BASIC PATHOLOGY

THIRD EDITION

ROBBINS
ANGELL
KUMAR

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STANLEY L. ROBBINS, M.D.

Visiting Professor of Pathology,
Harvard Medical School;
Senior Pathologist, Brigham and
Women's Hospital, Boston, Massachusetts

MARCIA ANGELL, M.D.

Deputy Editor, New England Journal
of Medicine, Boston, Massachusetts

VINAY KUMAR, M.D.

Associate Professor of Pathology,
University of Texas Southwestern
Medical School, Dallas, Texas

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Preface to the Third Edition

It is a pleasure to write this preface for the third edition of *Basic Pathology*, only in part because it marks the completion of a long and arduous labor. The warm acceptance of its two progenitors confirmed our view that there was a need for a "thin" book in pathology. We are therefore especially pleased that we were successful in maintaining the slim figure of the previous editions, despite the continually expanding body of knowledge. To achieve this goal, it was necessary to make difficult judgments on nearly every page as to what to include, what to leave out, and, more important, how best to present the material in a communicative fashion while maintaining brevity. Since we are convinced that learning is maximal when the text is readable, a strong effort was made to avoid both a telegraphic presentation and a "telephone book" compilation of facts. Rare diseases have necessarily been omitted and many uncommon ones have been treated only very briefly. This has permitted us to discuss the important disorders in some detail, so that students can gain a reasonably full understanding of the diseases frequently encountered in usual clinical practice. These judgments were necessary, with the ever-increasing demands on a student's time, if the book was to retain its usefulness to medical and dental students, as well as to nurses and paramedical personnel.

We can say with assurance that keeping the third edition svelte does not reflect a timid rewrite of the second edition. More than half the book is entirely new. Many chapters, e.g., Genetic Diseases and Disorders of Immunity, have been completely reorganized and rewritten; the order of chapters has been changed, and a separate chapter on Nutritional Disorders has been added. Certainly each line of the previous edition has been evaluated before being retained or discarded. We have elected to reorganize the chapters on diseases of organs and systems by presenting the various disorders according to structure rather than within clinical categories based on major presenting signs and symptoms. This approach, we now believe, provides better opportunity for comparison of morphologically similar derangements and permits the bringing together of disorders that have similar causes. Nonetheless, the discussions retain a strong clinical orientation because ultimately the importance of pathologic lesions lies in their impact on the patient.

Despite the changes, the basic concepts of earlier editions have been preserved. The first portion of the book covers general principles and mechanisms of disease, as well as its terminology. As before, emphasis has been placed on the causation and pathogenesis of pathologic processes. We believe that only within this context can the evolution of illness be understood. Much attention has been given to the relationships between morphologic and functional changes, to the origins of signs and symptoms and to their clinical significance. Since biochemical, metabolic and ultrastructural

changes antedate and underlie the development of gross and microscopic morphologic changes, these areas have been detailed to the extent that they are understood and relevant. Where gaps in our knowledge exist, as they do in virtually every area, these too have been flagged in order to indicate the current state of the art.

The second half of the book deals with individual diseases of the various organs and systems of the body. While the presentation is by no means encyclopedic, it covers the great burden of diseases encountered in clinical practice. Within reasonable limits, the space accorded to the various disorders is proportional to their frequency.

Our goal has been to convey as simply and directly as possible the basic body of knowledge in pathology, along with clinical correlations and what is known about the origins of the various diseases. We hope we have succeeded in achieving this goal and in a manner that is both effective and enjoyable.

Stanley L. Robbins
Marcia Angell
Vinay Kumar

Acknowledgments

Few tasks are more enjoyable than acknowledging our gratitude to all those who have helped in this effort in so many ways. Foremost among these is our editorial assistant, Laura Duffy, who not only typed and retyped and retyped much of the manuscript, but also helped in the library research, edited the manuscript, reviewed the proofs and, more important, kept in order the reams of notes, references and text that accumulate during the preparation of a book. Her commitment went far beyond duty; it was a labor of love for which we are indeed grateful. We would like to acknowledge the staff at the Boston University Medical School library, specifically Chris Bell and Sandy Worley, for their freely offered help. Thanks are also due to Mary Carol Barnes for lending a secretarial hand during periods of need. We are also grateful to Mrs. Lucy Ruiter, administrator. She struggled valiantly to keep the calendar of one of the authors (SLR) free of unnecessary intrusions, thus making time available for work on the book.

