Principles of HUMAN PATHOLOGY

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INDIANAPOLIS

New York · OXFORD UNIVERSITY PRESS · 1959

Library of Congress Catalogue Card Number: 59-9815

PRINTED IN THE UNITED STATES OF AMERICA

TO OUR WIVES

Preface

THE ESSENTIALS OF EDUCATION are the student and the subjects for study; the instructors are adjuncts. The abilities of the student are not readily changed, but the learning process may be made more efficient by improvement in the selection and sequence of the subject matter. With these points in mind, a group of four instructors with varied special interests have collaborated to emphasize important general facts and theories of pathology.

The contents of this text are so arranged that, initially, the student should develop an overall appreciation of the wide scope of pathology with its broad categories of disease. The presentation of details is postponed until the student has the fundamental principles well in mind. Secondly, the student should understand the dynamic forces in diseased tissues, including the chemical reactions to injury, the movements of fluids and cells, the development of immunity, the ways of eliminating noxious substances, and the mechanisms for alteration and repair. Thirdly, the student should recognize that pathologic processes occur in the bodies and minds of his patients with varied and important relationships to sociologic, biologic, and geographic environments.

The authors have tried to correlate the facts of the basic sciences with the clinical features of diseases. An attempt has been made to direct the student toward the use of basic information in a dynamic approach to disease. Cause, pathogenesis, and effect have been discussed extensively when clearly established. In dealing with psychosomatic disorders, the theoretical, anatomic, and functional observations have been set closely together to indicate certain associations, if not actual cause and effect relationships. Tenuous explanations have been avoided if they are merely products of logic and are not supported by scientific facts.

In certain areas the discussions exceed the scope of the usual textbook of pathology. These broader explanations deal with the effects of bacterial endotoxins and exotoxins, the enzymatic factors in inflammation, chemical processes in metabolic diseases and vitamin deficiency states, the noxious effects of chemicals and of therapeutic agents, medicolegal responsibilities of the physician, the medicolegal autopsy, and abnormalities of pregnancy and the placenta. Many diseases have been discussed briefly or not at all because they are of minor interest, except to certain specialists. Some rare lesions, however, are treated fully because of an important teaching point.

The references to the literature are not necessarily the initial contributions in a given field but include more recent, readily available articles. Most of the references are in English because the already encumbered student so often finds it difficult to review articles in an unfamiliar language. Not all statements are documented from the literature. The authors have drawn upon their own experiences in their fields of special interest.

Neither the instructor nor the material for study guarantees success in medical education. The value of the instructor is determined by his ability to give the student optimal quantities of inspiration, "spoon-feeding," encouragement, and coercion, with proper timing. The effectiveness of the subjects presented to the beginning student of pathology depends upon the sequence, emphasis, basic relationships to previous subjects, and relative simplicity. These have been important considerations in the organization and development of the material presented here.

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September, 1959

Acknowledgments

THE AUTHORS OWE SPECIAL THANKS to Dr. Frank Forry and Dr. Clyde G. Culbertson, and others who preceded us, for the preparation of specimens and the collection of photographs for the departmental files, from which much of the illustrative material was taken.

Thanks are due to Messrs. James F. Glore, Paris C. Johnson, and Joseph M. Demma, Department of Illustration, Indiana University Medical Center, all of whom co-operated enthusiastically in the preparation of the illustrations.

Our appreciation goes also to Dean John D. VanNuys, and to our colleagues, who gave information and advice in certain instances, especially Dr. William G. Shafer, Associate Professor of Oral Pathology; Dr. Paul R. Lurie, Associate Professor of Pediatrics; and Dr. Robert A. Garrett, Professor of Urology.

The efforts of Mrs. Marilyn C. Siderewicz, Miss Donna K. King, and Miss Frances A. Cunningham, who prepared the typescript, and of Mrs. Isabella Rowlison and Miss Sally Buchanan, who assisted with the reading of proof and with the indexing, are greatly appreciated.

The suggestions and criticisms of numerous resident physicians contributed during the preparation of the text are gratefully acknowledged.

The excellent co-operation, efficiency, and kindly spirit of the staff of the Oxford University Press were of inestimable value in the completion of this work. James W. Zarbock, Douglas C. Ross, Katharine O. Parker, and John A. Begg deserve special recognition.

Errors and omissions in this volume remain the responsibilities of one or more of the four of us.

