A Textbook of PATHOLOGY

Structure and Function in Diseases

By

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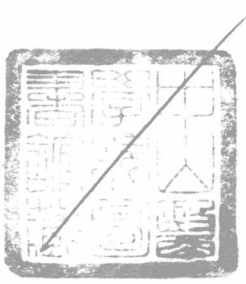

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Preface

There is more than one way to revise a medical textbook. The author can collect all the new material he would like to insert. This is patching the old coat. At the same time he can delete material which he thinks is no longer of value. Dead wood must be pruned, as every gardener knows, leaving room for the new shoots. Or he can attempt something more drastic. I have tried to rewrite rather than merely to revise the book, with function as well as structure in mind. The difference between the new and the old is illustrated by a comparison of Chapter I, dealing with the Pathology of the Cell, with the corresponding Chapter 2 of the previous edition describing Degenerative Processes.

I have sought to emphasize the general principles governing disease processes, and have entitled the first part of the book Principles of Pathology rather than the more customary General Pathology, used in previous editions. General pathology may be regarded in a sense as representing the theory of disease, while special or regional pathology is the practical application of that theory to individual instances. The reader of Part I is a student of disordered biology. When he comes to Part II he becomes the future doctor of medicine. The student who has mastered such subjects as inflammation, thrombosis and neoplasia can apply his knowledge to disease problems like acute appendicitis, coronary thrombosis and bronchogenic carcinoma without much outside assistance. He will also learn to recognize that ignorance, however aptly veiled in an attractive phraseology, still remains ignorance.

Disease, whether of the heart, the kidney or the brain, is disturbed function, not merely disordered structure, for pathology in the modern sense is physiology gone wrong, and not just the morphological changes we call lesions. A world of disordered function lies revealed in any lesion, if only we have the eye to see it. It is the high function of the pathologist not merely to attach correct labels to the lesions which he sees, but to reconstruct the course of events from the earliest inception of the disease to the final moment when we fall out of "the splendid procession of life." Altered structure corresponds to the *lesions* studied by the pathologist, but it is disordered function that is responsible for the *symptoms* which bring the patient to the doctor. It is the functioning of the lung rather than its structure which determines whether or not a person is short of breath. It is for this reason that I have devoted what may seem at times an inordinate amount of space to physiological considerations.

This concept is of course in no sense new. In 1847 Rudolf Virchow, the father of modern pathology and then only twenty-six years of age, wrote these words: "Pathological physiology is the main fortress of medicine, while pathological anatomy and the clinic are outlying bastions." Unfortunately those who followed Virchow were apt to forget this great truth, and indeed prided themselves on being "morbid anatomists," an unpleasant term in itself. To be able to give a name to some pathological lesion, and to make it fit into some accepted scheme of classification, is a very limited concept of pathology. But morbid anatomy is not dead and never has been, except in the hands of those whose dull minds would take the breath of life from the most vital subject. The world of medicine did not think that there was anything dead about cellular pathology when Virchow poured the new wine of his vital spirit into the old bottles of tradition. And today the bottles are not yet full. It is *pathological processes* with their morphological basis with which we are concerned, both as biologists and physicians. Let us not forget that pathology is a discipline in its own right, not merely a diagnostic tool.

With this in view I have opened several chapters in Part I and almost every chapter in Part II with a section on General Con-

siderations, a conveniently vague and noncommital term which allows a review of anatomical, physiological and biochemical facts that may have a bearing on the diseased states which are presently to be considered. In such a disease as diabetes it is physiology rather than morphology that concerns us. These sections afford a convenient place to consider the startlingly new details of fine structure which electron micrography has introduced, suggesting that we stand on the threshold of a new era in our concept of the cell, as indicated in the opening chapter. No better illustration of the importance of this new technique can be imagined than in studies of the changes in the glomeruli and tubules of the kidney in various forms of renal disease.

As we have already suggested, the day of morphological pathology is by no means past, a fact evidenced by the emphasis placed by the radiologist on gross morbid anatomy, more particularly in relation to disease of the lungs. Examples of new techniques opening doors for further exploration in microscopic morphology are afforded by the application of fluorescence antibody methods in the study of immunity, the demonstration of abnormalities of individual sex chromosomes and autosomes in cytogenetic studies, and the laying bare of too much or too little enzyme activity by new cytochemical and histochemical staining methods. In these days of multiple authorship, not only of books but also of articles, the solitary author takes on himself a heavy burden and responsibility for which he may well be criticized for undue presumption at at a time when explosive advances are shattering the boundaries and frontiers of knowledge.

Although clinical diagnosis is still dependent on the recognition of the presence of structural changes, from the point of view of the patient damaged structure and disturbed function are only of significance in relation to the symptoms from which he suffers. The sections on the Relation of Symptoms to Lesions which close the account of most diseases have been expanded in many instances and introduced for the first time in others, with emphasis on the concept that disease is a manifestation of disordered function rather than altered structure. To enumerate a list of symptoms and then a list of lesions is not enough. It is the relation of one to the other which counts, just as in a well ordered clinical pathological conference it is to the explanation of the clinical picture in all its aspects that the pathologist should bend his energies, rather than merely to lay bare the lesion which he thinks was responsible for death. Sometimes this is easy, sometimes difficult, and sometimes impossible at the present time. The value of a persistent endeavour to correlate symptoms with lesions lies not so much in the number of facts the student may succeed in memorizing, as in the development of an attitude of mind which may color the whole of his future career. In Osler's memorable words: "As is our pathology, so is our practice." For the student of medicine, then, pathology has a threefold interest, for it comprises a study of: (1) structural changes, (2) disturbance of function, and (3) the relation of the lesions to the symptoms which represent disease in the patient. This has been the aim of the present edition.

