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A Textbook of

EIGHTH EDITION

908 Illustrations

Preface

WHEN it comes to writing a preface for an eighth edition of a textbook, it is not too easy to know what to put in and what to leave out. I have taken refuge in the labor-saving device of using much of the material from the preface of the previous edition. 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 and may well be accused of presumption. My only excuse is that the book is designed for the undergraduate student, the beginner, who is apt to be borne down by the erudition of the real expert. The new Chapter 1, Disease and Its Causes, which no self-respecting pathologist would think of reading, is the most obvious example of this truth.

The objective of the book is indicated by the subtitle of this edition, namely to present the structure and function of disease to the undergraduate, with increasing emphasis on function, for it is disturbed function rather than disordered structure which is responsible for the symptoms of the patient. To give a name to some lesion, and to make it fit into some accepted scheme of classification, is a very limited concept of pathology, just as it is not enough to enumerate a list of symptoms and then a list of lesions in a clinical-pathological conference worthy of the name.

The person of central, indeed commanding interest, is the sick man, woman or child, and it is the undergraduate, when he begins to practice medicine, who is going to relieve the sick person's suffering by virtue of knowledge supplied by the scientist. Pathology in relation to the living patient is the motif of the book, although at times this fact may be hard to discern. The sections on the relation of symptoms to lesions are therefore of special importance to the future doctor. A world of disordered function lies revealed in any lesion, if we only have the eye to see it.

At the present time, each department is so specialized that the student is made to feel that *its* content is all-important. As Arnold Toynbee puts it, specialization makes human minds strangers to each other. Integration and coordination of this factual mass become ever more important, and I have tried to keep this as a guide line in the present edition.

In the practice of medicine we are concerned with three main questions: What is wrong? (diagnosis); what is going to happen? (prognosis); what can be done? (treatment). To these we must add a fourth: Why did it happen? This is the question which presents the great challenge to the student of pathology. We still have to ask ourselves why cancer of the lip is so common in men and so rare in women, and why carcinoma of the hypopharynx is almost confined to women. The geography of cancer still presents a mass of questions demanding an answer. And the student should try to cast a questioning eye on what he reads. As an undergraduate, I was taught that pernicious anemia was caused by hemolytic streptococci living in the intestine and hemolysing the red blood cells! The treatment was equally absurd and useless. I have tried in places to emphasize our ignorance of some basic problems, as in the case of gout. This is especially true of the relation of symptoms to lesions.

Among the major changes in this edition, the following may be mentioned. A new Chapter 1; extensive changes in discussion of the cell, more especially the normal cell; the internal environment (formerly Derangement of Body Fluids); immunity and hypersensitivity, including the relation of the thymus to immunity and the startling new advances in our knowledge of the thymus; organ transplantation with a comment on the concept of death; coagulation and thrombosis, together with new work on the blood platelets and the microcirculation; amplification of the spontaneous regression of cancer; the systemic manifestations of

cancer, which illustrate the truth that disease is disturbed function as well as altered structure; interferon; slow-acting viruses; persisting tolerated infection; calcitonin and its relation to C-cell tumors of the thyroid; mind and brain, with notes on the mechanism of memory and its loss. Much new material has been added to the chapter on genetics, and the same is true of the chapters on the kidney and the respiratory system, with considerable rearrangement in the latter. Inflammation and repair have now been combined in one chapter. Polyarteritis nodosa and Wegener's granulomatosis have been transferred from the chapter on the blood vessels to that on immunity.

Fortunately the changes have involved deletions as well as additions. This has been most marked in the chapters on the arteries, the peritoneum, the pituitary, and the adrenal, but no chapter has escaped entirely. This is indeed inevitable when we consider that the new replaces the old.

I have taken the liberty of borrowing some passages and pictures from my own *Pathology for the Physician,* more particularly where these emphasize the clinical significance of a pathological lesion.

Bold face and italics have been used to a much greater degree than formerly, with the object of helping the student when he wishes to review the subject for one reason or another. The use of this device is obvious in the case of such a tediously long discussion as that on carcinogenesis. A number of discussions have been put into small type, although this is always a contentious subject involving the question of what is important and to whom. In this respect, it is natural that I should have the undergraduate in mind.

