PATHOPHYSIOLOGY

Clinical Concepts of Disease Processes

SECOND EDITION

Sylvia Anderson Price, R.N., Ph.D.
Lorraine McCarty Wilson, R.N., B.S., M.S.

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List of Contributors

Gerald D. Abrams, M.D.
Professor of Pathology
Department of Pathology
The University of Michigan
Medical School
Ann Arbor, Michigan

Catherine M. Baldy, R.N., M.S.
Clinical Nurse Specialist in Hematology
Henry Ford Hospital
Detroit, Michigan

Jeffrey P. Callen, M.D.
Assistant Clinical Professor of Medicine (Dermatology)
University of Louisville
School of Medicine
Louisville, Kentucky

Daniel J. Fall, M.D.
Clinical Associate Professor of Internal Medicine
The University of Michigan
Ann Arbor, Michigan

Penny J. Ford, R.N., M.S.
Cardiovascular Clinical Nurse Specialist
Massachusetts General Hospital
Boston, Massachusetts

Cathy Szczesny-Idema, B.S.N., M.P.H.
Associate Director of Ambulatory Care Nursing
Metropolitan Hospital
New York, New York

Marie Trava King, R.N., B.S.N., M.S.N.
Assistant Professor of Nursing
Indiana University
Bloomington, Indiana

Mary Carter Lombardo, R.N., B.S.N., M.S.N.
Assistant Professor of Nursing
Howard Community College
Columbia, Maryland

Larry S. Matthews, M.D.
Associate Professor of Surgery
Section of Orthopaedic Surgery
The University of Michigan
Medical School
Ann Arbor, Michigan

Sylvia Anderson Price, R.N., Ph.D.
Assistant Professor of Nursing
Former coordinator of pathophysiology course
The University of Michigan
Ann Arbor, Michigan

David E. Schteingart, M.D.
Professor of Internal Medicine
The University of Michigan
Medical School
Ann Arbor, Michigan

William R. Solomon, M.D.
Associate Professor of Internal Medicine
The University of Michigan
Medical School
Ann Arbor, Michigan

Marek A. Stawiski, M.D.
Clinical Assistant Professor of Dermatology and Postgraduate Medicine
The University of Michigan
Ann Arbor, Michigan
Clinical Assistant Professor of Internal Medicine
Michigan State University
East Lansing, Michigan

Lorraine McCarty Wilson, R.N., B.S., M.S.
Ph.D. Candidate at Wayne State University
Former coordinator of pathophysiology course
The University of Michigan
Ann Arbor, Michigan

Preface to the Second Edition

The second edition of *Pathophysiology: Clinical Concepts of Disease Processes* retains the same philosophy and organization as the first edition, which has been very well received. Our focus is on alterations in biological processes which affect the body's dynamic equilibrium or homeostasis, a conceptual approach that is designed to integrate knowledge from the basic and clinical sciences. This edition incorporates many minor and a few major changes suggested by faculty, students, and others who have used the textbook.

Major additions include Part XII, "Dermatology," with seven chapters and over eighty illustrations, and a new chapter in Part IX on disorders of the reproductive cycle. Part III, "Hematologic disorders," has been rewritten and made more comprehensive. The introductory chapter of Part VIII, on selected topics in neuroanatomy, has been rewritten to provide a more adequate background for the understanding of neurological disorders. This chapter now has ninety-five new review questions for self-testing on the content. Further additions in Part VIII discuss the pathogenic mechanisms involved in headaches and herniated discs.

Other representative changes include the updating of information on cardiac electrophysiology, ventricular function, mechanisms of premature beats, pathophysiology of rheumatic fever, post-myocardial infarction, enzyme changes, and refractory angina. The sections dealing with neoplasia, hypertension, hyperlipidemia, and congestive heart failure have been greatly expanded. There is new material on pulmonary function testing, the staging of lung cancer, and tuberculosis. The middle molecular hypothesis is discussed in relation to the pathophysiology of uremia. Some recent experimental methods of solute removal in renal failure are also discussed.