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DECLARATION OF GENEVA

(Adopted by the General Assembly of the World Medical Association, Geneva, Switzerland, 1948)

I solemnly pledge myself to consecrate my life to the service of humanity.

I WILL GIVE TO MY TEACHERS THE RESPECT AND GRATITUDE WHICH IS THEIR DUE;

I WILL PRACTICE MY PROFESSION WITH CONSCIENCE AND DIGNITY;

THE HEALTH OF MY PATIENT WILL BE MY FIRST CONSIDERATION;

I WILL RESPECT THE SECRETS WHICH ARE CONFIDED IN ME;

I WILL MAINTAIN BY ALL THE MEANS IN MY POWER THE HONOR AND THE NOBLE TRADITIONS OF THE MEDICAL PROFESSION;

MY COLLEAGUES WILL BE MY BROTHERS;

I WILL NOT PERMIT CONSIDERATIONS OF RELIGION, NATIONALITY, RACE, PARTY POLITICS OR SOCIAL STANDING TO INTERVENE BETWEEN MY DUTY AND MY PATIENT;

I WILL MAINTAIN THE UTMOST RESPECT FOR HUMAN LIFE, FROM THE TIME OF CONCEPTION; EVEN UNDER THREAT, I WILL NOT USE MY MEDICAL KNOWLEDGE CONTRARY TO THE LAWS OF HUMANITY.

I make these promises solemnly, freely and upon my honor.

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Pathology: The Medical Science Dealing with Disease

"Our study is man, as the subject of accidents or diseases. Were he always, inside and outside, cast in the same mould, instead of differing from his fellow man as much in constitution and in his reaction to stimulus as in feature, we should ere this have reached some settled principles in our art."

—SIR WILLIAM OSLER

The Doctor of Medicine is privileged and honored to devote his life to a high calling in which he is expected to display skill, adroitness, and dexterity in a comprehensive understanding and application of basic scientific principles to the preservation of good health in human beings, individually and collectively.

The ideal student and practitioner of medicine and surgery should have a penetrating knowledge of himself, a wealth of factual information dealing with normal and abnormal conditions in the human body, and a sympathetic, compassionate understanding of persons, particularly his patients. Based on broad principles of human conduct, his ultimate aim should be to make the lives of others happier and more wholesome, especially with regard to their physical and mental health. This is a truly significant and vital responsibility, inasmuch as "the health of the people is really the foundation upon which all their happiness and powers as a state depend." (Disraeli)

The physician is trained in basic sciences and in pathology, which represents an introduction to clinical medicine and surgery.

Pathology and the Pathologist

Pathology (Greek *pathos*, meaning suffering or disease, and *logos*, meaning discourse) is the medical science that deals with diseases, that is, with regard to their essential nature, causes, and development, as well as the structural and functional changes that result from the disease processes. Although there are disciplines known as animal pathology and plant pathology, the term is ordinarily construed to mean *human* pathology when it is used without a modifier that indicates otherwise.

As a result of the published observations of various anatomists (*e.g.*, Benivieni, Bonetus, and Morgagni) who studied postmortem specimens, the discipline of pathology had its origin during the sixteenth and seventeenth centuries as a study of abnormal anatomy. Subsequently, the first systematic textbook on this subject was written by Baillie and published in England in 1793. Relatively soon thereafter, particularly through the influence and leadership of Rudolph Virchow, *pathologic anatomy* became a well-recognized discipline.

The other major field in pathology, *i.e.*, *clinical pathology*, originated largely through the interests and efforts of clear-sighted and discerning practitioners of clinical medicine, among them Sir William Osler, who developed laboratories in which they used the theory and technics of basic sciences as aids in the diagnosis, treatment, and prevention of disease. Persons trained in the fields of

bacteriology and virology, mycology, parasitology, chemistry, and so on, were frequently included in the staffs of such laboratories as experts in supervising the various aspects of the clinical laboratory.

In the early years of the twentieth century, pathology was developing in the United States largely under the influence of William Henry Welch and others who were "academic children" of the German and Austrian pathologists. As a result, pathologic anatomy tended to become a separate academic discipline in the medical schools and larger hospital centers. On the other hand, clinical pathology was integrated into clinical departments, particularly internal medicine. In several instances, surgical pathology (actually a part of pathologic anatomy) was included in the organization of departments of surgery. As the years passed, and numerous smaller hospitals came into operation, there was a growing need for medical men who were competent to perform (or supervise) all of the services of a hospital laboratory in relation to the care of patients.