Many new references have been added, not for the benefit of the casual reader, but for the student who has to prepare a paper or give a talk on a particular subject. It has been said that an educated man is one who knows how to use a library. Education is the process whereby a pupil who must be taught is transformed into a student who teaches himself. The student should be provided with a stream of knowledge, not a stagnant pool from which to drink. For the picture of disease is changing before our very eyes. Old diseases are passing away as the result of prevention and the assaults of modern therapy, but new ones are continually taking their place, including those that are the result of the well-meant but injudicious use of drugs. The inn that shelters for the night is not the journey's end.

A number of the old illustrations have been discarded, including those in color, and many new ones substituted, with natural emphasis on electron micrographs. In this respect, I am particularly indebted to Dr. Henry Z. Movat. For the generous gift of black and white pictures I wish to thank Mr. Arthur Smialowski, Dr. Ashton B. Morrison, Dr. S. E. Gould (Microscopic Pathology), Dr. Donald West King (Ultrastructural Aspects of Disease), and Dr. J. L. Hollander (Arthritis and Allied Conditions). Dr. Charles A. Lupton, Jr., of Birmingham, Ala., has been most helpful with critical and suggestive comments regarding the old illustrations.

I must thank Dr. E. L. Ritcey for adding a note on alpha-1-antitrypsin globulin in relation to panlobular emphysema, and to Dr. N. B. Rewcastle for extensive and painstaking additions to the neurolipidoses and allied subjects for the reprinting of the Eighth Edition.

Without Miss Laura McKinnon's invaluable stenographic assistance this revision would have been impossible.

My long-suffering publisher, Lea & Febiger, has been ever obliging and I must mention in particular Miss Mary E. Mansor, who has been in charge of editing both the new and the old material, and has accepted last minute additions with apparent equanimity.

WILLIAM BOYD

Toronto

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Part I
Principles of Pathology

1

Disease and Its Causes

DISEASE

PATHOLOGY is the study of disease, its nature and its causes, and is basic to both the clinical and the laboratory phases of medicine. It is this connection that makes it the most exciting and stimulating subject that the medical student encounters in his undergraduate years. He is interested in disease for two reasons: first, it is fascinating and challenging in itself, and second, he is going to spend the rest of his life treating it, investigating it, or trying to prevent it. *But he must begin by giving some thought to the words we use when we are speaking of it.*

At first sight there would appear to be no difficulty in forming a concept of what we mean by disease, but the more closely the matter is considered, the more difficult it becomes—and the same is true of pathology. *Health* is a condition in which the organism is in complete accord with its surroundings, with that exquisite coordination of the different functions which characterizes the living animal or plant. *Disease* is a change in that condition as a result of which the organism suffers from discomfort (dis-ease). But we must not confuse disease with illness. Disease suggests an entity such as typhoid fever, with a recognized cause, structural changes, and clinical manifestations. When we say that a person is *ill* we merely mean that he suffers from a physiological disturbance characterized by *symptoms* (headache, pain in chest, shortness of breath) or *physical signs* (pallor, rapid pulse, swollen feet). This is the clinical viewpoint, the viewpoint of the patient and his doctor. It was the viewpoint of that supreme clinical genius Hippocrates, born about 460 B.C., and contemporary of some of the greatest men of all time. He stressed the study of the patient and the symptoms the patient presented. He applied his ear to the chest and listened for the bubbling of fluid or the friction of pleurisy. He founded the bedside method of study which after him remained neglected for many centuries, and he recorded 42 clinical cases, including his failures as well as his successes, which were almost the only record of the kind for the next 1700 years. His clinical descriptions could still find a place in a modern textbook of medicine.

We must also recognize that in addition to disease entities, each with its specific cause, there are syndromes. A *syndrome* (from the Greek meaning running together) is an aggregate of symptoms not due to a specific disease factor, but to interference at any point with a chain of physiological processes and as a result some impairment of bodily function. We shall have to consider many such syndromes in the chapters that follow, as can be seen by a glance at the index.