Throughout this edition, the authors have incorporated recent research findings and current treatment principles. References have been brought up to date and selected passages have been rewritten for greater clarity. Many illustrations have been replaced and over 100 new ones have been added. There are over 200 new end-of-chapter questions.

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Sylvia Anderson Price
Lorraine McCarty Wilson

Contents

PART V CARDIOVASCULAR PATHOPHYSIOLOGY
Penny J. Ford

PART VI RESPIRATORY PATHOPHYSIOLOGY
Lorraine M. Wilson and Sylvia A. Price

PART VII RENAL PATHOPHYSIOLOGY
Lorraine M. Wilson

PART VIII NEUROLOGIC DISORDERS
Marie Trava King and Mary Carter Lombardo

PART IX ENDOCRINOLOGY AND METABOLISM. PRINCIPLES OF PATHOPHYSIOLOGY, CLINICAL PRESENTATION AND MANAGEMENT OF SELECTED CLINICAL DISORDERS
David E. Schteingart

Preface to the First Edition

Human pathophysiology is the science that focuses on the illnesses of humans. It is the study of disease, or "lack of ease." *Disease* refers to a state characterized by certain alterations in the body; alterations that presumably involve structure even though that structure may be microscopic. However, disease should not be regarded as a static state. Disease itself is a dynamic process. It is an abnormal form of life. Disease may be acute or insidious in its onset, variable in its duration, and it results in either the recovery (partial or complete) or death of the person.

Pathophysiology emphasizes the *dynamic* aspects of disease. It is concerned with the disruption of normal physiology; with the alterations, derangements, and mechanisms involved in disruption and how they manifest themselves as signs, symptoms, physical, and laboratory findings. Pathophysiology provides the basic link between the sciences of anatomy, physiology, and biochemistry and its application to clinical practice. The study of pathophysiology is essential to understanding the rationale for medical and surgical therapy.

In preparing this text on pathophysiology for health professionals, we are aware that the rapid accumulation of knowledge in the biomedical sciences poses a problem not only for the student but for the practitioner as well. The student must master clinically significant facts and must be prepared to continue learning as a practitioner. The role of the practitioner in the health care delivery system is also changing. Nurses and other health professionals are working more independently and they are assuming a more collaborative role with other practitioners. It is important for these practitioners to understand why certain manifestations of disease occur and why specific therapeutic regimens are prescribed. Therefore, we designed this book to meet the above objectives.

The uniqueness of this book is that the subject is presented in a self-instructional format. Objectives have been given for each part and chapter. These objectives focus the student's attention on the important concepts in the subject. Conceptual material is followed by questions and answers on the content presented. The answers give the student additional insight. This self-instructional method enables the student to actively participate in the learning process through reading, reasoning, and demonstrating in writing his or her mastery of the concepts. Active participation in the learning process is enhanced by this approach which also requires the student to apply concepts and not to merely memorize factual material. The authors believe that this method enables one to achieve maximum understanding of the subject material. In addition, the pace may be one that the student finds most comfortable.

Since numerous subject areas are involved, we have incorporated selected areas into what is referred to as "core" content. Our selection is based on areas where we feel in-depth coverage of the subject is deficient.

The subject is presented in the following fashion. First, the general concepts of disease are discussed. Additional parts examine the various disorders of an organ or organ system. Emphasis is placed on understanding the roots of a given disorder, which is an essential factor in the development of insight. For example, consider diseases of the kidney. The student who thoroughly understands the nephron, which is the fundamental work unit of the kidney, is better able to predict what diseases will occur when certain pathophysiological processes involve the kidney. That student will understand the basis for such diseases as pyelonephritis, glomerulonephritis, and the nephroses. Also, the student will understand the symptomatology and the rationale for the treatment.

In attempting to provide a text for the sophisticated learning needs of today's health professionals, the material is discussed in greater depth than is found in similar pathophysiology texts. In order to reduce the subject matter to manageable dimensions, the authors have focused on relevant concepts that are applicable to optimum practices of modern health care delivery.