It has long been our practice to ask students to criticize the manuscript in preparation; they are in the best position to judge what is helpful for their learning. Serving in this capacity were Mark Farb, Liane Hartnett, Harvey Kaufman, John Lust, David Oshin and Debbie Poutsiaka, to all of whom we extend our appreciation for their insightful and helpful criticisms and suggestions. Professional colleagues and friends—Drs. Michael Bennett, Ramzi Cotran, Phillip Gordon, Christian Haudenschild, Ray Koff, Richard Neiman and Hugues Ryser—have enhanced the book by valued suggestions and, in some cases, by contributing photographs from their personal collections or publications. We also thank our various professional colleagues who supplied illustrations and tables. Dr. Michael Bennett in particular made possible the continuation of the research of one of us (VK) by his generous encouragement and support.

Not to be overlooked is our publisher, the W. B. Saunders Company, and in particular, certain individuals there with whom we have worked very closely. The entire organization, headed by its President, Mr. Jack Hanley, must first be cited for its continued high standards of excellence and for its patient and indeed freely offered compliance with our foibles and changing demands. Nothing that would improve quality was ever challenged, nor was any request ever denied. Shepherd and guardian angel of this edition was Roberta Kangilaski, Medical Editor. It is hard for us at a distance to believe that Roberta had any other duties; she seemed to devote all of her time and loving care to this text and to its authors, and always with warmth and encouragement. To Catherine Fix, Copy Editor; Herbert Powell, Jr., General Production Manager; and Eugene Hoguet, Vice President, Manufacturing, our grateful thanks for jobs well done.

We owe more than a debt of gratitude to our families. Their patient acceptance of our work schedules and, indeed, their encouragement, made possible the many hours devoted to the book and did much to assuage our feelings of guilt about the time not spent with them.

VK wishes especially to express his gratitude to his wife, Raminder. She not only

was a constant source of encouragement but she also willingly gave up every moment of her free time to tend to the family singlehandedly and to fulfill her own professional responsibilities. He is also very grateful to his 6-year-old son, Rohit, who made himself believe that "Daddy's book was more important than playing chess."

Finally, the two senior authors wish to welcome publicly Dr. Vinay Kumar, who joined the team with this edition. Not only was he an unfailingly congenial co-worker, but in addition his fund of knowledge and dedication to the book have greatly added to its worth.

S.L.R.
M.A.
V.K.

Contents

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Disease at the Cellular Level

Begging the forgiveness of the clergy and the poets let us begin this consideration of pathology with the observation that man is basically a complex aggregation of highly specialized cells. The health of the individual has its origin in healthy cells. Disease, on the other hand, reflects dysfunction of a significant number of cells. It is necessary then to begin our consideration of pathology with an examination of disease at the cellular and, indeed, subcellular levels.

The normal cell is a restless, pulsating microcosm constantly modifying its structure and function in response to changing demands and stresses. Until these stresses become too severe, the cell tends to maintain a relatively narrow range of structure and function, designated as "normal." Thus, normal homeostasis is a fluid rather than a static, rigid state. Just as the individual must adapt to the constantly changing demands and stresses of life, so must the cell. Within limits, cellular adaptation achieves an altered but steady state, preserving the health of the cell despite continued stress. However, if the limits of adaptive capability are exceeded, injury or even cell death results. In response to progressive levels of stress, then, the cell may (1) adapt, (2) be reversibly injured or (3) die. We can draw an analogy to a stately tree exposed to a wind storm. Up to a point the tree bends and yields to the stresses of the wind forces but rapidly resumes its erectness when the stresses abate. The windswept conformation of the tree on the shoreline is a beautiful example of an adaptive, altered, but steady state permitting continued survival and growth. More severe wind may break branches and strip leaves, but such injury is compatible with recovery and survival. A hurricane, however, may be more than the tree can withstand and leave it an uprooted victim of stresses too great for survival.

The normal cell, the adapted cell, the injured cell and the dead cell are hazily delimited states along a continuum of function and structure. In response to moderate stress the cell might pass through a succession of stages of adaptation and injury, only to die eventually. More severe stress might induce direct injury and, of course, intense injury might kill immediately. One cannot assume that all stressed or injured cells pass through every stage of reaction. Whether a specific form of stress induces adaptation, injury or cell death depends not only on the nature and severity of the stress, but also on many variables relating to the cells themselves, e.g., particular vulnerability, dif-

ferentiation, blood supply, nutrition and previous state of the cell.