An Outline of Contents has been placed at the beginning of each chapter. I have found the compilation of this outline of great value to myself, because it has enforced on me a more orderly arrangement of material, as well as a due regard to classification. These considerations may also prove of value to the student, particularly in the revision of his work before having to face the examiners. It is perhaps in the chapters dealing with such complex subjects as immunity and hypersensitivity, carcinogenesis, ionizing radiation, and diseases of the kidneys, the lungs, the blood and the nervous system that a review of the outlines may be of value. Even the pathogenesis of atherosclerosis becomes slightly less confusing when the possibilities are listed. A glance at the Outline of Contents of Chapter 1 will show that the subject of pathological calcification has been omitted inadvertantly. It is discussed in connection with diseases of bone in Chapter 43.

New chapters have been introduced on immunity and hypersensitivity, derangements of body fluids, pigments and pig-

mentation, ionizing radiation, and a fuller discussion of medical genetics, because of the dominant place which these play in the science of pathology today. The chapter on tumors now becomes two, the first on the principles of neoplasia, the second on specific tumors. The kidney, as a member of the cardio-vascular-renal system, is now considered in Chapter 23, a more fitting position for it, and the lower urinary tract in Chapter 31.

I have endeavoured, perhaps unsuccessfully, to curtail the second part of the book dealing with Regional Pathology, formerly called Special Pathology, partly by abbreviating the accounts of a number of diseases regarded as of lesser importance, partly by omitting many of the rarer conditions which the undergraduate, once he becomes a doctor, may not see once in a lifetime. In other cases I have merely mentioned the condition, giving a reference to some review article which may be consulted if desired for any special reason.

The references are intended for the student who has to prepare a paper or write a thesis on a particular subject. Knowledge is of two kinds: we may know a subject ourselves, or we may know how and where to find the necessary information. The value of what has been termed the "look-it-up technique" is becoming more generally recognized. It has been said that an educated man is one who knows how to use a library. The student should be provided with a living stream of knowledge, not a stagnant pool from which to drink. The references are indicated in the text by the name of the author rather than by a number, because it is felt that the reader should become familiar with the names of some of those who have advanced the science of pathology, even though he may never have time to consult the original paper. For the same reason I have sometimes quoted a sentence or two from a writer, because to do so makes the man more living. The list of references at the end of the chapter are now arranged alphabetically rather than grouped according to subjects.

Use of the library makes us aware of the fact that the picture of disease is changing before our very eyes. Old diseases are passing away as the result of the assaults of modern therapy, but new ones are continually taking their place. The inn that shelters for the night is not the journey's end. Many of these new diseases are iatrogenic (*iatros*, a physician) in nature, that is to say, they are the result of the well-meant but injudicious use of therapeutic agents. In these days when tranquilisers take the place of baby-sitters, blood transfusions are given thoughtlessly, indiscriminately and often needlessly, exposure to diagnostic or therapeutic ionizing radiation has become so universal, antibiotics are regarded as the cure-all for the most minor infections, and steroid therapy is the refuge of the destitute, it is small wonder that the old maladies are replaced by new man-made ones, and that allergies to a multitude of antigens have become so commonplace that they are said to exceed pathogenic microorganisms in number. I must apologize for the too frequent use of the words "what is powerful for good can be potent for evil," but this is true of so many situations created by modern therapy that I have been unable to resist the temptation. If we continually interfere with nature, we must pay the penalty. The idea is of profound importance to the medical student who is to become the future doctor with the safety and welfare of his patient at heart.

It may not be out of place to remark here that the student, beguiled by the fascination of pathology, must not regard clinical medicine as merely the application of physics, chemistry and physiology to the sick person. Medicine can never be purely a science; it contains too many immeasurables. The patient with heart disease is not just an internal combustion engine with a leaking valve but a sensitive human being with a diseased heart. Disease in man is never exactly the same as disease in the experimental animal, for in man the emotions come into play. It may be the man or woman rather than the disease that needs to be treated. There is always the psyche to be considered as well as the soma.

The use of small print is always a contentious subject. Some textbooks of pathology do without it, while others use it liberally. The object of small print is

two-fold, partly to save space, partly to indicate to the student what is of lesser importance and need not be read if time is limited. The difficulty is to decide what is unimportant. What is rare in one part of the world may be very common in another, and in these days when air travel between distant countries has become an everyday affair, the geographic demarcation of disease is no longer as sharp as it used to be. For better or worse, I have used small print to a much less extent than formerly. The book is designed for the medical student who is going to devote his life to the diagnosis and treatment of disease. In spite of that it has been difficult to resist the temptation to include a few conditions which the reader will almost certainly never encounter. Kuru is an example of such a disease which, because of its unusual and dramatic character, makes an irresistible appeal. At least I have put it in small type.