PART I Introduction to General Pathology: Mechanisms of Disease

GERALD D. ABRAMS

The intent of Part I of the text is to provide the reader with the background necessary for the understanding of the many different diseases to which human beings fall victim. The number of specific human diseases is immense, and the variety is great, given the fact that no organ or organ system within the body is exempt from disease. However, the basic ways in which an organ can become diseased are quite limited, and the large and bewildering array of diseases actually represents different combinations and permutations of a smaller number of basic biological processes leading to the alterations of structure and function that are recognized clinically. It is on these basic biological processes that this first section will be focused.

The study of such basic disease processes is usually called *general pathology*. Pathology is the science or study of disease. In its broadest sense, pathology is literally abnormal biology, the study of sick or disordered life. As a basic biological science, the study of pathology includes such fields as plant pathology, insect pathology, and veterinary and comparative pathology, as well as human pathology, which is the major focus of this text.

Pathology, in the context of human medicine, is not only a basic or theoretical science but also a clinical medical specialty. Pathologists are specialists in laboratory medicine, providing a consultative service to other physicians, thereby assisting in the diagnosis and treatment of disease. The scope of laboratory medicine is such as to include all of the many types of studies performed on samples derived from patients, including samples of tissue, blood, and other body fluids. Some laboratory studies which fall under the general heading of "anatomic pathology" involve the study and assessment of morphologic alterations in cells and tissues. Surgical pathology, exfoliative cytology, and autopsy pathology are included in this division. Many types of studies are done by other than morphologic means, and these areas of "clinical pathology" include such things as clinical chemistry, microbiology, hematology, immunology, and immunohematology.

In this part the specifics of individual diseases will not be discussed. However, fundamental disease processes, such as inflammation, neoplasia, and immunologic injury, will be described. Following the elucidation of these fundamental processes, the details of specific illnesses will be addressed in later parts of the text.

OBJECTIVES

At the end of Part I you should be able to:

1 Describe the essential features of basic disease processes including the body's reactions to injury and infection, the immune response, disturbances of circulation, and abnormalities of cellular growth.

2 Interpret the natural history and clinical manifestations of specific illnesses in terms of their etiology and pathogenesis.

CHAPTER 1 General Concepts of Disease—Health vs. Disease

OBJECTIVES **At the completion of Chap. 1 you should be able to:**

1 Define *pathology*.

2 Distinguish between anatomic and clinical pathology.

3 Explain the concept of normalcy.

4 Describe the essential components involved in the disease process.

5 Differentiate between etiology and pathogenesis in relation to disease.

6 Identify and use the following terms when describing the manifestations of a disease: symptom, sign, lesion, sequel, complication.

CONCEPT OF NORMALCY

In terms of their personal experiences, most people have some notion of what it is to be "normal" and would define disease or illness in terms of deviation from or absence of that normal state. However, on closer scrutiny, the concept of normalcy turns out to be a complex one which cannot be defined succinctly; and correspondingly, the concept of disease is far from simple.

Selecting any parameter of measurement which might be applied to an individual or group of individuals, we define *normal* as some sort of average value for that parameter. Thus, average values for parameters such as height, weight, and blood pressure are derived from observations on many individuals. Implicitly, a certain amount of variation from the average is accepted as being permissible or normal. Thus, the usual concept of normalcy involves both an average value and some range of variation either above or below that value.

Variation in normal values actually stems from several different sources. First, it is recognized that individuals differ from one another because of differences in their genetic makeup. Thus, no two individuals in the world, except for those derived from the same fertilized ovum, have exactly the same genes. Then, there is variation related to the fact that individuals differ in their life experiences and in their interaction with the environment. Third, even in a single individual, many physiologic parameters vary because of the way in which the control mechanisms of the body function. For instance, measurement of blood glucose concentrations in a healthy person would reveal significant variations at different times during the day, depending upon food intake, activities of the individual, and so forth. These variations would generally occur within a certain range. The situation is somewhat analogous to a room with thermostatically controlled temperature which may dip slightly below the desired or ideal level before such a drop is sensed by the thermostat. The corrective action then triggered by the thermostat may, in turn, overshoot the ideal slightly before the heat input is halted. Indeed such variations in body temperature, even in the normal state, do occur in all individuals. Finally, for those physiologic parameters that must be measured by fairly intricate means, a significant amount of variation in observed values may be derived from error or imprecision inherent in the measurement process itself.