In many instances there are ready explanations for particular cell vulnerabilities. Carbon tetrachloride, inhaled or ingested, is metabolized in the liver and free radicals (discussed later), which are far more toxic than the parent compound, are released there. Thus, liver cells bear the brunt of this form of injury (Figs. 1–1 and 1–2). Since ganglion cells are dependent entirely upon oxidative phosphorylation, they are vulnerable to oxygen deprivation. Cardiac muscle cells have a high rate of metabolism and thus are very susceptible to hypoxia. Sometimes the site of attack or delivery of the stressful influence determines the particular cells affected. For example, the pulmonary parenchyma is attacked directly by inhaled toxic gases. Despite these obvious explanations there are other instances in which stressful agents induce changes in mysterious sites. We do not know why, for example, the poliomyelitis virus, which usually enters the body through the gastrointestinal tract, attacks principally anterior horn ganglion cells in the spinal cord or why a toxic level of lead absorbed into the bloodstream exerts its effect principally on the hematopoietic system, the central nervous system and the kidneys. Nonetheless, it is important to know the major targets of the various forms of stress in order to make an educated guess at the etiology of the cellular change from the selective sites of involvement. Thus, the child with an anemia and manifestations of diffuse central nervous system involvement may well be a victim of lead poisoning.

All stresses and noxious influences exert their effects first at the molecular level. Regrettably, such deeply fundamental early molecular changes are only rarely detectable, even with sophisticated methods of study. The molecular and functional changes always precede and, indeed, induce the morphologic alterations. The time lag required to produce the recognizable changes of cellular adaptation, injury or death varies with the discriminatory ability of the methods used to detect these changes. With histochemical or ultrastructural techniques changes can be seen in minutes or hours, but it may be much longer before they become evident with the light microscope or on gross examination of the tissue. Despite sophisticated methods of morphologic and biochemical investigation, the boundary lines between these stages are still difficult to define, and there are no clear benchmarks by which the severely stressed but still normal cell can be distinguished from the cell that has been taxed to the point of injury. Similarly, there are no certain parameters by which the injured but still viable cell can be differentiated from one that is fatally injured.

The following sections consider first the broad categories of stresses and noxious influences that induce cellular adaption, injury and death; then each of these three states will be taken up individually.

Figure 1–1. Rat liver cell 4 hours after carbon tetrachloride intoxication, showing well-developed swelling of endoplasmic reticulum and shedding of ribosomes. Mitochondria at this stage are unaltered. (From Robbins, S. L., and Cotran, R. S.: Pathologic Basis of Disease, 2nd ed. Philadelphia, W. B. Saunders Company, 1979. Courtesy of Dr. Iseri.)