The pathologist of modern times is a medical specialist, a Doctor of Medicine who is adequately trained in pathologic anatomy and clinical pathology, including chemistry, microbiology, serology, hematology, blood banking, and other sciences in which laboratory technics may be used as aids in diagnosing, treating, and preventing disease. He may have relatively little direct, personal contact with patients, but his professional services (and those of his staff) are usually significantly involved in the medical and surgical care and welfare of virtually every patient in the hospital, as well as the relatives and friends of the sick person. The pathologist is frequently referred to as "the doctor's doctor."

Probably the chief duty of the pathologist is to serve as a *consultant* to his clinical colleagues, particularly with regard to (1) diagnoses of disease processes in tissues removed from living persons (*i.e.*, *biopsy*), and (2) the proper selection of diagnostic laboratory tests and interpretation of the results. Furthermore, the pathologist performs *autopsies* (*i.e.*, postmortem examinations) of patients who have been diagnosed and treated by his clinical associates. Such studies provide a means of continuing the education of the professional staff of the hospital, owing to the fact that significant clinicopathologic correlations may be based on the findings of the postmortem study. Frequently, the pathologist's experiences with specimens for biopsy, tissues and fluids removed at autopsy, various laboratory tests, and experimental work of varied sorts lead to the acquisition of new knowledge in the practice of medicine and surgery (*i.e.*, *research*). Owing to the rapidly expanding knowledge in the various areas included in the field of pathology, and as a result of their own special interests, many pathologists prefer to devote most of their medical practice to one of the subspecialties. Thus, some become chiefly pathologic anatomists, whereas others may be clinical pathologists, sometimes with special competence in one or more divisions of that field, *e.g.*, clinical chemistry, clinical microbiology, clinical hematology, and so on.

Health and Disease

Health (Middle English, *helthe*, from Anglo-Saxon, *haelth*, meaning *hale* or *sound*) is that ideal mode or form of existence wherein a person is free from defect, disease, or infirmity. In general usage, the term health deals particularly with soundness or wholeness of the body, especially as this relates to freedom from physical pain or discomfort that may result from (1) abnormalities of structure, (2) dysfunctions of major parts (*e.g.*, an arm or a leg), or organs, or tissues, or (3) a combination of two or more of these situations. The usual tendency is to evaluate good health in terms of physical well-being, but such a concept is restricted. Analysis of the broad definition reveals that a truly healthy person also has soundness or wholeness of the mind and spirit. Thus, ideally, a state of perfect health represents a completely harmonious existence, despite the del-

eterious effects of numerous factors (internal as well as external), but such perfection is probably never observed.

Disease (Middle English, *desese,* from Old French, *desaise,* meaning *lack of ease* or *discomfort*) is the antithesis of health. The word designates any condition in which health is attacked, deranged, or impaired, thereby resulting in (1) an anatomic alteration, or (2) an interruption or disturbance in performance and function, or (3) a combination of the two.

The terms *health* and *disease* are relative and exceedingly difficult to define precisely. As we have indicated, a perfectly healthy state probably does not exist in any human being, or, as a correlative, every person probably has some degree of disease (however slight it may be), if we consider the broad definition of the term. For practical purposes, the health of a person, or the disease that affects him, is usually evaluated on the basis of recognizable signs or symptoms (*i.e.,* objective or subjective indications) of a derangement or disorder. Thus, a person who seems to be healthy may be (at that very moment) afflicted with a highly significant disease process that (1) may not be detectable by the physician and (2) has not caused any discomfort to the patient.

It is the obligation of the Doctor of Medicine to evaluate prudently and sagaciously the state of health or the significance of disease in his patient by means of (1) thorough observation of the patient, (2) proper evaluation of facts that the patient (or a qualified informer) relates, (3) factual data from laboratory studies, (4) logically sound reasoning, and (5) a certain amount of intuition derived from continuing, comprehensive study and experience.

The Origin and Development of Disease

Disease may result whenever one or more normal structures or normal functions are altered, deranged, impaired, or completely destroyed as the result of the effects of one or more, exogenous or endogenous, causal factors or agents. As previously emphasized, disease may be present, but may not have been recognized by the physician or perceived by the patient.