A number of the old pictures and one-half of the color plates have been discarded. Many new ones have been introduced, including a selection of electron micrographs. Some of these pictures have been taken from my book, *Pathology for the Physician.* I am much indebted to the W. B. Saunders Company for permission to use both color plates and black and white photographs from my *Pathology for the Surgeon,* as well as a number of extracts from that book, more particularly the account of shock.

One of the pleasant features of writing a preface is the opportunity it affords the author to express his appreciation to those who have made the final result possible.

Of my associates in the University of Toronto I wish in particular to thank Dr. John Hamilton for suggesting the desirability of including a chapter on immunity and hypersensitivity, to Dr. Henry Z. Movat for criticism and help with that chapter and for a number of electron micrographs, and to Dr. John Paterson and Dr. H. A. Hunter for invaluable suggestions regarding the chapters on the Respiratory System and the Teeth respectively. Much stimulus has come from the men I have worked with at the University of Alabama Medical Center. I must thank Dr. J. F. A. McManus for acting as my guide in the labyrinth of histochemistry, especially in relation to the kidney, Dr. Sidney P. Kent for much needed assistance with the chapter on Ionizing Radiation, and, in particular, Mr. Ralph F. Coleman, an undergraduate student who has helped to give me the point of view of the medical student, has read the entire manuscript, has provided most of the tables summarizing a subject, and has impressed on me the value of italics for emphasizing the salient features of a subject, an emphasis particularly useful when reviewing the work later.

Without a library an author would be helpless. In this respect I am deeply indebted to Miss Marian Patterson of the Academy of Medicine, Toronto, and to Mrs. Hilda Harris of the University of Alabama Medical Center. I am grateful to those who have sent me reprints of their papers, and I would very much appreciate others following their example.

For the laborious and exacting task of transcribing illegible writing to type script I must thank Miss Linda Cox of Toronto and Mrs. Carol Cross of Birmingham.

Finally I must thank my long-suffering publishers, Lea and Febiger, for having completely reset the type, which is in double column, and in particular Mr. John F. Spahr and Mr. V. J. Boland for the remarkable patience they have displayed with the endless demands of an author who insists in making last minute additions not only of manuscript, but also of illustrations, in an endeavour to bring the book more or less up-to-date at the moment of publication.

WILLIAM BOYD

Toronto, Canada

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Part I. Principles of Pathology

Chapter 1

Pathology of the Cell

INTRODUCTION

It is not necessary to impress on the medical student the importance of the cell. His study of histology and embryology has already made him fully conscious of that fact. Life on earth began with the appearance of the first cell, and to this day each of us begins life as a single cell, the fertilized ovum. The origin of modern pathology, on which present day medicine is based, dates from the publication of Rudolf Virchow's "Cellular Pathology" in 1858, over one hundred years ago.

Before commencing a study of the pathology of the cell, it might be well if we paused for a moment to enquire as to the meaning and connotation of the term pathology. Pathology is *the study of disease by the methods of the laboratory*, just as medicine and surgery are the study of disease by the methods of the bedside. The practice of medicine is, will always be, and always should be both an art and a science. The clinician studies illness, while the pathologist studies disease. It is with the *science* of medicine that pathology, is concerned, for, in the telling words of Sir Roy Cameron, its aim is a "welding together of structural and functional observations into a coherent story." When a clinician makes a diagnosis he is merely expressing an opinion as to the underlying pathology, so it is evident that he must become familiar with the fundamentals of that science.

Pathology is concerned with answering, or trying to answer, the questions What, How and Why in relation to disease. The answer to *What* consists in a description of the structural changes produced by the disease process. In the beginning, and indeed until recent years, such a description of the gross and microscopic changes, known as the *lesions*, constituted the bulk of the science, and the pathologist was known as a morbid anatomist (suggesting a diseased anatomist) or morbid histologist. But the student of pathology must not content himself with such a description. He must also try to answer the much more difficult questions, *How* and *Why*. As a matter of fact, when we read a complete autopsy report we may find ourselves asking how the patient continued to live, not why he died, so roughly has the sharp tooth of time dealt with his body. In the following pages the student must ask what is going on inside the cell. The present day pathologist, studying sections of the kidney with modern histochemical technique, is as much concerned with

fundamental changes involving the enzyme systems of the cells of the convoluted tubules as in the structural changes he sees under the microscope. Disease may be defined as merely a summation of chemical reactions that have gone wrong.