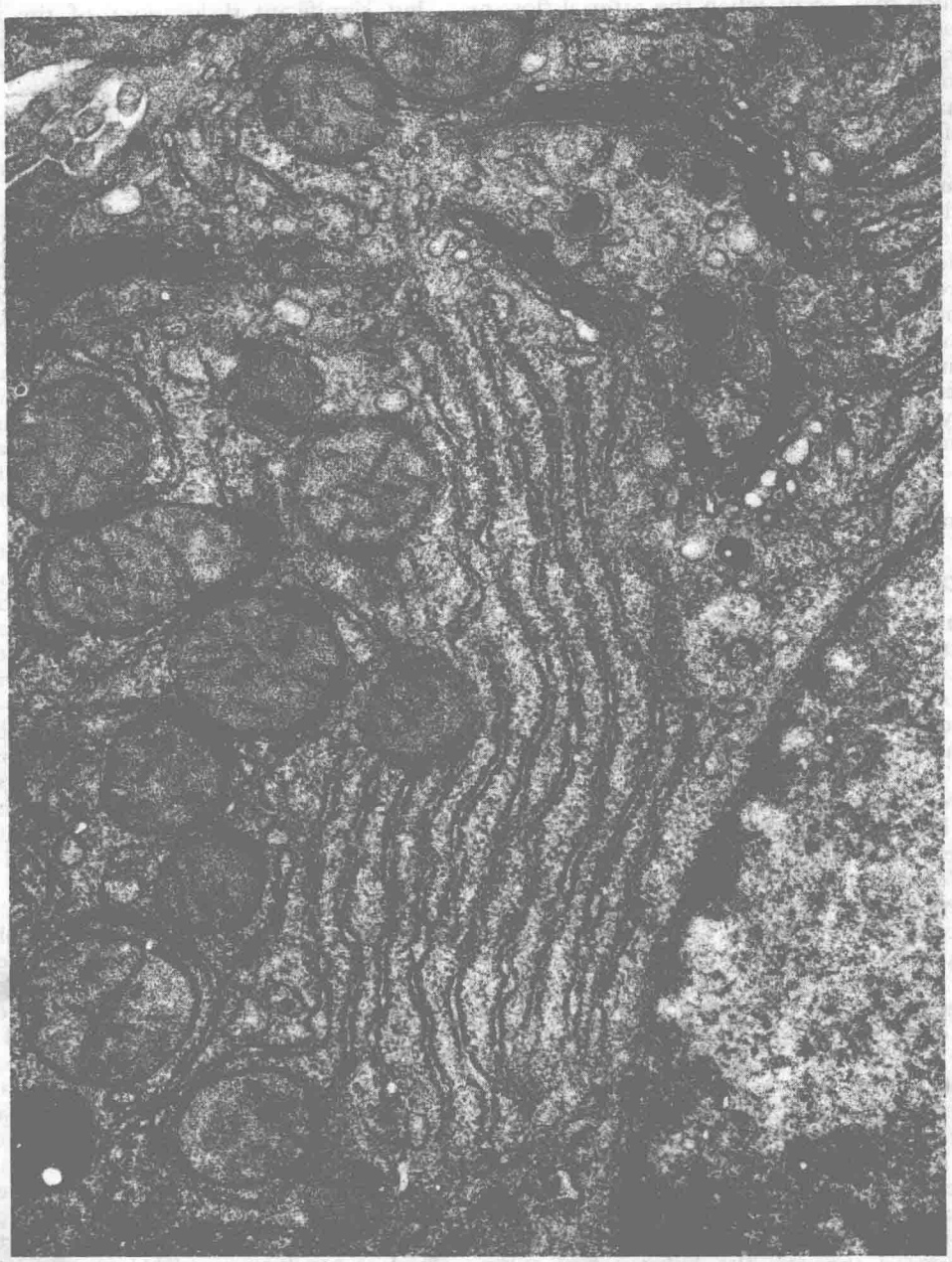

Figure 1–2. Electron micrograph of a portion of a normal rat liver cell (for comparison with Fig. 1–1). The nucleus with its double membrane is at lower right. Golgi complexes are seen in the upper right as parallel arrays of membranes associated with small vesicles. Evident also are the mitochondria and stacks of rough endoplasmic reticulum studded with ribosomes.

CAUSES OF CELLULAR ADAPTATION, INJURY AND DEATH

The stresses that induce altered morphologic states in the cell range from the gross physical violence of a crushing blow to the subtle dislocations involved in the absence of a single enzyme, as occurs in many genetic conditions. The broad categories of adverse influences known to affect cellular functions include (1) hypoxia, (2) chemicals and drugs, (3) physical agents, (4) microbiologic agents, (5) immune mechanisms, (6) genetic defects, (7) nutritional imbalances, and (8) aging.

HYPOXIA

Hypoxia, an extremely important and common cause of cell injury and cell death, impinges on aerobic oxidative respiration. Loss of blood s

ply, which may occur when the arterial flow or the venous drainage is impeded by vascular disease or luminal clots, is the most common cause of hypoxia. Another frequent cause is inadequate oxygenation of the blood due to cardiorespiratory failure. Loss of the oxygen-carrying *capacity* of the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage) is a third, less frequent basis for oxygen deprivation. Cyanide too is a cellular asphyxiant, inactivating cytochrome oxidase within the aerobic oxidative phosphorylation sequence. Depending on the severity of the hypoxic state, cells may adapt, undergo injury or die. For example, if the femoral artery is narrowed, the skeletal muscle cells of the leg may shrink in size (atrophy). This reduction in cell mass achieves a balance between metabolic needs and the available oxygen supply. More severe hypoxia would, of course, induce cell injury or cell death.