Just as anatomy and histology are the study of the normal body, gross and microscopic, and as physiology is the study of the working of the body in health, so *pathology is the study of the structure and function*

of the body in disease. Thus the word pathology (from Greek *pathos*, suffering) has, like the word disease, acquired a meaning different from its original one. Pathology used to be mainly a study of lesions, both gross and microscopic. Now we have become interested in the causal factors responsible for the lesions (*etiology*), the way in which the lesions are produced (*pathogenesis*), and the effect on the person involved (*the patient*). Disturbance in function may show itself as symptoms of disease, or it may not be recognized for a time, either by patient or by doctor, because of the remarkable compensating power of the body as a whole and of its individual organs in particular.

We must realize, therefore, that the patient may be diseased (not ill) without showing any clinical evidence of the fact. His heart valves may be thickened, the lining of his aorta no longer smooth, but rough and cracked, for a time without any physiological evidence of the fact. The best example of this truth is cancer. A man with cancer of the lung or liver may feel in perfect health for a long time, and yet surely we must regard him as diseased. It becomes evident that the pathologist's concept of disease, with which we are concerned in this book, is not necessarily identical with the concept of the clinician.

The study of pathology is largely carried out by the methods of the laboratory, just as medicine and surgery are, or used to be, the study of disease by the methods of the bedside. Pathology not only serves as a bridge between the basic sciences of anatomy, physiology, and biochemistry on the one hand, and medical and surgical treatment on the other, but it is the keystone of that bridge. Moreover, more than any of the other disciplines in medicine, it is ***essential to an understanding of disease***. And without understanding, how can a doctor be expected to treat a disease with success? You can be trained to do an operation perfectly, but you also must be so educated as to know when and whether an operation should be done. It is obvious that the term pathology has a wide connotation. It has been said that in essence the practice of medicine is a search for answers to three questions: What is wrong (diagnosis)? What is going to happen (prognosis)? What can be done about it (treatment)? But the pathologist asks a fourth and even more penetrating question: Why did it happen (etiology and prevention)?

The term *morbid anatomy* refers to the actual structural changes produced by disease, whether these changes are gross or microscopic. 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 bases 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.

Virchow was naturally handicapped by his ignorance of the intimate structure of cells, for he could not even guess at the existence of mitochondria, and ribosomes, and lysosomes, and genes, and DNA and RNA. And yet in 1898, four years before he died, he could write these words:

> We must strive to understand what is *happening* during a morbid process, and not be content merely with the existent condition. We must endeavor to dissect the cell, to take it apart and find out what each portion contributes to cellular function and how these parts go wrong in disease.

That was in 1898, but only in the last few years have we learned how to dissect the cells by means of the ultracentrifuge, to look at its parts with the electron microscope, and to determine what they are doing with the help of cytochemistry.

Of course 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. Altered

structure corresponds to the *lesions* studied by the pathologist, but it is disordered function that is responsible for the *symptoms* that bring the patient to the doctor. It is the functioning of the lung rather than its structure that determines whether or not a person is short of breath.

Pathology had its beginnings on the autopsy table. Wilens opens his delightful *My Friends the Doctors* as follows:

> The old adage that dead men tell no tales does not hold true as far as the medical profession is concerned. Dead men have for centuries been telling doctors the story of *how* they got sick and *why* they died, and doctors have made use of this information very effectively in the treatment of other sick people. . . . The public owes to the dissectors of the dead a debt that it has seldom recognized or acknowledged.

As the Latin inscription in one autopsy room puts it: "This is the place where death delights to serve the living." It was only when Morgagni in Italy in the middle of the eighteenth century and Louis and Laennëc in France at the beginning of the nineteenth century began to keep clinical records of hospital cases and to correlate the signs and symptoms with the lesions revealed on the autopsy table that some real understanding of disease became possible. The work was done in the place unpleasantly named the dead house.

There is still no substitute for the careful postmortem examination. It is a basic research procedure which not only throws light on the pathogenesis of disease, but shows the physician disease as it is within the human body, as well as revealing the good and bad effects of all forms of therapy, including drug therapy, and the embarrassing discrepancies between antemortem and postmortem diagnosis, from which the clinician has learned so much in the past and will continue to learn in the future.