Exogenous Causal Agents. Causal agents of this type may be considered in three categories: (1) *physical agents,* for example, heat, cold, X rays, ultraviolet rays, blasts from explosions, and various sorts of mechanical traumas; (2) *chemical agents,* for example, lead, mercury, phosphorus, carbon tetrachloride, cyanide, alcohols, sulfonamide drugs, and several other chemical compounds; (3) *biologic agents* (including noxious substances elaborated by living forms), for example, filtrable viruses, true bacteria and higher bacteria, fungi, protozoa, helminths, and insects and arthropods, as well as certain higher plants.

Although all of these are examples of causal agents that may cause disease directly, exposure to the agent, or its presence on or in the body, does not necessarily mean that disease will develop. Various factors, such as (1) the amount and duration of exposure, (2) interfering substances and conditions, and (3) the relative resistance or susceptibility of the individual person, modify the origin and development of disease. For example, a person who is protected with a thin coating of oil is not as susceptible to the ultraviolet rays in sunlight as the unprotected individual, or a person who has an adequate amount of natural resistance may not develop disease from exposure to a virus that causes serious illness in another person.

Endogenous Causal Factors. Disease sometimes originates and develops directly as the result of factors that are existent within the person's body: (1) *deficiencies in vitamins;* (2) *deficiencies in minerals;* (3) *deficiencies in nutrition,* other than specific factors included in the first two categories. These factors are discussed at greater length in subsequent chapters, but a few examples are cited at this time in order to illustrate their roles in disease.

A deficiency of vitamin D in children may

lead to rickets, in which there is defective calcification of bone, thereby resulting in "bow legs," "knock knees," a contracted pelvis, and other deformities. Similarly, a deficit in the ingestion and metabolism of phosphorus and calcium frequently results in troublesome defects in the skeleton, particularly during the ages when bone is actively growing. Furthermore, inadequacies in the amount of food ingested, digested, and metabolized may lead to undesirable loss of weight, fatigue, retarded growth, increased susceptibility to infectious agents, and other unhealthy conditions.

Miscellaneous Nonspecific Factors in Disease. In addition to the agents and factors listed in the preceding sections (*i.e.*, direct causes of disease), there are several that may be arbitrarily termed *accessory* factors in the development of disease. These are mentioned in relation to specific diseases in subsequent chapters, but the examples cited will help provide a broader understanding of the complex dynamics of disease:

Climatic Conditions. Excessive sunlight and strong winds, for example, have a role in the origin and development of cancer of the skin of the face in persons who are constantly exposed. Respiratory diseases are frequently more serious in cold, damp climates.

Occupation. Persons who must earn their livelihood by working in a granite quarry are usually exposed to silica dust, the inhalation of which may cause a devastating disease in their lungs. Similarly, persons who formerly worked with radium in watch factories manifested a high frequency of poisoning, including deleterious effects on bone marrow and, sometimes, the development of osteogenic sarcoma.

Sex. Cancer of the esophagus is several times more frequent in men than in women, and, of course, sex has a significant role in relation to cancer of the breast and various diseases of the urogenital system.

Age. Certain fungi that commonly cause "athlete's foot" in adult persons seldom cause infections of children's feet, but children are more frequently the victims of "ringworm" of the scalp than are adult men and women.

Development in the Uterus. Defects may occur while the embryo and fetus is developing *in utero*, thereby resulting in *congenital* (meaning *begotten with* or *born with*) abnormalities. Some of these lead to conditions that make it impossible or extremely difficult for the newborn infant to survive, whereas others result in unsightly or troublesome physical defects, and still others may be relatively insignificant. Examples of these are, respectively, failure of the heart to develop in such a manner that it can function properly, birthmark on the face, talipes (*i.e.*, clubfeet), and harelip. In most instances, the underlying reasons for the developmental anomalies are not known.

Race. Pernicious anemia, a disease of the hematopoietic system, is observed frequently in white persons, but it is unusual in Negroes. On the other hand, the incidence of certain diseases may be virtually identical in two races, but the intensity of the condition may vary greatly. For example, the frequency of primary coccidioidomycosis, a disease caused by a fungus, may be approximately the same in Caucasian and Negro persons, but the incidence of generalized dissemination in the infected person's body is possibly ten or twelve times greater in the colored race.

Constitution and Disease. Constitutional factors in disease are somewhat difficult to define and describe precisely, inasmuch as the term constitution represents an all-inclusive summation of relatively many heterogeneous features (inherited as well as acquired) that have a role (direct or indirect) in the growth, development, and performance of a person in his environment. For example, differences in the build of the body seem to be reflected in increased susceptibility to certain diseases, such as tuberculosis in the tall, lean, hollow-chested person. Another example is provided by the recognized differences in the time required for various persons to mature, or to become senile, and so on.