CHEMICALS (INCLUDING DRUGS)

Chemicals and drugs are important causes of cell adaptation, injury and death. Virtually any chemical agent or drug may be implicated. Even an innocuous substance such as glucose, if sufficiently concentrated, may so derange the osmotic environment of the cell that it causes injury or cell death. The habitual use of barbiturates evokes adaptive alterations in liver cells. Agents commonly known as poisons may cause severe cell damage and possibly death of the whole organism. We know disappointingly little about the pathways by which many of these chemicals and drugs effect their changes, but presumably they all act on some vital function of the cell, such as membrane permeability, osmotic homeostasis or the integrity of an enzyme or cofactor. As mentioned earlier, the individual agent usually has specific targets within the body, affecting some cells and sparing others. In some cases this selectivity reflects the cell populations involved in the absorption, transport and metabolism of the agent. Barbiturates evoke changes in liver cells because it is these cells that are involved in the degradation of such drugs. When mercuric chloride is ingested it is absorbed from the stomach and excreted through the kidneys and colon. Thus it exerts its principal effects on these organs. Here the mercury presumably inactivates enzymes or competes for radicals such as —SH. As was pointed out earlier, however, we do not always have such simplistic explanations for the selective points of attack of the many chemicals and drugs that induce cellular changes.

PHYSICAL AGENTS

Trauma, extremes of heat or cold, sudden changes in atmospheric pressure, radiant energy and electrical energy all have wide-ranging effects on cells. *Mechanical trauma* may cause subtle but significant dislocations of the intracellular organization of organelles or, at the other extreme, may destroy the cell by completely disrupting it.

Cold and heat are evident causes of stress, cell injury and even cell death. *Low temperature* acts in a number of ways. At first it induces vasoconstriction and impairs the blood supply to cells. Injury to the vasomotor control, with marked vasodilatation, stagnation of blood flow and sometimes intravascular clotting, may follow. When the temperature becomes sufficiently low, intracellular water crystallizes. Damaging *high temperatures* may of course incinerate tissues, but long before this point is reached increased temperature causes injury by inducing hypermetabolism, exceeding the capacity of the available blood supply. Hypermetabolism also leads to the accumulation of acid metabolites, which lowers the pH of the cell to critical levels. Moreover, heat may denature proteins, including vital enzymes.

Sudden changes in atmospheric pressure also may lead to impairment of the blood supply to cells. Deep sea divers or tunnel diggers, when working under increased atmospheric pressure, have higher levels of atmospheric gases dissolved in their blood. If such individuals return to normal pressure too quickly the dissolved gases come out of solution rapidly and form air bubbles within the circulation. Oxygen is readily redissolved, but nitrogen is less soluble and may persist as small bubbles that become trapped in the microcirculation, blocking blood flow and ultimately causing hypoxic injury to cells. This disorder is called caisson disease.

The damaging effects of *radiant energy* were all too vividly illustrated by the atomic bombs dropped on Japan (p. 252). Less grotesque exposure to radiant energy may also be injurious, either because of direct ionization of chemical compounds contained within the cell or because of ionization of cellular water, producing free "hot" radicals that secondarily interact with intracellular constituents. Radiant energy also induces genetic mutations which may injure or even kill cells.[1]

Electrical energy generates heat when it passes through the body and may thus produce burns. More importantly, however, it may interfere with neural conduction pathways and often causes death from cardiac arrhythmias. The extent of damage induced by electrical current depends on its voltage and amperage, the tissue resistance (hence the generation of heat) and the pathway followed by the current from its point of entrance in the body to its point of exit.

MICROBIOLOGIC AGENTS

A host of living agents, ranging in size from the submicroscopic viruses to grossly visible nematodes, may attack humans, causing cell injury, cell death, or death of the individual. Here it is possible to discuss only a few generalizations

about how these living forms affect cells. *Viruses* and *rickettsias* are obligate intracellular parasites — that is, they can survive only within living cells. The interaction between viruses and host cells takes many forms. Many viruses parasitize cells apparently without affecting them; these have been termed "passenger viruses." Those that induce cellular changes fall into two broad categories: (1) agents capable of causing cell death (cytolytic) and (2) agents that stimulate cell replication and possibly cause tumors (oncogenic).