Because of the above considerations, establishing limits on this "normal" range of variation from an average value is a matter of some complexity. This complexity relates to such things as knowing the degree of physiologic oscillation of a particular measurement, accounting for the degree of variation among normal individuals even under baseline conditions, and figuring the precision of the measurement method. Then, finally, the biological significance of the measurement must be estimated. It is thus evident that single measurements, observations, or laboratory results which seem to be indicative of abnormality must always be judged in the context of the entire individual. A single reading of elevated blood pressure does not make an individual hypertensive; a single slightly elevated blood glucose level does not relegate an individual to the category of diabetic; and a single hemoglobin value lower than average does not necessarily indicate anemia.

Finally, to place all of the above considerations in perspective, it should be noted that concepts of normalcy and even disease are, to an extent, arbitrary and are influenced by cultural values as well as by biological realities. For example, in our culture, a defect of central nervous system function manifesting itself as a significant reading disability would be labeled as an abnormality, whereas the same defect might never be noted in a primitive culture. Furthermore, a trait which might be average and thus normal in one population might be considered distinctly abnormal in another. Consider, for instance, how a "normal" person from our population would be viewed by a group of central African pygmies; or conversely, how an infant from a primitive culture, with the "normal" chronic diarrhea and poor weight gain might be viewed in one of our well-baby clinics!

CONCEPT OF DISEASE

Bearing in mind the many nuances in the concept of normalcy, *disease* can be defined as a form of life beyond the limits of normal. The most useful yardstick of these limits of normal relates to the ability of the individual to meet the demands placed on the body, to adapt to these demands or changes in the external environment in order to maintain reasonable constancy of the internal environment. All cells in the body need a certain amount of oxygen and nutrients for their continuing survival and function and also require an environment which affords such things as narrow ranges of temperature, water content, acidity, and salt concentration. Thus, the maintenance of internal constancy is an essential feature of the normal body. When some of the structures and functions of the body deviate from the norm to the point that this constancy is destroyed or threatened or that the individual can no longer meet environmental challenges, disease is said to exist.

Another important element in the concept of disease is the recognition that disease does not involve the development of a completely new form of life but rather is an extension or distortion of the normal life processes that are present in the individual. Even in the case of an obviously infectious disease, where the body is literally invaded, the infectious agent itself does not constitute the disease but only serves to evoke the changes in the subject that ultimately are manifested as disease. Thus, disease is actually the sum of the physiological processes which have been distorted. In order to understand and adequately treat the disease one must take into account the identity of the normal processes interfered with, the character of the disturbances, and the secondary effects of such disturbances on other vital processes.

An alternative view of disease, certainly not unknown in history, holds that disease is actually a new form of life, a sort of possession of the body by an outside agent. From this notion it would follow that some form of exorcism, which is directed at driving out that agent, is proper therapy of disease. However, even in the instance of an invasive infectious agent, attempted treatment with antibiotics alone may not be sufficient to cure the patient if proper attention is not directed toward the intrinsic bodily processes.

A theme that will recur, with variations, throughout this volume is that disease above all is part and parcel of the patient. *Normal and abnormal processes represent different points on the same continuous spectrum.* In fact, very often the seeds of disease actually lie within the adaptive machinery of the body itself, machinery which constitutes a potential two-edged sword. For instance, the very same machinery which allows us to become immune to certain infections evokes reactions such as hay fever and asthma when some of us are challenged by particular environmental agents. Similarly, the machinery of cellular proliferation that allows us to repair wounds and constantly to renew cell populations in various tissues may run amok, giving rise to cancer.