Heredity. Conditions that are inherited result from specific genes (in the chromosomes

of the parent's sperm or ovum) being passed to the child. Members of the various filial generations may not manifest the conditions, but, at some future time and under certain circumstances, descendants of the original mating may develop obvious diseases as a result of their hereditary characteristics. The harmful agent is sometimes in the cytoplasm of the ovum (rather than in the nuclear chromosomes), and thereby may lead to certain conditions in persons from the same parentage, but not in accordance with Mendelian inheritance.

Inherited conditions may be passed to descendants by means of the following mechanisms: (1) dominant traits, (2) recessive traits, (3) sex-linked recessive traits, (4) incompletely sex-linked traits, and (5) *y*-chromosomal inheritance. Three examples of inherited diseases are amaurotic familial idiocy (recessive Mendelian trait), hemophilia (sex-linked recessive Mendelian trait), and zygodactyly (*y*-chromosomal inheritance).

Reactions and Effects in the Host

One or more of a large variety of anatomic alterations or disturbances in function, or both, may result when the agents or factors enumerated in the preceding section affect a host, even during early embryonic life. Sometimes an anatomic change of rather considerable extent may develop, but there may be no significant alteration in the function of the organ or tissue. For example, a relatively large focus of dilated vessels (*i.e.*, a birthmark or hemangioma) in the skin is unslightly, but it is not likely to bring about significant dysfunction of the integument. On the other hand, a relatively small cancer or a gallstone impacted in the common bile duct usually results in serious disturbances in the liver and eventually leads to death. Furthermore, there may be a serious derangement in metabolism, such as that in a person who has diabetes mellitus, but with no identifiable, associated anatomic change in the pancreas. Thus, in general, the various factors or agents related to the origin and development of disease may lead to relatively innocuous anatomic or functional changes, or they may result in rapid or slow deterioration of the host, and, eventually, in death.

Fundamental Pathologic Processes. For practical purposes, the effects of disease in the host may be considered in three broad categories, sometimes termed the fundamental or basic pathologic processes:

1. Degenerative or retrogressive alterations in structure and abnormalities in metabolism.
2. Inflammation and repair, as well as other mechanisms of resistance.
3. Abnormalities in the origin, growth, and maturation of cells and tissues.

The Study of Pathology

A paraphrasing of Osler's remarks is appropriate: Our study is man, as (1) a person who frequently develops disease as the result of injury by physical, chemical, and biological agents, or (2) a person who may be predisposed to develop disease as the result of several additional factors that have direct or indirect effects on his health. Were his constitution, heredity, and capability of reaction to injury always identical to these features in his fellow man, we should ere this have solved more problems in our science and art.

The following chapters deal with the basic principles of: degenerative or retrogressive changes in the structure of organs and tissues; abnormalities in metabolism; disturbances in the origin, growth, and maturation of cells and tissues; and the effects of injury by biologic, physical, and chemical agents, including certain substances that are used for therapeutic purposes. This portion of the book may be regarded as the general principles of pathologic anatomy and pathologic physiology.

Medicine and surgery are generally practiced in accordance with a fairly well-established modus operandi. By and large, disease is recognized, identified, and treated on the basis of the tissues or organ systems that are

the chief sites of involvement and manifest the predominant signs and symptoms in the patient. For this reason, after the discussion of general principles, the clinical and pathologic features of various disease entities are considered in greater detail in the subsequent chapters dealing with the organ systems that are predominantly affected.

ABRIDGED LIST OF PERIODICAL JOURNALS FREQUENTLY USED IN PATHOLOGY

A. M. A. Archives of Pathology
American Journal of Clinical Pathology
American Journal of the Medical Sciences
American Journal of Medicine
American Journal of Pathology
Annals of Surgery
Blood, Journal of Hematology
British Journal of Experimental Pathology
Cancer
Cancer Research
Geriatrics
Journal of Clinical Pathology
Journal of Experimental Medicine
Journal of Histochemistry and Cytochemistry
Journal of Infectious Diseases
Journal of Laboratory and Clinical Medicine
Journal of Pathology and Bacteriology
Laboratory Investigation
Proceedings of the Society for Experimental Biology and Medicine
Surgery, Gynecology and Obstetrics
Virchow's Archiv für pathologische Anatomie und Physiologie
Zentralblatt für allgemeine Pathologie und pathologische Anatomie