The cytolytic viruses behave in a varied fashion. In general they have a high degree of specificity for certain cell types, reflecting at least in part the presence of appropriate membrane receptors in some cells. Alternatively, cell *cytotropism*, as this phenomenon is called, may result from the cell's ability to engulf or incorporate the virus following adsorption. For example, the virus of poliomyelitis (acquired as an enteric infection) destroys only ganglion cells in the central nervous system, particularly anterior horn cells. The virus of viral hepatitis (acquired either as an enteric infection or by contamination of the blood from the use of infected hypodermic needles or blood transfusions) injures only hepatocytes. On the other hand, other viruses, such as the cytomegalovirus, attack cells in a variety of organs. Some viruses, such as that causing herpes simplex, may remain latent in the cells of the body throughout life. However, when the resistance of cells is only slightly reduced, the virus may cause disease. Thus, herpes simplex may cause vesicles in the oral cavity or on the lips ("cold sores") when the patient is suffering from a respiratory illness, when his lips have been exposed to intense sunburn or when his general immune status is depressed. Yet the virus can be isolated from many individuals in the absence of such lesions. The cytomegaloviruses, also latent in many healthy individuals, may cause death when the patient is immunodeficient or develops some severe debilitating disease. The term "opportunistic infection" is applied to these disorders produced by microorganisms that generally are not pathogenic (disease producing) unless the individual is predisposed. Some cytolytic viruses cause disease soon after they parasitize human cells, as for example the viruses causing influenza, measles and mumps. Conversely, it has become apparent that certain viruses, appropriately termed "unconventional" or "slow" viruses, require months or years to evoke cellular changes and disease. Two uncommon central nervous system disorders, kuru and Creutzfeldt-Jakob disease, are examples of slow viral infections.[2]

We still do not understand the complexities of the cell-virus interaction. Certainly viruses possess no endotoxins or exotoxins. They may subvert the metabolism of the host cell, or possibly introduce lethal "misinformation" into the genome of the host. Clearly, some alter replicative programs, since certain viral infections induce the formation of syncytia and multinucleate giant cells. Virtually all viruses are strongly antigenic (the viral coat proteins) and evoke enduring immunity. Perhaps the immune response against viral or virus-altered cell antigens destroys the host cell. In any event, viruses are patent causes of cell injury and cell death.

As mentioned earlier, when some viruses (oncogenic viruses) infect the cells of animals they do not cause cell death. Instead they not only stimulate cellular replication but also induce changes in the genotype and phenotype of the cell (transformation). This is the basis for the viral induction of cancers, which has been established in animals and is suspected in humans (p. 104).

Bacteria are almost as unpredictable in their effects as viruses. Some are harmless commensals and some even contribute to human survival. The *Escherichia coli* flora of the gut, for example, constitutes a valuable source of vitamin K. However, even *E. coli* may cause disease in infants, who have little or no immunity to these otherwise innocuous organisms, or in debilitated or immunodeficient adults. Similarly, many individuals harbor potentially pathogenic bacteria in the oropharynx but develop a significant clinical infection only when rendered vulnerable. The administration of broad spectrum antibiotics may destroy the normal coliform flora of the gut and permit swallowed staphylococci to multiply wildly within the intestinal tract. A staphylococcal enteritis then ensues, which can lead to bacteremia and death. In contrast, other bacteria, such as the agents causing syphilis, gonorrhea or plague, almost always cause disease if the organism gains a portal of entry. To the best of our knowledge there is no counterpart of slow viral infections among the bacterial diseases.

How bacteria evoke cellular injury and disease is imperfectly understood. Some organisms liberate exotoxins capable of causing cell injury at a distance from the site of implantation of the bacteria. Other agents elaborate endotoxins that are released only on disintegration of the organisms. In addition, some bacteria may damage cells by elaborating a variety of enzymes such as lecithinase *(Clostridium perfringens)*, capable of destroying cell membranes, or hemolysins (beta-hemolytic streptococci), which lyse red cells. Another potential mechanism of bacterial injury is the development of hypersensitivity to the agent, leading to damaging immunologic reactions.

We know little about how *fungi*, *protozoa* and *helminths* cause cell damage and disease. Some, such as the Histoplasma, Coccidioides and the blastomycetes, induce sensitization reactions; but others, such as actinomycetes, do not. How protozoa induce cell injury is sometimes remarkably clear and at other times obscure. Amebiasis is caused by a protozoan that elaborates powerful proteolytic enzymes and so destroys tissues wherever it implants. The plasmodia of malaria invade and eventually destroy red cells by releasing toxic metabolites as well as malarial pigment derived

from hemoglobin. The causative agent of toxoplasmosis, however, is an obligate intracellular protozoan that causes considerable tissue damage in its sites of localization by obscure mechanisms. Helminthic infections have their own specific sites of localization and induce cell injury for the most part by obscure means. The agent of trichinosis preferentially invades striated muscle (cardiac and skeletal) and eventually destroys parasitized cells. The trichina worm may usurp the energy supplies of the cell, or possibly its metabolic endproducts are toxic, but these explanations are speculative. Filariasis is characterized by intense fibrosis at sites of localization, but we do not understand why such inflammatory fibrosis evolves. In conclusion, it must be admitted that with microbiologic infections, the ultimate mechanism of cell injury and cell death often remains uncertain.

