SECOND EDITION

# PATHOPHYSIOLOGY

## The Biological Principles of Disease

LLOYD H. SMITH, Jr., M.D.

SAMUEL O. THIER, M.D.

Second Edition

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# FOREWORD

> "Medicine is the only world-wide profession, following everywhere the same methods, activated by the same ambitions, and pursuing the same ends."
>
> *Sir William Osler*

> "From the earliest time, medicine has been a curious blend of superstition, empiricism, and that kind of sagacious observation, which is the stuff out of which ultimately science is made. Of these three strands—superstition, empiricism, and observation—medicine was constituted in the days of the priest-physicians of Egypt and Babylonia; of the same strands, it is still composed. The proportions have, however, varied significantly. An increasingly alert and determined effort, running through the ages, has endeavored to expel superstition, to narrow the range of empiricism, and to enlarge, refine, and systematize the scope of observation.
>
> *Abraham Flexner*

The traditions of medicine are as old as recorded history and are interwoven into all civilizations, both past and present. Avicenna, Galen, Hippocrates, Maimonides, Harvey, Pasteur, Koch, and many others, celebrated and obscure, have created that tradition, which is still being modified in our time. Clearly, superstition in medicine is not yet expelled nor empiricism sufficiently narrowed. They remain to adulterate and diminish the science and humanism of medical practice.

The science of medicine is universal in its origins and in its relevance. In fact, universality in time and place is the bedrock of scientific observation. Human biology is basically the same in Sri Lanka as in Sweden. It is true that biological variation exists. Gene pools have been modified by mutation and natural selection. Balanced polymorphism, for example, seems to have created a high incidence of sickle cell disease only where the associated increased resistance to falciparum malaria constitutes a significant biological advantage. Such examples of differing gene pools in ethnic groups abound. Much more impressive, however, is the constancy of human biology, representing a high conservation of the human genome and therefore close homology of gene products. Out of infinite possibilities, the same molecular species transport oxygen, capture energy from carbohydrates, and transmit nerve impulses in all humans without regard for national borders. It would be astonishing if it were otherwise in view of the recentness of the "ascent of man" from a common ancestry. It is reasonable, therefore, to present Volume I of this textbook as "international." Its discussions of cell biology, genetics, immunology, hematology, metabolism, endocrinology, cardiology, respiration, nephrology, gastroenterology, neurology, connective tissue, and dermatology are universally relevant. They are the disciplines that underlie the practice of medicine in whatever setting that practice may occur.

Although human biology is relatively constant, the environments in which men exist are extraordinarily diverse. Differences in nutrition, culture, education, economics, climate, crowding, application of the technologies of public health and preventive medicine, and many other environmental influences dictate the occurrence of disease and the maintenance of health far more than do differences in genomic nucleotide sequences. Disease presents in different patterns, therefore, throughout the world (geographic medicine) and in subsets within a given society (epidemiology). Differences exist in the incidence of all kinds of diseases (cancer, cardiovascular disorders, rheumatic diseases); in fact, it is difficult to find any disorder with equal geographical prevalence. Nutritional disorders, the infectious and parasitic diseases, and their deadly interactions are without question the medical problems with the most sharply defined geographical and economic foci—largely in the developing countries of the world.

All living things protect themselves as vigorously from invasion by smaller living things as they do from engulfment by larger ones; for it is as bad to rot from within as to be eaten from without—at least it is as decisive. Poor nutrition causes that protection to falter in ways not yet fully explained. Inadequate sanitation, poverty, and crowding have their own epidemiology and assist the invasion by smaller living things. Furthermore, some infectious diseases, once comfortably remote from western countries, are now alarmingly close in a shrinking world marked by increasing commerce in goods and people. Lassa fever, although still confined to Africa, warrants attention; kuru may be an analog for slow virus diseases yet to be detected. Volume II, edited by Doctors Braude, Davis, and Fierer, is truly international in its description of the parasitic and infectious diseases. Fifty-eight participants from 27 countries outside the United States have contributed to its completion with the authority of direct personal observation. More than any single book now available, it describes the world experience with the parasitic and infectious diseases.

The first two volumes of the *International Textbook of Medicine* were designed to articulate with the *Cecil Textbook of Medicine,* which has had an international audience in internal medicine for more than half a century, to complete this "system of medicine." The practice of clinical medicine requires a frame of reference, which for this series is the western world with its assumption of the availability of high technology and its recommended therapeutic programs.