THE DEVELOPMENT OF DISEASE

Etiology

Etiology, in its most general definition, is the assignment of causes or reasons for phenomena. A description of the etiology of a disease includes the identification of those causal factors that acting in concert provoke the particular disease. Thus, the tubercle bacillus is designated as the etiologic agent of tuberculosis. Other etiologic factors in the development of tuberculosis which influence the course of the infection include the age, nutritional status, and even the occupation of the individual. It is sufficiently important to mention again that even in the case of an infectious disease such as tuberculosis the agent itself does not constitute the disease. Rather, the resultant of all the responses to that agent, all the perversions of biological processes taken together constitute the disease. In the etiology of a particular disease then, a range of extrinsic or exogenous factors in the environment must be considered along with a variety of intrinsic or endogenous characteristics of the host.

Pathogenesis

Pathogenesis of a disease refers to the development or evolution of the disease. To continue with the above example, a description of the pathogenesis of tuberculosis would indicate the mechanisms whereby the invasion of the body by the tubercle bacillus ultimately leads to the observed abnormalities.

Such an analysis of pathogenesis would relate the proliferation and spread of tubercle bacilli to the evolving inflammatory responses, to the immunologic defenses of the host, and to the actual destruction of cells and tissues. The pattern and extent of the tissue damage would ultimately be related to the overt manifestations of clinical disease. The study of pathogenesis also takes into account the sequential occurrence of certain phenomena and the temporal aspects of the evolving disease. Implicit in this approach is the notion that a given disease is not a static affair, but rather a dynamic phenomenon with a rhythm and natural history of its own.

When considering the totality of human disease, the number of etiologic factors and the number of separately named diseases seem to be endless. However, even though there are many different diseases with unique natural histories, the situation is not as difficult as indicated by sheer numbers. The response mechanisms of the body are finite. Therefore, disease A differs from disease B because it varies somewhat in terms of this or that pathogenetic mechanism being exaggerated. Thus, the understanding of a manageable number of pathogenetic mechanisms and their evolution permits understanding of a very large number of seemingly different diseases.

Manifestations of disease

Early in the development of a disease, the etiologic agent or agents may provoke a number of changes in biological processes which can be detected by laboratory analysis even though there is no recognition by the patient that these changes have occurred. Thus, many diseases have a *subclinical stage* during which the patient functions normally even though the disease processes are well established. It is important to understand that the structure and function of many organs provide a large reserve or safety margin, so that functional impairment may become evident only when disease has become quite advanced anatomically. For example, chronic renal disease could completely destroy one kidney and partly destroy the other before any symptoms related to decreased renal function would be perceived. Conversely, it is important to recognize that some diseases seem to begin as functional derangements and actually reach the clinical horizon although no anatomic abnormalities can be detected at the time. Such functional illnesses may lead ultimately to secondary structural abnormalities.

As certain biological processes are encroached upon, the patient begins to feel subjectively that something is wrong. These subjective feelings are termed *symptoms* of disease. By definition, symptoms are subjective and can only be reported by the patient to an observer. When, however, the manifestations of the disease involve objectively identifiable aberrations, these are termed *signs* of the disease. Nausea, malaise, and pain are symptoms, while fever, reddening of the skin, and a palpable mass are signs of disease. A demonstrable structural change produced in the course of a disease is referred to as a *lesion*. Lesions may be evident at a gross and/or a microscopic level. The outcome of a disease is sometimes referred to as a *sequel* (plural, *sequelae*). For example, the sequel to an inflammatory process in a given tissue might be a scar in that tissue. The sequel to acute rheumatic inflammation of the heart might be scarred, deformed cardiac valves. A *complication* of disease is a new or separate process that may arise secondarily because of some change produced by the original entity. For example, bacterial pneumonia may be a complication of viral infection of the respiratory tract. Fortunately, many diseases can also undergo what is termed *resolution*, and the host returns to a completely normal state, without sequelae or complications. Resolution can occur spontaneously, i.e., owing to bodily defenses, or can be a result of successful therapy.