IMMUNE MECHANISMS

Immune reactions have come to be recognized as not uncommon causes of cell damage and disease. The trigger antigen may be exogenous in origin, as for example the resin of poison ivy, or it may be endogenous, e.g., cellular antigens. The latter evoke so-called autoimmune diseases. The effect of immune reactions on cells is discussed in Chapter 7, page 183.

GENETIC DERANGEMENTS

Critical to the cell's homeostasis is its normal genetic apparatus. Mutations, whatever their origin, may have no recognizable effect, may deprive the cell of a single enzyme *(inborn errors of metabolism)* or may be so severe that they are incompatible with cell survival. The mutation may appear during gametogenesis, in the early zygote or in adult cells (a somatic mutation). Indeed, as will be discussed, somatic mutations may underlie the origins of cancerous transformation of cells. As is well known, some genetic abnormalities are transmitted as familial traits, such as sickle cell anemia. More is said about genetic derangements in Chapter 6, page 133.

NUTRITIONAL IMBALANCES

It is sad to report that deficiencies in nutrition not only are important causes of cell injury today, but threaten to become devastating problems in the future. Protein-calorie deficiencies (which scourge many developing nations) are the most obvious examples. Avitaminoses also are rampant in deprived populations and are not uncommon even in industrialized nations having relatively high standards of living. Ironically, excesses in nutrition, privileged only to upper economic groups, are important causes of morbidity and mortality. Excess calories and diets rich in animal fats are now strongly implicated in the development of atherosclerosis. Obesity alone leads to an increased vulnerability to certain disorders. Unfortunately, both obesity and atherosclerosis have become virtually epidemic in some countries, such as the United States. All of these disorders are obviously associated with cell injury and cell death.

AGING

Aging has many dimensions and can be characterized in many ways. Shakespeare probably did it best in his elegant description of the seven ages of man.[3] It begins at the moment of conception, involves the differentiation and maturation of the organism and its cells and, at some variable point of time, leads to the progressive loss of functional capacity characteristic of senescence, and ends in death. Here we are concerned with cells on the "downhill" side of this sequence. Just as the organism progressively loses its ability to adapt to stress and becomes extremely vulnerable to lethal injury, so do senescent cells. Philosophically, the onset of this loss of recuperative and functional capacity may be said to begin at the moment the cell is "born," since all of life is a terminal disease. However, recognition of these changes is at best difficult, and the alterations are more apparent in some systems and cells than in others. Clearly, the postmenopausal ovary no longer matures follicles and is senescent; analogously, the accumulation of the age-related pigment lipofuscin in the heart, liver and brain (described in more detail on p. 24), is another manifestation of aging change. In our present context, a question arises — are the changes of senescence the consequence of genetic programs inherent in cells or are they the consequence of the accumulation over time of cell injuries? These two possibilities are by no means mutually exclusive, and it is highly likely that both contribute. On the one hand, cells grown in culture acquire with time a variety of detrimental, functional and morphologic changes suggesting cell injury as a consequence of in-built programs.[4] On the other hand, the accumulation of lipofuscin may reflect exposure of cells over the years to "toxic free radicals," as will soon be explained, leading to ever more significant cell injury and aging (the so-called "free radical theory of aging"). Only a few observations can be offered regarding these issues, but many reports are available.[5, 6, 7]

According to one somewhat controversial theory, cells are programmed to mature, differentiate and die after a finite number of replications. The *Hayflick theory* points to the fact that when fibroblasts are grown in vitro, they undergo 50 ± 10 doublings and then stop replicating.[4] By transplanting nuclei, it can be shown that the governing mechanism resides within the nucleus.[8] However, other workers contend that the limited replication of diploid fibroblasts in vitro is an artifact of the cultural process.[7] According to this dissenting view, cells are potentially immortal but mitotic errors produce cells that are committed to die, and these eventually replace the immortal cells. This in essence is the "intrinsic