Death. Death, its results, and its causes are studied in the autopsy room. But this raises a question which has only recently aroused acute interest and concern: What is death, and when is a person dead? At first sight the answer would seem to be simple; when the heart has stopped beating, when the patient no longer breathes, when the brain has ceased to function. But from the biologist's point of view death is a process, not a moment of time. There is a major difference between the life of a person and life of tissue within that person. After the patient is pronounced dead the cells of the body, those of the skin, the kidneys, or the heart, can continue to function if placed in the right environment. The individual dies by degrees, and he may be maintained "alive" by the heart-lung machine and other wonders of modern physics and chemistry. Finally, an organ or organs from another person may be used to replace one that has failed. The whole subject of tissue transplantation, particularly that of the heart, has been brought before the public eye and ear to an embarrassing degree. There are two major questions to be faced: (1) When is a person sufficiently "dead" to justify removal of his heart? (2) To what extent is it justifiable to keep the moribund person "alive" by the heart-lung machine and other heart, lungs, or kidneys, even though the brain has ceased to function normally? It was the author of the book of Ecclesiastes who said. "There is a time to be born, and a time to die." Fortunately it is the clinician, not the pathologist, who has to make this difficult decision. Sometimes, however, the kindly doctor may find himself murmuring those moving lines from the last act of King Lear:

> O, let him pass! he hates him
> That would upon the rack of this tough world
> Stretch him out longer.

The pathologist has two great functions to perform, which may be called the academic and the service functions, although they frequently blend and overlap. Each is of fundamental importance.

The *academic function* concerns the nature of disease and the mechanism of the disease processes. It must be realized that pathology is first a science, a branch of biology which can be studied in its own right in the human subject, in animals, and even in plants. It is only later, after the fundamental scientific knowledge has been acquired, that pathology becomes the hand-

maid of medicine. It is obvious that the problem of cancer, the unlimited multiplication of cells which normally are sharply restricted in their growth, is a fascinating subject in itself, quite apart from any relationship it bears to human health and happiness. The object of the autopsy is not merely to determine the cause of death, but to throw light on the disease process and to explain, if possible, how the symptoms of the patient were produced. It is possible that in the future a computer will listen to the complaints of the patient and arrive at a correct conclusion, but for the present the clinician must look to the pathologist for assistance.

When the doctor stands for the first time at the bedside of the patient or asks him questions in the office, his mind begins to work toward a diagnosis. Patients do not come to physicians bearing labels that designate their diseases. The questions are directed towards symptoms, which we have seen to be an expression of disordered function. It has been said that young doctors, perfectly trained in scientific medicine, do not listen to the patient any more. The next step is to make a "physical examination." Great numbers of largely unnecessary laboratory tests often take the place of a painstaking physical examination, which may be much more informative about the condition of the patient. Percussion and auscultation of the chest may tell the physician more about the lung and pleural cavity than a radiological examination.

We must not fall into the error of regarding disease as merely a state, something revealed in the autopsy room. It is rather a *process*, ever changing in its manifestations, a process that may end in recovery or in death, may be acute and fulminating in its manifestations, or may represent the slow aging of the tissues brought about by the sharp tooth of time. To rest content with recognizing and correctly naming a mitral stenosis at autopsy is to be satisfied with playing the part of a technician. For the lesion has been present during many years of life, and its presence is not sufficient to explain the final end. Moreover the pathologist has to try to explain not only why the patient died, but how he was able to live with a body so maimed, disordered, and worn out. We must concern ourselves with processes that have got out of place, out of time, and out of tune, as well as with disorder of structure, for disease may be defined as merely a summation of chemical reactions that have gone wrong. It is the high function of the pathologist not merely to attach correct labels to the lesions when he sees them, but to reconstruct the course of events from the earliest inception of the disease to the final moment when we have to fall out of "the splendid procession of life." In speaking of the microscopic study of the kidney from a case of chronic Bright's disease, Rich paints a picture of the true pathologist:

> In that minute film of tissue he plainly sees dynamic disturbances of renal function with alterations in the composition of the blood, the tissue fluids, and the urine, the elevated blood pressure, the hypertrophied heart with its constant threat of decompensation, the anemia with its debilitating effects, the disturbances of vision, the impending symptoms of uremia.
>
> In brief, in that bit of dead tissue, altered by the effects of fixatives and stains, he sees the general outlines of a living patient progressing along the path from health to death.