Finally, it is essential to reemphasize that disease is dynamic rather than static. The manifestations of disease in a given patient may change from day to day as biologic equilibriums shift and as compensatory mechanisms are brought into play. Environmental influences that are brought to bear upon the patient will also affect the disease. Therefore, every disease has a *range* of manifestations and a *spectrum* of expressions which may vary from patient to patient.

QUESTIONS

General concepts of disease—health vs. disease—Chap. 1

Directions: Answer the following questions on a separate sheet of paper.

1 Define pathology.

2 What is the difference between anatomic and clinical pathology? List at least three examples of types of studies included under each of these divisions.

3 What is the difference between etiology and pathogenesis?

4 Explain the concept of normalcy.

Directions: Circle the letter preceding each item below that correctly answers each question. More than one answer may be correct.

5 In the course of a disease process, a demonstrable structural change which is produced is termed a:
a Symptom *b* Sign *c* Lesion *d* Sequel
e Complication

6 Which of the following would be considered symptoms?
a Edema *b* Pallor *c* Cyanosis *d* Headaches

CHAPTER 2 Heredity, Environment, and Disease; Interaction of Heredity and Environment

OBJECTIVES **At the completion of Chap. 2 you should be able to:**

1 Differentiate between extrinsic and intrinsic factors in relation to the disease process.

2 Describe the importance of hereditary factors in disease.

3 Describe how DNA is involved in programming the function of cells.

4 Explain what occurs with regard to DNA and chromosomes during the process of cell division, distinguishing between mitosis and meiosis.

5 Describe the process of differentiation.

6 Explain the process by which genes control the development of a particular trait.

7 Define *mutation.*

8 Differentiate between dominant and recessive characters.

9 Explain the ways in which chromosomal abnormalities can develop.

10 Describe the importance of karyotypic anomalies.

11 Identify the way in which genetic abnormalities may be expressed as disease.

12 Discuss the purposes of genetic counseling.

EXTRINSIC FACTORS IN DISEASE

If one were asked to list some of the important causes of human disease, such things as infectious agents, mechanical trauma, toxic chemicals, radiation, extremes of temperature, nutritional problems, and even psychological stress would likely be mentioned. All of these, along with many others usually placed on such a list, actually represent variations in the environment which can produce disease when brought to bear upon the subject. Certainly it is true that such *extrinsic factors* are exceedingly important causes of human misery, and attention is directed to them in an attempt to prevent and alleviate disease. However, since disease is actually part of the life of the afflicted individual—the sum of the physiological processes which have been distorted—a view of disease causation that takes into account only extrinsic factors is necessarily incomplete. The intrinsic biological processes must also be taken into consideration.

INTRINSIC FACTORS IN DISEASE

Many characteristics of the individual host must be considered as *intrinsic factors* in disease, inasmuch as they will have significant impact on the evolution of various conditions. Age, sex, and even abnormalities acquired in the course of previous illnesses are factors that need to be considered in the pathogenesis of a disease. Above all, the genetic constitution or genome of the individual is an essential part of the "equation." This is true because the anatomic characteristics of the host, the myriad of physiological mechanisms of everyday life, and the modes of responding to injury are all determined by the genetic information assembled at the moment of conception of the individual. A more familiar way of stating this principle is that in studying the biology of disease one must always take into account both heredity and environment.

Interaction of extrinsic and intrinsic factors—a spectrum

We often hear the question, "Is this disease hereditary?" In a sense, that question is improper. Recognizing that heredity is almost always vitally important, the question should be phrased, "To what extent is heredity important in this disease?" The exceptions to this principle are relatively few and quite extreme. Admittedly, heredity plays no real role in determining the outcome when one is involved in an explosion or struck by a speeding truck; but, such instances aside, it is always a factor. Even in an exogenous infectious disease, it is clear that genetic factors can influence susceptibility to the infectious agent and also the pattern of disease produced by that agent.