The *International Textbook of Medicine,* then, has created two new books designed to be used with a third, a well known classic textbook of medicine. All three of these textbooks are capable of standing alone and each will have its specific audience. What is the motivation for presenting them in such a series or system of medicine? More than three fourths of the earth's population live in the developing countries of the world. Achievement of better health is one of the highest aspirations of the people of these countries. "The health of all the people is really the foundation upon which all their happiness and all their powers as a state depend" (Disraeli). The prospects for better health in most of these countries, even in those that are wealthier and more fortunate, depend more directly upon the ultimate conquest of persistent poverty, malnutrition, illiteracy, and a multitude of other social problems than upon expansion of personal health services. These are problems that transcend the work of the physician, although the physician may be unusually influential in their alleviation. This is perhaps particularly true in countries where physicians constitute one of the few highly educated segments of society.

Despite the crushing burden of these external factors, most of which are beyond the traditional purview of medicine, the education of physicians and other health workers remains a top priority. The number of medical schools, medical students, and physicians continues to rise throughout the world. A severe limitation to both undergraduate and continuing medical education, however, has been a deficit of appropriate textbooks. Students living in the developing countries of Asia, Africa, or Latin America often have no easy access to libraries and can rarely afford to own the required textbooks. In most circumstances the student must rely on didactic lectures or notes distributed by teachers.

On the basis of these observations, as well as from many years of personal experience in medical education in developing countries, one of us (AHS) conceived this plan to publish a comprehensive textbook of medicine to meet the needs of students and physicians in the international medical community. Not unexpectedly, this turned out to be impossible to attain in a single volume. Volume I was therefore designed to give a comprehensive presentation of the most pertinent aspects of basic science and pathophysiology for medical practice. In view of the importance of infectious diseases as the leading cause of morbidity and mortality in the developing countries, it was considered essential to devote an entire volume to microbiology and to the clinical problems of infectious diseases. Of the many authoritative textbooks of clinical medicine, the *Cecil Textbook of Medicine* was judged to lend itself most readily to this series. At this time, the *International Textbook of Medicine* does not attempt to encompass all aspects of medical practice, such as pediatrics, surgery, or psychiatry. As such it is not totally comprehensive, but it is a start. It is also not a primer but rather presents medicine and its relevant pathophysiology at a level of rigor consistent with that taught at advanced medical schools throughout the world.

The practice of medicine is truly international in its scope. The editors hope that the *International Textbook of Medicine* will make a contribution to its common purposes.

ABDOL HOSSEIN SAMIY
LLOYD H. SMITH, JR.
JAMES B. WYNGAARDEN

# PREFACE
## TO THE SECOND EDITION

The first edition of *Pathophysiology, The Biological Principles of Disease,* defined as its goal the integration of science in a rational analysis of disease states. The text was meant to bridge the gap between the basic sciences as separate disciplines and the whole patient in whom knowledge of these disciplines can be integrated to explain clinical disorders. The reader is referred to the Preface to the First Edition, which elaborates upon the purposes for which this book was conceived. During the four years since the first edition appeared, the advance of knowledge in the basic biological sciences has, if anything, accelerated. The second edition attempts to keep pace with this new information and responds to many of the constructive criticisms that we have received. The text has been compressed and focused on human rather than on animal biology. Details have been limited as much as possible to those required to define broad concepts. Discussions of the clinical aspects and the natural history of diseases have been limited in this book, as being more appropriate for its companion, the *Cecil Textbook of Medicine.*

Cell biology and genetics remain a solid foundation for the understanding of other sections. A newly authored discussion of immunology is now followed by a new section on infectious diseases and host defense mechanisms, which provides a logical extension of the discussion of immunity and leads readily to a number of topics presented in the subsequent section on hematology. Metabolism and nutrition, a single section in the first edition, have been separated into independent sections. The sections on endocrinology and on neurology have been completely reorganized under new authorship. As part of this reorganization of the book, the sections on neoplasia and on clinical pharmacology have been omitted. It is believed that the concepts relevant to pathophysiology in those sections are adequately covered elsewhere in the book. All sections in this second edition have been updated to reflect recent advances and changing concepts.

Books do not simply congeal from submitted manuscripts. They require a considerable editorial effort. This effort varies from the development of a unified concept of scale, scope, and format to close attention to an enormous number of details necessary for accuracy and clarity of fact and of exposition. In all of these activities we have been greatly assisted by J. Dereck Jeffers at the W. B. Saunders Company and by the skilled editorial and production team that was assigned to this complex task: Lorraine Kilmer, Donna Walker, Edna Dick, and Frank Polizzano. The editors also depended heavily upon the invaluable contributions made by their editorial colleagues in San Francisco (Judith Serrell) and in New Haven (Jacqueline McKim). Without the coordinated effort of all of these individuals, this second edition would not have been possible.