In the course of his clinical studies the student will soon realize that in many cases it is not possible to demonstrate a gross or even a cellular organic basis for the patient's symptoms. Such cases have been classified in the past as examples of "functional disease." With advances in knowledge this vague group is undergoing a wholesome shrinkage. Much of the failure to demonstrate a structural change has been due to inability to lay bare submicroscopic changes in the cell or disturbance of its enzyme systems. These *biochemical lesions* are now being revealed by the demonstration of the fine structure of the cell by the electron microscope, by remarkable advances in cytochemistry, and by what is termed molecular pathology. For disease may be produced at a molecular level, the level of the constituent metabolic units. One of the best known examples of a molecular disease is sickle-cell anemia with its abnormal hemoglobin molecule which is genetically inherited. We shall encounter a biochemical lesion in the poisoning of the enzymatic activity of the mitochondria by arsenic. All hereditary diseases have as their basis a genetic abnormality which expresses itself as an altered metabolic pathway, another example of a biochemical lesion. There can be little doubt that such an apparently purely functional mental disease as schizophrenia, with its distressing delusions and hallucinations and split personality, has a biochemical lesion as its basis. These are some of the things which make pathology so exciting a study at the present time.

But the student in his new-found enthusiasm for pathology must not forget that it is the whole patient who comes to consult the doctor, not just a disordered liver, a cardiac lesion, a lump in the breast, or a painful knee. In the words of an Old French proverb: "There are no diseases, but only sick people."

With this brief review of the content of pathology and the changes which it has undergone since the publication of Virchow's "Cellular Pathology" one hundred years ago, we may now pass to a consideration of the cell in health and in disease. In this chapter we shall consider the normal cell, the sick cell, and the dying and dead cell. The sick cell is likely to show changes which are grouped under the rather old fashioned term, the *degenerations*, but we have already seen that sometimes the change is a biochemical lesion rather than a histological one, in which case the microscope will reveal no abnormality. As a matter of fact all lesions are primarily biochemical, but some also become visible. The changes associated with the death of a cell are known as necrosis. They demand time to develop. Every cell we see under the microscope is of course dead, killed by the fixative, but it is not necrotic. Before considering the sickness and death of cells it may be useful to recall one or two simple facts about normal cell structure and function. The student who wishes to delve deeper into the subject of the cell in health and disease could not do better than read Sir Ray Cameron's pleasantly small book "New Pathways in Cellular Pathology." If he wishes more detailed information he may consult "The Cell" by the same author, 840 pages long with 126 pages of references.

THE NORMAL CELL

The three principal constituents of the cell are: (1) cell membrane, (2) nucleus, and (3) cytoplasm. The nucleus contains (*a*) the chromosomes, which are the carriers of the genes, and (*b*) the nucleolus. The cytoplasm contains a variety of structural constituents known as *organelles* or little organs. Of these we shall consider the *mitochondria* and the *endoplasmic reticulum*. Two others may be mentioned: the *microsomes*, which are innumerable submicroscopic particles, and the *Golgi apparatus or complex*, an assembly depot of various kinds of secretions. As so little is known of their function and next to nothing of their reaction to injury, they will be passed by.

In recent years enormous advances have been made in our knowledge of the structure and function of the cell in health and to a lesser degree in disease. We owe these advances in the main to two new methods of

technique. (1) When cells are disrupted by mechanical means, the contents are liberated, and when these are suspended in a suitable medium and the homogenate is spun in a centrifuge, the largest and heaviest particles come down first, followed later by the smaller and lighter particles. By this means first the nuclei, then the mitochondria, and finally the microsomes can be separated, and examined histologically and biochemically. (2) The electron microscope has given us a new insight into the structure of these units and brought the microsomes into view.

The cells are not the static structures that they appear when viewed in fixed tissues under the microscope. They are as alive and active as the animal or person from whom they are removed. Each cell, which is really a biochemical machine, contains chemical and physical mechanisms designed to obtain material from its environment to satisfy the nutritional and energy requirements of the organ concerned. When these mechanisms, which involve a relationship between structure and function, are impaired, the result is sickness and it may be death.

Metabolism (*metabole*, change) is the sum total of the chemical reactions which proceed in the cells. The tools of these reactions are the *enzymes* or metabolic catalysts which are present in vast numbers in every cell. Protoplasm consists largely of enzymes, each of which is extraordinarily specific, acting on its own particular substrate by combining with it. Part of the activity is *anabolic*, involving the synthesis of protein, whilst part is *catabolic*, being concerned with the breaking down of food substances and protoplasm. The energy yielded by catalysing reactions is used in part for the resynthesis of the enzymes concerned. The enzyme reactions are extremely sensitive to injurious influences such as poisons, loss of nutrition, *etc.* The breakdown of the enzyme systems results in sickness or death of the cell.

Chemical poisons such as carbon tetrachloride can pass through the surface membrane as through a sieve, finally reaching the mitochondria and disrupting the respiratory enzymes, so that the whole complex structure of the cell crumbles. For instance, the nitrophenols lead to an increased consumption of energy in the cell, but the enzymes are not able to use the energy so liberated, with the result that adenosine triphosphate, the great energy-carrier, is not synthesized, and the life of the cell suffers.

Bacterial toxins may also inhibit the enzyme systems, as we see in the case of Cl. welchii, tetanus, botulinus and diphtheria. Botulinus toxin causes severe muscular paralysis without any observable structural changes even in fatal cases. The same is true of tetanus toxin. These are examples of *biochemical lesions, in which the function of an enzyme but not the structure of the cell is disrupted*, with "jamming" of the metabolism as the result.