So far we have been speaking of pathology as if it were synonymous with the examination of diseased tissues, whether gross or microscopic, either human or in the experimental animal. This is the impression that the undergraduate student is likely to get from his contact with the academic department of pathology. But when he enters the wards of the hospital, or if he himself should become a patient, he at once encounters a very different and profoundly important aspect of the laboratory investigation of disease. This is the function of *service pathology*, which, as the name implies, is concerned with giving service to the individual sick person in the hospital by assisting the clinician in his task of arriving at a correct diagnosis. It is commonly known as *Clinical Pathology*, because some of the work, and especially the collection of material, is done at the bedside (*clinis*, a bed), although the tests on the material collected are carried out in the laboratory by highly

trained technicians under the general supervision of the clinical pathologist. Originally *laboratory medicine,* as it is sometimes called, comprised a few simple tests such as analysis of the urine, counting the number of the blood cells to determine whether the red cells were diminished (anemia) or the white cells, the leukocytes, were increased (leukemia), and examination of the sputum for pneumococci in cases of pneumonia, for tubercle bacilli in cases of suspected tuberculosis, and so on.

In recent years the scope of clinical pathology has increased to such an extent as to be almost unrecognizable. Even a short account of the subject is quite impossible in this place, but a list of some of the activities of such a laboratory or group of laboratories may convey some idea of the work. Among these activities are urinalysis; blood counts; the determination of blood groups, including the Rh factor, in connection with blood transfusion; blood chemistry, a vast subject in itself including the use of special apparatus such as the flame photometer and paper electrophoresis; examination of the cerebrospinal fluid to determine whether the clinical picture of meningitis is due to bacterial infection, for which there is efficient treatment with modern drugs, or to virus infection, for which there is no such treatment; tests for liver and kidney function in suspected disease of those organs; the bacteriological examination of the blood and excretions for microorganisms and viruses, including a determination of the sensitivity of any bacteria found to antibiotics such as penicillin; and last, but by no means least, the examination in the surgical pathology laboratory of biopsy material removed in the operating room to decide whether the lump in the patient's neck, breast, or leg is cancer or only an innocent growth, as well as an examination of the cells (*cytology*) shed from the uterus or lung in a case of suspected cancer.

In the course of his clinical studies the student soon realizes 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 that 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 that 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, a total human being with a past, present, and future, not just a disordered liver, a cardiac lesion, a lump in the breast, or an electrolyte disturbance. The art of healing is the true function of the medical profession and science is only one of its instruments. It is true that one of the greatest changes has been from empirical to scientific medicine, and knowledge of causes has brought a spectacular upsurge of preventive medicine. But biochemistry cannot predict what the clinical course will be in any particular patient, nor the reason for the occurrence of individual symptoms in one patient and not in another, nor even the variation in the intensity of symptoms in different patients.

Man is more than a sum of his parts, and the future doctor must remember that his vocation is not only to treat disease, but to

care for his patient. In the words of an old French proverb: "There are no diseases, but only sick people." It has been estimated that at least 50 per cent of all patients consulting a physician have no real organic trouble. The young recruit waiting to make his first parachute jump often has albumen and red blood cells in the urine and no eosinophils in the blood, but the real disturbance is in the mind rather than in his kidney or his bone marrow. Plato's profound remark in the Phaedrus is as true today as when it was first uttered some 2400 years ago: "For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body," or in the memorable words of Francis Peabody: "The care of the patient is caring for the patient."

THE CAUSES OF DISEASE

All reasoning about matters of fact, all physical science, depends on the relation between cause and effect. But we must admit, however unwillingly, that we seldom or never really know the cause of anything. Many a beautiful idea has been slain by ugly fact. We merely note a constant association with one thing always following another. We say that the tubercle bacillus is the cause of tuberculosis. That is merely a way of saying that the bacillus is associated with a constant type of lesion; it is no explanation of how the lesions are produced by the bacillus. Nor does it explain why some persons and animals are susceptible to the infection while others are immune. Moreover we must recognize that the pattern of disease has changed out of recognition during the last thirty to forty years owing to modern drugs, particularly the antibiotics. Death from acute infections has largely disappeared. Young people are more likely to die now from an accident than from infections, although antibiotic-resistant microorganisms unfortunately have already established a foothold. Sir Macfarlane Burnet, in a stimulating paper entitled *A Modern Basis for Pathology*, remarks that disease may be due to (1) impact of the environment, or (2) processes intrinsic in the individual. Causal agents may accordingly be classified as exogenous and endogenous.