With regard to the relative balance of heredity and environment in the causation of disease, there exists a broad spectrum. At one end of the spectrum are those diseases which are largely determined by some environmental agent irrespective of the individual's hereditary background, while at the other end are those diseases which represent faulty heredity, that is, faulty genetic programming of the body's machinery. These latter diseases include those usually identified as *hereditary diseases*, diseases which are expressed in almost any bearer of the faulty genetic information regardless of extrinsic influences. Between these two ends of the spectrum most human diseases occur and involve a significant interplay between genetic and extrinsic factors. A brief commentary on heredity and an exploration of some of the ways that inherited abnormality can be expressed would be instructive at this point.

THE NATURE OF THE GENOME

The "stuff" of heredity

Deoxyribonucleic acid, or DNA, is the chemical material which is responsible for storing, duplicating, and transmitting literally all of the information needed for programming the function of a given single cell and even of an entire individual. There is an endless variety of ways that the chemical building blocks of DNA can be assembled, so that there are virtually limitless numbers of different kinds of DNA. A given particle of DNA may "instruct" a cell to produce a specific chemical product. To do this, the DNA "tells" the cell what raw materials to select from the passing circulatory stream and how to assemble them into the desired product. Similarly, other kinds of DNA can instruct cells to develop certain kinds of structures. Ultimately it is the DNA that determines exactly how the billions of cells which make up the body are assembled, and, in fact, whether the individual will be a dog, a cat, or a human. Portions of the DNA also determine the limits of the individual's stature, the facial features, and a multitude of traits and processes that characterize the individual. Some DNA is even used to control other DNA, by instructing the cell when to "switch on" and use some portion of the DNA information stored in it. Finally, DNA molecules can instruct the cell to make exact duplicates of themselves when the cell is about to divide, ensuring that the genetic information is passed on appropriately to the two daughter cells.

In a nondividing cell, the DNA is found almost entirely within the nucleus. Even with the microscope, individual DNA molecules cannot be seen as distinct structures but only as part of ill-defined, deeply staining material within the nucleus (Fig. 2-1). As the cell begins to divide, the material in the nucleus arranges itself into strands called *chromosomes* (Fig. 2-2). The cells of the human body generally contain 46 chromosomes, or 23 pairs each (22 pairs of autosomes plus 1 pair of sex chromosomes). During the process of cell division the DNA is duplicated, and there is splitting of each chromosome and then a separation of the newly formed structures, so that identically endowed daughter cells are formed. By means of this form of cell division, termed *mitosis*, beginning with the fertilized ovum, identical genetic information is passed to every somatic or non-

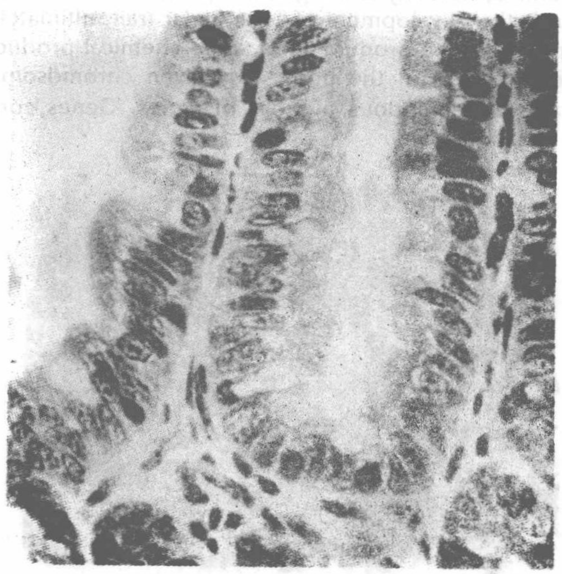

***FIGURE 2-1** Nuclei of nondividing cells. The ovoid nuclei of these intestinal lining cells are arranged in regular rows. The DNA that controls the cells is within these nuclei, forming part of the deeply stained material called chromatin. (Photomicrograph, ×800.)*