We have already enumerated the structural elements in the cell which interest the student of pathology. These are the cell membrane, the nucleus with its chromosomes, and the cytoplasm with its organelles, more particularly the mitochondria, and cell inclusions. In cell death the nucleus claims our attention as pathologists, whereas disorders of the cytoplasm are more likely to result in sickness of the cell. As Ham puts it in his chapter on The Cell, the nucleus is the heart of the cell, so that when it dies, the cell dies, whereas the cytoplasm performs the ordinary day-to-day work of the cell.

Amongst the dominant constituents of both nucleus and cytoplasm are the *nucleic acids*, complexes of bases, sugars and phosphoric acid. They are divided into two groups, namely ribose nucleic acid (RNA) and deoxyribose or desoxyribose nucleic acid (DNA), the two groups being distinguished by their sugar component. Both are basophilic, but they can be differentiated by means of the Feulgen reaction which is based on the difference in the sugars. Mild hydrolysis liberates aldehydes from DNA but not from RNA, and these aldehydes stain purple or magenta with the Schiff reagent. DNA is said to be Feulgen-positive, whilst RNA is Feulgen-negative. The two nucleic acids can also be distinguished by observing the action of the specific enzymes desoxyribonuclease and ribonuclease on the constituents of the cell. By the use of these methods it becomes evident that DNA is confined to the nucleus, and in particular the chromosomes, whereas RNA is present mainly in the mitochondria of the cytoplasm, but also in the

nucleolus. It is the DNA of the fertilized ovum which determines the species of animal that will develop, as well as the individual characteristics of that animal. The nucleoproteins of cells can be changed by the incorporation of nucleoproteins of viruses, as well as by chemical and even physical agents such as radiation, a point to which we shall return when we consider the causation of cancer.

A working model of DNA (Watson-Crick model) has been devised to fit the fact that it seems to represent what has been called "the hereditary codescript" of the cell. The giant molecule is pictured as consisting of a pair of chains wound in a double helix. Each chain consists of alternate desoxyribose and phosphoric acid groups. The chains are cross-connected by two pairs of four nitrogenous bases, namely adenine with thymine and guanine with cytosine. If a molecule contained a large number of these nucleotide pairs, their arrangement could be varied almost endlessly, and such a structure could code an organism's characteristics for hereditary transmission. It seems sufficient to dictate the formation of every kind of protein to be formed from a choice of 20 amino acids, thus every possible enzyme, thus every sort of cellular organization and function. The genes consist of DNA, and the chromosomes are assemblies of genes, so that the part played by chromosomes in determining structure and function is evident.

Just as the body as a whole operates on the principle of the division of labor, so also does the secret of the complex activity of the individual cell lie in the isolation of its various activities. If the cell is a biochemical machine, its separate parts such as the nucleolus and the mitochondria are similarly distinct machines. This isolation is achieved by the presence of various membranes (Bourne). Thus the *nuclear membrane* isolates the activities of the nucleus from those of the cytoplasm. It is now known that this is only a partial isolation, for the electron microscope has shown the membrane to be perforated with pores, through which materials are transferred from the nucleus to the cytoplasm. RNA molecules labelled with radioactive atoms have been followed from the nucleolus through these pores to the endoplasmic reticulum. where they preside over protein synthesis, while DNA presides over the synthesis of RNA in accord with the genetic plan borne by the chromosomes. This migration can be best seen in the gigantic cells of the salivary glands of Drosophila, the fruit fly. The mitochondria and the Golgi complex also have their membranes, so that their activities are carried on in partial but not complete seclusion.

With this review of what is going on inside the cell we are in a better position to appreciate the meaning of its finer structure, and we shall now consider in more detail the cellular constituents which have already been mentioned.

Cell Membrane.—With the light microscope the cell membrane is only visible in red blood cells from which the hemoglobin has been removed, but the electron microscope reveals that every cell has its membrane. It is an all-important structure, for it regulates the internal environment of the cell, determining what goes in and what comes out. It is at this surface structure that many reactions take place. If the cells are very active they need a correspondingly large surface, so that they may be studded with microvilli in the intestine or show infoldings in the renal tubules, much as the cerebral cortex is thrown into convolutions to gain increased surface without expanding the skull unduly. Water and all food particles must pass through the membrane freely, whilst metabolites must pass out. The membrane consists largely of lipid molecules, polysaccharides, and a much smaller number of protein molecules. Cameron pictures the lipid molecules as behaving like swing doors hinged to the protein molecules. A chemical poison is not toxic for the cell unless it can penetrate the cell membrane. Unfortunately the lipids of the membrane can act as a solvent for many hydrocarbons, amongst which are some powerful carcinogenic (cancer-producing) agents.