If clinical medicine is to be understood in terms of our growing basic knowledge of biology, then pathophysiology must be a dynamic and changing field. We hope that this second edition of *Pathophysiology, The Biological Principles of Disease,* reflects that change and presents important knowledge to students and practicing physicians in a clear and usable form.

LLOYD H. SMITH, JR.

SAMUEL O. THIER

# PREFACE
## TO THE FIRST EDITION

By tradition, the practice of medicine is based on the personal qualities of the good physician. Each physician must discover these qualities for himself and within himself and each will attain and value them in different measure. Without compassion, dedication, equanimity, common sense, and the highest of ethical standards, no one can be a good physician. But these do not suffice. Compassion will not impede the logarithmic phase of bacterial growth; dedication will not diminish renal tubular reabsorption of sodium; equanimity is not sufficient as a response to cardiopulmonary arrest. The physician must apply, with skill and understanding, the most current medical science and technology of his time in the prevention, diagnosis, and treatment of disease. Medical science is merely a branch of applied biology, which is innately relevant, not antithetical, to the best in medical practice. The highest compassion may be that of making the right diagnosis. The complete physician is one who can synthesize both science and humanism within the traditions and ethical standards of the profession.

The biological sciences have grown enormously within the past generation. If the first half of the 20th century can be considered to have belonged to physics, the second half can equally be considered to belong to biology. New disciplines have evolved and have grown to maturity in this short time. In 1950, the structure of DNA was unknown and even its function was being debated despite the seminal work of Avery. Thirty years later, human genes are being sequenced, synthesized, and inserted into bacterial hosts by recombinant DNA technology. In 1950, the lymphocyte was a rather uninteresting small blue cell seen with Wright's stain of a blood smear, laboriously recorded in the differential count of leukocytes but otherwise relegated to obscurity. A generation later, the immune system has been revealed as an elaborate network for surveillance, communication, and defense, with circuits of specialized cells that secrete a variety of immune globulins and lymphokines. In endocrinology, the radioimmunoassay has allowed new orders of sensitivity and precision in measurement; the intricacies of hormone receptors, messengers, and cellular response have been considerably elucidated; new endocrine systems have been discovered (the prostaglandins, endorphins, the vitamin D system, calcitonin, somatomedins, and so on). Similar examples can readily be supplied within all of the biological sciences related to medical practice.

Each discipline is being investigated by scientists who have concentrated their scholarship on that particular sphere of biology. Intense scrutiny of a field is, of course, necessary for scientific progress. The science of medicine, however, has no such natural or contrived boundaries. It has a limitless scope that adds to its interest but makes more formidable the task of gaining and maintaining proficiency in it. Almost eight centuries ago, Alexander Neckam, Abbot of Cirencester, wrote an encyclopedia of current science entitled "The Nature of Things." He stated: "Science is acquired at great expense, by frequent vigils, by great expenditure of time, by sedulous diligence of labor, by vehement application of mind." This précis from a 13th century monastery is nowhere more pertinent than in the biological sciences applicable to medical practice. In the first two years in most medical schools in the United States, and with different packaging but similar effect in other countries, the student is assailed by scientific data that beat upon receptor mechanisms dangerously overloaded despite "sedulous diligence of labor." Within this brief period of time, the student is expected to master the scientific basis for a medical practice that may extend over four decades. Too often, also, the Henry Adams effect is at play: "Nothing in education is more pernicious than the amount of ignorance it accumulates in the form of inert facts."

Pathophysiology is a hybrid phrase that presumes a certain amount of hybrid vigor. It attempts to explain the biological basis of disease, making use of whatever scientific disciplines may be pertinent. Its goal is to integrate science in a rational analysis of a disease state. As such it can be broadly conceived as the ultimate scientific tool of the physician, who must see things whole rather than in separate compartments labeled anatomy, biochemistry, physiology, or pharmacology. This book attempts to integrate key aspects of the scientific basis of medical practice.

The editors asked Doctors George Palade and Marilyn Farquhar to introduce the book with a chapter on cell biology, a topic of basic importance in biology and one with which few physicians are now conversant. As the cell is composed of cytoplasm, organelles, supporting structures, and membranes, functional systems and organs are composed of specialized cells. Common to all nucleated cells is the transmission of genetic material and the potential for unregulated growth; these subjects are covered in chapters on genetics and oncology. Immunology encompasses one of the most rapidly expanding bodies of knowledge in medicine and has importance in pathologic processes affecting virtually every other organ system. Hematology, which overlaps with immunology, is then followed by chapters on most functional and organ systems—metabolism, endocrinology, connective tissue, nephrology, respiration, cardiovascular, neurology, gastroenterology, hepatology, and dermatology. We conclude with a chapter on clinical pharmacology, a subject critically dependent on an understanding of pathophysiology and one bridging the gap between mechanisms of disease and strategies of therapy. An understanding of basic disease mechanisms and clinical pharmacology, together with a knowledge of the clinical manifestations and natural history of disease, allows the development of a therapeutic strategy; the sum comprises the scientific basis of clinical medicine.