Exogenous Agents

The most readily recognized exogenous agent is trauma. In the middle of the nineteenth century the recognition of bacteria transformed medical science, to be followed presently by viruses. Poisons no longer occupy the important position they used to in the Middle Ages, except in murder thrillers, but their place has been taken by radiation and atomic fallout, pesticides and weed-killers.

Deficiency Disease. The suggestion that disease might be due to a *deficiency* of some element necessary for the welfare of the body opened up an entirely new line of thought. Work was at first confined to the vitamins, and it was learned that one vitamin is necessary for the health of the central nervous system, another for the epithelium of mucous membranes, a third for intercellular substance, and so on. In the course of time the idea of deficiency disease has widened, and it is now realized how potent a causal agent of disease may be deficiencies of various kinds, so much so that the modern classification of the anemias is based on the deficiencies concerned.

Trauma. As we have seen, the first exogenous agent to be recognized was trauma. This recognition was easy, because effect followed cause at once or after a short interval. The onset of traumatic disease, however, may be insidious, and its origin correspondingly obscure and mysterious, not to be recognized by simple observation. An excellent example of this truth is afforded by subdural hemorrhage (see page 1220). A person sustains a comparatively trivial injury to the head, and weeks, possibly months later, when all recollection of the injury may have been lost, a train of mysterious cerebral symptoms develops which terminates in death, unless the attending doctor recognizes the pathological basis of the clinical picture, and is thus able to save the patient's life by removing the blood clot pressing on the brain. One of the most difficult questions to answer is the causal

relation of trauma to the subsequent development of cancer at the site of the trauma (see page 242). It is surely significant that the vast majority of instances of cancer supposedly due to trauma have been workmen's compensation or insurance cases.

Bacteria. It is difficult for us to picture the practice of medicine or the approach to disease before the development of the theory of bacterial infection, and yet that is only about one hundred years ago, a mere moment in the long history of man. Even the idea that such apparently diverse processes as fermentation, putrefaction, and infection of the living body were in reality intimately associated was long rejected by many authorities.

But when we ask for *proof* that a bacterium is the cause of a given disease we have need of every critical faculty that we possess. The first step is the demonstration of the germ in the affected tissues, coupled with its absence from healthy tissues. This was the method employed by Koch in his investigation of the cause of tuberculosis. But if we try to prove the nature of a syphilitic gumma by demonstrating the Treponema pallidum in the tissues, we shall almost certainly fail. More subtle methods for solving the problem are required. Moreover, the mere presence of bacteria in the tissues does not of itself constitute proof that they are of etiological significance. The organisms of typhoid fever, diphtheria, and meningococcal meningitis can lead a harmless saprophytic existence in carriers. They become *commensals,* a pleasant word meaning "one who eats at the same table."

In order to prove the causal relationship of a bacterium to a disease, isolation of the microorganism from the tissues is, of course, no longer necessary in every case. More indirect methods are available, such as the demonstration of specific immune bodies in the host's serum against the bacterium, e.g., agglutinins, precipitins, and fixation antibodies, not to mention the Wassermann reaction, which is not specific.

Viruses. If it is sometimes difficult to prove conclusively the causal relationship of a bacterium to a disease, this difficulty becomes very much greater in the case of viral diseases. In addition to being ultramicroscopic in size, although now demonstrable by the electron microscope, a virus refuses to grow on nonliving bacteriological media. It can therefore only be recognized by the effect it produces, or by injection into living tissues such as chicken embryos. This effect may be clinical or histological. Sometimes the clinical effect is unequivocal, as in the paralysis that follows inoculation with poliomyelitis virus; sometimes it is of the type in which certainty is extremely difficult, as in the case of influenza. Similarly, the histological change produced by a virus may be characteristic or indeterminate. *Necrosis of a specific cell type* may be pathognomonic, as exemplified by the destruction of the anterior horn cells produced by the virus of poliomyelitis. The peculiar features known as *cell inclusions* have been regarded as the tell-tale fingerprints left by a virus, and with such inclusions as the Negri bodies in rabies this is undoubtedly true. It is now recognized, however, that identical appearances may be produced by nonviral agencies. A new tool, the use of fluorescent antibodies, permits very rapid diagnosis in rabies.