It is to the surface structure that many substances such as chemical dyes become attached. Effective drugs probably react first with specific surface constituents. An enzyme seems to fit into the cell surface in which its substrate is embedded. Antigens react at the surface of the cell with the for-

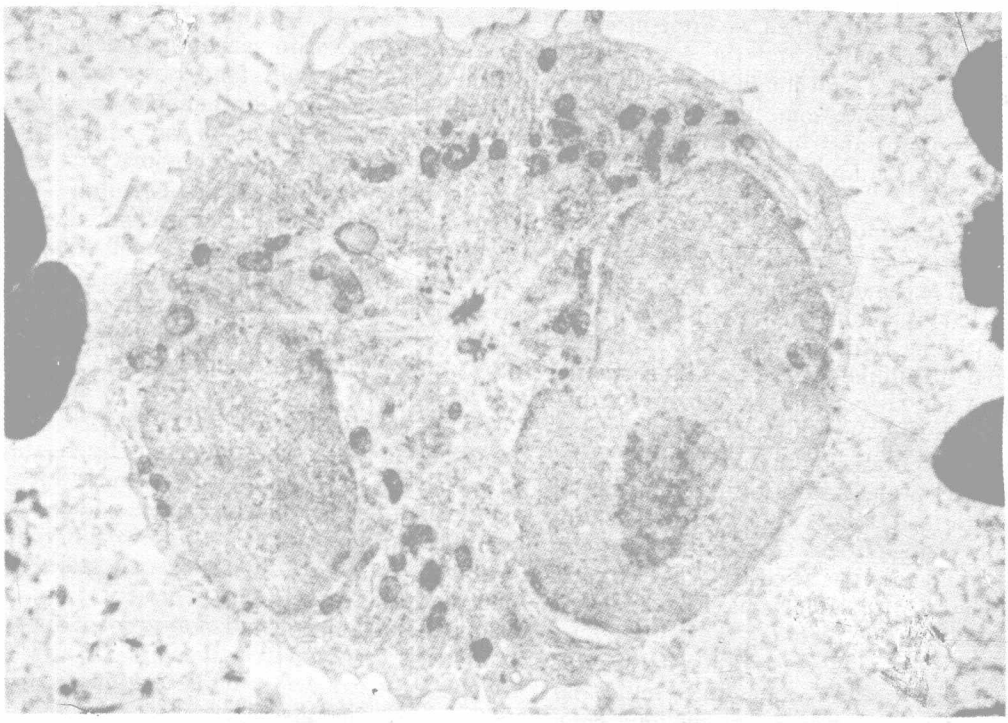


FIG. 1.—Electron photomicrograph of plasma cell. Note the wealth of fine detail barely suggested in the same cell seen with the light microscope. To the right is the eccentric nucleus containing a prominent nucleolus of dense reticular composition. To the left there is a second nucleus. The cytoplasm is filled with organelles, including a highly developed endoplastic reticulum and dense mitochondria. The structure in the center is the centrosome. The cell membrane shows slender projections and invaginations. × 22,000. (Kindness of Dr. Alice Smith, Wadley Research Institute, Dallas).

mation of antibodies which are then cast off to enter the blood stream. This is the basis of Ehrlich's side-chain theory which marked the beginning of our modern concepts of immunity, a subject to which we shall return in Chapter 5. Virus particles are adsorbed to the surface of the cell before penetrating to the interior. Poisons can alter the permeability of the cell membrane, so that some ions stream in and become attached to the mitochondria, whilst other ions stream out, with resulting sickness of the cell or it may be death. From these facts it becomes apparent that the cell membrane is a structure of paramount importance.

The Nucleus.—We have already seen that the nucleus may be regarded as the heart of the cell, although a cell from which the nucleus has been removed may live for three days. If such a cell is given another nucleus by modern microsurgery, it will continue to live. The nucleus houses the apparatus for maintaining the genetic constitution of the cell, namely the *chromosomal network* with its infinite tally of *genes*, the arbiters of hereditary characteristics. It is also concerned with cellular reproduction and multiplication, the development of separate chromosomal threads from the network being the first step in mitosis or cell division (*mitos*, a thread). We shall return to the subject of normal and abnormal cell division when we come to the subject of cancer or neoplasia in Chapter 8. Finally, the nucleus is believed to control the production of the cytoplasmic enzymes which are responsible for the chemical transformations associated with life. Reference has already been made to the nucleolus with its rich RNA content, and the fenestrated character of the nuclear membrane.

Mitochondria.—The principal organelles of

the cytoplasm with which we are concerned are the mitochondria and the endoplasmic reticulum (Fig. 1), although the Golgi complex and the centrosome deserve mention. The ground substance in which the organelles are suspended is known as the cytoplasmic matrix.

The mitochondria are not visible with hematoxylin and eosin staining, yet they are present in enormous numbers, with an average of 2500 in the normal rat liver cell. As seen with the electron microscope they are far from threadlike (*mitos*, thread; *chondros*, granule), but are rod-shaped or like a cucumber. They are surrounded by a double-layered membrane, and folds of the inner membrane project inward in the form of shelves termed *cristae*. They are in constant motion, change their size and shape very readily, and provide a sensitive indicator of cell injury. Mitochondria have been likened to the main power plants of the cell, because by virtue of the 25 or so different enzyme systems they contain, they utilize molecular oxygen and distribute energy-yielding components to other organelles; in other words, they are responsible for cell respiration.

