduction of the organisms from handkerchiefs, etc. Ulcers



Fig. 346.—Tuberculous lenticular ulcers of the trachea.

are formed and may extend to the underlying bone and to the communicating sinuses. Tuberculous ulceration of the larynx is common, and although thought to be sometimes primary, is without doubt most often caused by the passage of tuberculous sputum.