In each case the authors chosen are clinicians who both teach and utilize pathophysiology in medical practice. They were asked to describe within the space available the scientific basis of that system with which, in their opinion, the practicing physician should be conversant. For if, as John P. Peters said, "the disorders encountered in disease may be regarded as normal physiologic responses to unusual conditions," that scientific basis should be an essential need of the scholarly clinician.

LLOYD H. SMITH, JR.
SAMUEL O. THIER

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SECTION I

# CELL BIOLOGY

GEORGE E. PALADE, M.D.,
*and* MARILYN G. FARQUHAR, PH.D.

## Introduction

### THE STUDY OF CELL BIOLOGY IN PREPARATION FOR A CAREER IN MEDICINE

The human organism consists of a very large number of cells, perhaps $1 \times 10^{17}$, that belong to a wide variety of cell types, each differentiated so as to perform a specific function with utmost efficiency. Each of these cell types is the result of the preferential expression of those genes (of the common genome* of all cells) that relate to its specialized function. Cells of one or more types—together with their products—form tissues. And tissues—integrated according to specific patterns—form organs. The next steps, toward still more elaborate organization, are tracts or systems that consist of organs performing complex, highly integrated functions. The final step is the human organism itself. The whole organism could be viewed as a vast aggregate of myriads of cells living together, performing their functions, and interacting with one another without detectable perturbations as long as the organism is healthy. Diseases, irrespective of the level at which they manifest themselves—the whole organism, a system, a certain organ, or a specific tissue—originate in cells or affect cells. Hence, diseases are basically the result of cumulative cell malfunction.

In the present state of development of the life sciences, it is possible to investigate and eventually to understand disease processes in terms of what is already known about normal cell function. Moreover, in many cases investigations can be carried out on human tissues or cells cultured in vitro as an extension of clinical research done (or being done) on human patients. Cellular pathology is increasingly becoming the natural basis of medicine. The trend is rapid enough to be expected to affect a good part (if not all) of medicine during the future professional career of today's students.

### FUNDAMENTAL IMPORTANCE OF THE CELL IN BIOLOGY

*The cell is the structural and functional unit of all living matter.* This means that all living species are either single cells or orderly cell aggregates. Biologic organization can be regarded as a hierarchy of progressively more complex levels of structure that starts with simple molecules and ends with whole organisms. Within this hierarchy, the cell is the simplest level at which emerges the most important characteristic of living matter: the capacity for self-reproduction. In fact, the whole organization of the cell can best be explained in terms of this dominant propensity. In order to reproduce itself, the cell must replicate its genome and must transcribe and translate the information encoded in it so as to generate the molecules and macromolecules needed for all the structures of its duplicate. These operations require a continuous supply of metabolic energy and a carefully controlled environment. Specialized cell organs (or subcellular components) carry out each of these operations and satisfy each of these requirements.

### UNITY OF LIVING MATTER AT THE SUBCELLULAR AND CELLULAR LEVEL

Biochemistry has already established the general principle of unity of living matter at the molecular level. All living beings use essentially the same amino acids, the same nucleotides, and basically the same lipids and monosaccharides to build their specific macromolecules and to satisfy their metabolic needs. Their metabolic pathways follow the same steps or involve alternative reactions leading to similar products. Modern cell biology has taken the unity of living matter a few steps further. It has established the existence of two basic cell types, *prokaryotic* and *eukaryotic,* which (for the purpose of avoiding confusion) could be described as archetypes, and it has shown that the basic organization of all cells belonging to each archetype is essentially the same irrespective of taxonomy and cell differentiation. Since all cells possess the same kinds of macromolecular assemblies and subcellular components, the unity of living matter appears to extend—all the way up—to the cellular level of biologic organization.

#### THE ARCHETYPES

Bacteria and blue-green algae are prokaryotes; protozoa and the cells of all metazoa are eukaryotes, as are unicellular and multicellular plants. Eukaryotic cells are considerably larger than prokaryotes and

*Genome:* totality of the genes (hereditary determinants) of a cell, organism, or species.

generally have an elaborate system of intracellular membranes that defines a characteristic set of intracellular compartments. One of these compartments, *the nucleus,* is the residence of the genome, which is thus clearly separated from the rest of the cell—that is, *the cytoplasm*—through most of the cell's existence. The name eukaryote reflects this condition, since it means "properly nucleated." In prokaryotes the genome is not separated from the cytoplasm by any partition; thus these cells lack a distinct nucleus. Prokaryote means "prenucleated."