In *cellular respiration* the enzymes catalyze the oxidation of pyruvic acid to CO_2 and H_2O by way of the citric-acid Krebs cycle. It must be borne in mind that oxidation no longer refers merely to the addition of oxygen to a substance, but now includes the removal of hydrogen atoms from a substance, and indeed any process in which electrons are lost. The enzymes of the Krebs cycle have been pictured as arranged in an orderly way on the inner surface of the mitochondrion and on the shelves of the cristae. The ultimate purpose of the mechanism is oxidative phosphorylation and the synthesis of adenosine triphosphate. When a fat-soluble poisonous compound such as carbon tetrachloride enters the liver cells, it attacks the mitochondria physically, so that they lose the power of retaining enzyme co-factors, and this disrupts the Krebs cycle. It may be noted in passing that cancer cells have fewer mitochondria than normal, because these cells unfortunately are more concerned with reproduction (mitotic division) than with functional activity.

Cell respiration seems to govern *water balance* in the cell, because not only is water formed together with carbon dioxide by the reaction of oxygen with food, but some of the energy released is used for the active transport of water from the cells. As water is continually entering the cells it is obvious that this transport mechanism is of importance. As Cameron puts it, the cell is like a leaking ship kept steady by the pumps. If cell respiration decreases, the water content will increase and the cell will become waterlogged. This is the condition known as *hydropic degeneration*, which is discussed later in this chapter.

It must be realized that energy can be furnished in the absence of oxygen by means of *fermentation*. Oxidation suppresses fermentation, but this does not mean that fermentation and oxidation are two different mechanisms; they are rather two steps in normal cell respiration. Fermentation is glycolysis without the aid of oxygen. Glycolysis is the first step in cell respiration and is followed by oxidation. The enzymes concerned with the glycolysis of fermentation seem to be situated in other parts of the cytoplasm than the mitochondria. Cyanide is a deadly poison because it instantly arrests the oxygen transport system in the cells. It is of interest to note that cancer cells use anaerobic glycolysis more than do normal cells, and we have already seen that cancer cells have fewer mitochondria than normal cells.

Endoplasmic Reticulum.—This is a series of vesicles and intercommunicating canals, whose primary function is the manufacture of protein. It probably also provides a large amount of floor and wall space for the placement of the enzymes which constitute the machinery of the cell. The elements of the reticulum do not extend into the outer layer of cytoplasm known as the ectoplasm—hence the term endoplasmic. The membranous vesicles are usually flattened, so that with the electron microscope they are seen as double black lines, but sometimes they are in a distended form. Many of the vesicles are dotted on their outer surface with fine dark granules known as *Palade granules*. Such vesicles are called rough-surfaced vesicles, the smaller vesicles near the surface of the cell being smooth-surfaced. The granules

consist of RNA, and are responsible for the basophilia of cytoplasm. They constitute a pattern or template for the manufacture of proteins. The amino acid building blocks are first arranged in proper order, and are then united by the enzymes in the wall of the endoplasmic reticulum to form the needed protein.

Cytoplasmic Inclusions.—Inclusions are not, like organelles, part of the living systems of the cell. They are of three main types: (1) stored foods, (2) secretion granules and globules, (3) pigments. It is the stored foods which are of interest in relation to sickness of the cell, but pigments will be discussed later in this chapter. Food stored in the cell can be drawn on during periods of starvation, allowing the body to survive as long as there is a sufficient supply of water. The food may be protein, carbohydrate or fat. *Protein* does not need to be in the form of inclusions, because cytoplasm is composed mainly of protein which can be consumed when the need arises.

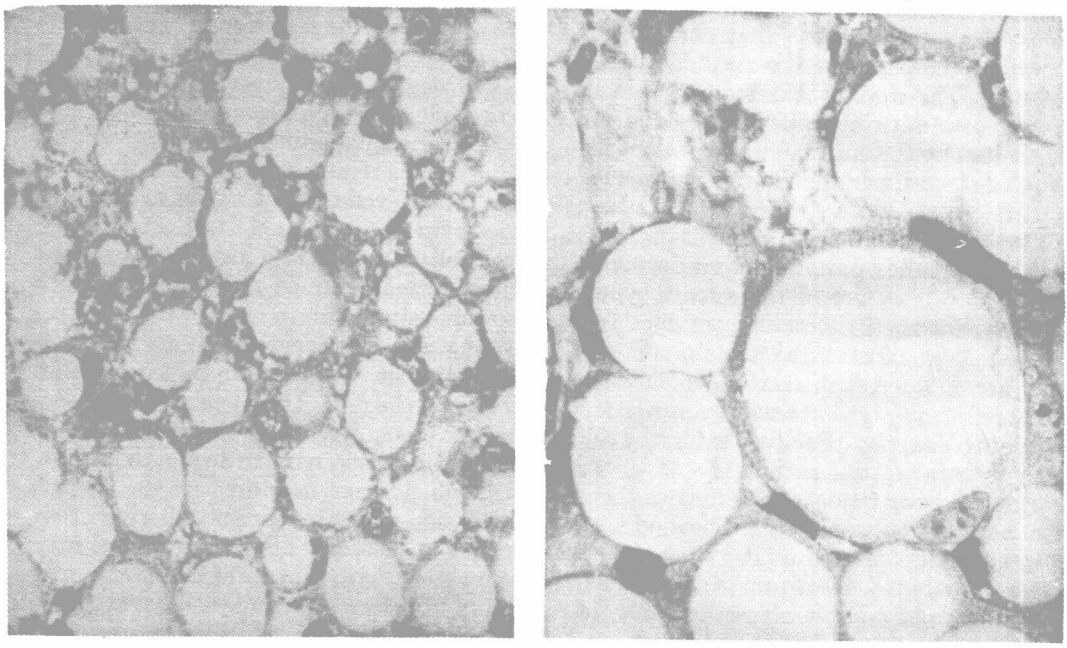
Carbohydrates are absorbed from the bowel as glucose and stored in the liver cells as glycogen. As glycogen is highly soluble in water the cytoplasmic inclusions are dissolved out when the tissue has been fixed in an aqueous solution such as 10 per cent formalin, being represented merely by spaces with a ragged outline. When alcohol is used as a fixative the glycogen is preserved, and can be stained by the periodic acid-Schiff technique. We have already seen that the Feulgen reaction for demonstrating DNA depends on the staining of aldehyde liberated by mild hydrolysis, using the Schiff reagent. When it was demonstrated by McManus and independently in the same year by Hotchkiss that periodic acid, a strong oxidizing agent, can liberate aldehydes from polysaccharides, it was then possible to stain the aldehyde with the Schiff reagent. This is the best method of staining cytoplasmic inclusions of glycogen, but of course the tissue must be fixed in alcohol. It must be noted that in the ordinary hospital patient who has died of a wasting disease we see very little glycogen in the liver cells, so that the medical student may come to think that this is the normal appearance. It is only when a well nourished person dies suddenly that we see the proper foamy appearance of the liver cells caused by the presence of glycogen.