In medicine, prokaryotes are of importance primarily as pathogens. Our concern is this chapter is with the eukaryotic cells of the human organism. Given the unity of organization already mentioned, it should not be surprising that human cells are very similar to the cells of other mammals and vertebrates. Differences from one differentiated cell type to another within the same species are relatively large and easily recognizable; but differences from one species to another are generally small when the same types of differentiated cells are considered.

# General Organization of the Eukaryotic Cell

## SIZE AND SHAPE

Although ~1000 times larger than prokaryotes, eukaryotic cells are small objects, usually smaller than the limit of resolution of the human eye—that is, smaller than 0.1 mm, or 100 μm. In their vast majority, they have diameters—or sides—of 10 to 30 μm; this fact explains why research in cell biology depends heavily on magnifying instruments—that is, light and electron microscopes. There are, however, a few notable or even striking exceptions: the human oocyte is ~ 100 μm in diameter, and the main body of many nerve cells is of comparable size; moreover, some nerve cells have processes that extend over centimeters or meters.

The shape of the cells varies with their habitat: they are prismatic when closely packed; spherical or glob-

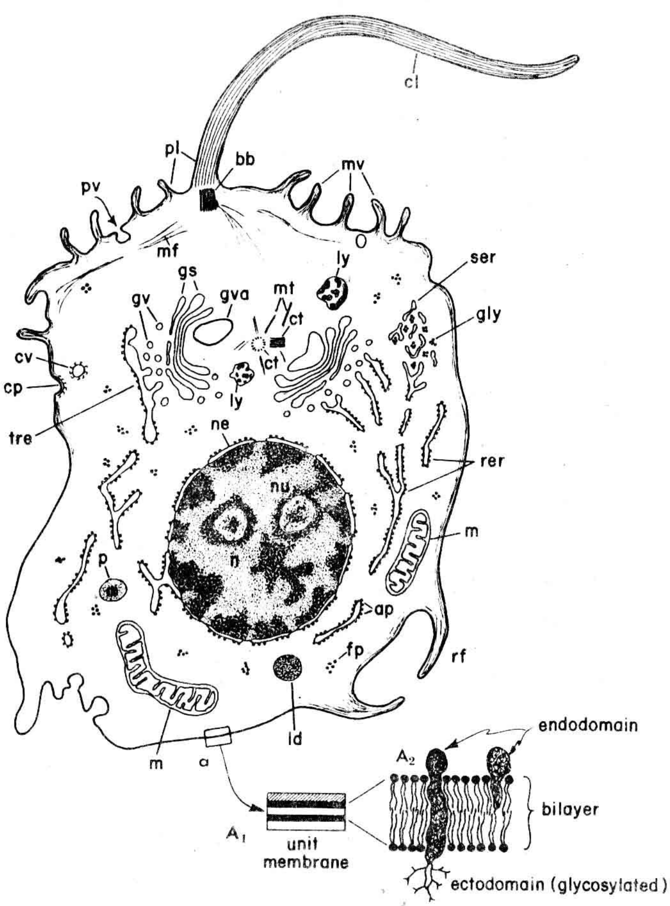


**Figure 1.** Diagram of a median section through an animal eukaryotic cell as seen at a magnification of ~10,000 ×.

n, nucleus; nu, nucleolus; ne, nuclear envelope; rer, rough endoplasmic reticulum; ser, smooth endoplasmic reticulum; tre, transitional element; gv, Golgi vesicles; gs, Golgi stacked cisternae; gva, Golgi vacuoles; ly, lysosome; fp, free polysome; ap, attached polysomes; ct, centriole; mt, microtubules; mf, microfilaments (in bundles); pl, plasmalemma; pv, plasmalemmal vesicle; cp, coated pit; cv, coated vesicle; rf, ruffle (lamellar pseudopodium); mv, microvilli; cl, cilium; bb, basal body; m, mitochondrion; p, peroxisome; ld, lipid droplet; gly, glycogen.

The rectangle marked a is further magnified (to ~100,000 ×) at $A_1$ to show the unit membrane structure of the plasmalemma. The diagram at $A_2$ gives the position of a transmembrane protein, of a protein buried half way in the bilayer, and of the head groups and fatty acyl chains of the phospholipids within the unit membrane at a magnification of ~500,000 ×.