Fat is stored in specialized fat cells and to a lesser degree in the liver, although in dietary deficiency cytoplasmic fat inclusions in the liver may dominate the picture. Just as glycogen is removed by aqueous fixatives, so fat is dissolved by the clearing agents used for paraffin sections It can be demonstrated in the cells in one of two ways: (1) by using frozen sections stained red with Scharlach R or some similar stain for fat; (2) by fixing the fat with osmic acid, which at the same time stains it black, after which paraffin sections can be cut. In ordinary routine sections we recognize fat in the cytoplasm as small spherical spaces with a smooth outline, which, when larger, may displace the nucleus to one side, in this respect differing from glycogen inclusions. The small droplets may fuse together, with rupture of the intervening walls and the formation of large spaces called by Hartroft *fatty cysts*, which are surrounded by the crescentic segments of the original cells that still persist (Fig. 2).

From this brief review of the structure and working of the normal cells of which the entire body is composed we can agree with Hamlet when he exclaims: "What a piece of work is a man!" Nor is it small wonder that this complex mechanism should sometimes go out of order.

THE SICK CELL: CELLULAR DEGENERATIONS

The infinitely complex and delicate structural and functional mechanism of the cell may be damaged by a variety of influences. If the damage is slight, the cell becomes sick with structural evidence of the sickness visible in the sections, although the very earliest lesions are purely biochemical in character, but the changes are reversible and recovery is possible. The fingerprints of disease can be seen in the tissue, but these prints can be erased. The changes in structure (and presumably in function) are described by the terms *degeneration* and *infiltration*. In the degenerations the primary change is presumed to be in the tissue elements, whilst in the infiltrations something unusual has been brought and added to the cell. As we shall



A *B*

FIG. 2.—*A*, Photomicrograph of a section of liver from a rat which had experienced a choline deficiency for 12 days. McGregor stain, × 600. The liver cells that are distended with fat are almost twice as wide as normal cells.

B, A similar preparation from a rat that experienced the same kind of deficiency for 45 days. Observe that individual cells have liberated their fat into a cyst which is surrounded by several cells. The black structures seen are capillaries that have been injected with India ink. (Hartroft, courtesy of Anat. Rec.)

soon see, this distinction is not as simple and clear as the foregoing statement would suggest. When the damage is more severe the changes are irreversible and we have a dying or dead cell, the condition described below as *necrosis*. If lime-salts are deposited in the dead tissue we speak of *pathological calcification*.

A few years ago the student was expected to be familiar with various abnormal appearances of cells under the microscope. These were empirically grouped together as degenerations, and the subject was generally ranked as perhaps the most dull in the entire study of pathology, because most of the changes seemed to have little if any connection with practical medicine. Advances in biochemistry and electron microscopy have begun to lift the curtain on their significance, and we are looking on the so-called "degenerations" with new interest, for they are sign-posts of various disturbances of the countless enzymes governing cellular activity. Sometimes they baffle us by their nonspecificity, sometimes they are so specific that a glance down the microscope at a single cell will tell us that the patient was suffering from potassium deficiency (the clear-cell vacuolation of the renal tubules in potassium loss), or a disturbance of phenylalanine metabolism (pigmentation of cartilage in alcaptonuria).

Most of these cytological changes depend on the appearance in the nucleus or cytoplasm of the normal components of the cell, components which are not usually visible because they normally occur in intricate combinations with the other components. When one or more enzyme system is damaged or blocked these intimate combinations may be broken down, or raw materials coming to the cell may remain unprocessed and