There are many other exogenous agents of a physical or chemical nature such as heat or cold, poisons, and more particularly radiation, which will be considered in later chapters. Mention has already been made of pesticides, injudicious use of which may lead to the accumulation of poisonous chemicals in the flesh of grazing animals and the milk of cows.

This leads to a breakdown of the vital process of decay which balances life in the natural world. Nature does not exist only to serve man; he must live in harmony with it, and at the present time man-made pollution, whether in the soil, the water, or the air, is wrecking the world. This is a problem that the doctor of the future will have to face.

Endogenous Agents

Medicine had its beginnings in mystery and superstition in the dark and backward abysm of time. In those days all illness and disease were due to the presence of evil

spirits that had to be exorcised. In more recent times dead men have been telling doctors the story of how they got sick and why they died. Now we are beginning to recognize that endogenous or intrinsic factors may be of even greater importance than exogenous ones. The science of genetics, which was born one-hundred years ago with Mendel's work on crossing peas of different color, has exploded during the last two or three decades, and now genes are used to explain almost everything that is not blamed on allergy or autoimmunity, that concept with the misleading name which is considered in Chapter 6. The general subject of genetic disorders is discussed in some detail in Chapter 20. The symptoms of the patient, the truest indicator of disease, are so often due to disturbance of intracellular enzymes, which in turn may be caused by endogenous factors.

Other examples of endogenous factors are hormonal disturbances, which can be so far-reaching in their results, but again we know the What, rather than the How and the Why. It is only recently that we have come to realize that we do not know the cause of diabetes mellitus. Nor, for that matter, do we know the cause of those great killers, atherosclerosis, coronary thrombosis, and cancer.

Multiple Causes

Perhaps one of our fundamental errors in discussing causation is to assume that there must be one and only one cause of a lesion or a disease. That, of course, is absurd. When an elderly woman falls on leaving an evening party and breaks the neck of her femur, a number of etiological factors may be involved. One is gravity, without which she would not have fallen. A second is alcohol, which undoubtedly assisted her fall. But in addition there may be a number of accessory factors such as age, sex (the bones of the aging female are more brittle), the activity of the parathyroid and other glands, and still other factors that we shall encounter in the course of our studies. Moreover we are apt to forget that with regard to the normal regulating mechanisms by which health is preserved there may so easily be too much or too little. Thus our red blood corpuscles are continually being destroyed, but if the process is unduly speeded up, we speak of hemolytic anemia. Fibrin is being continually formed, but normally it is kept in control by fibrinolysis. If, however, the control mechanism becomes too active or not active enough, the result may be disastrous. Inflammation is a defense mechanism, but it can be overdone.

Among the causal agents concerned with a disease, there may be one major factor and a number of accessory factors without which the major one would be impotent. Perhaps the best example of this truth is cancer. Many causes of cancer are already known. We do not have the slightest idea of how they act as pathogens, although we are beginning to suspect some interference with the genetic code which regulates the growth and development of cells. Cancer in the animal is identical with cancer in man, and experimental cancer can be produced by the application of tar and a host of synthetic products, by the injection of an ovarian hormone, by filtrable viruses, by exposure to x-rays and radium, and by yet other means. The more debatable question of the causation of human cancer will be discussed in the appropriate place (page 222). One thing, however, is certain: both in the experimental animal and in man a genetic factor may play an all-important part.

Iatrogenic Disease

It is sad to have to conclude this discussion of the causation of disease by reference to the doctor as a causal agent. In fear of the public we seek refuge in a mystic word, *iatrogenic*, trusting that the patient will not consult a medical dictionary and find that *iatros* is Greek for physician and *genetic* means produced by. Unfortunately what is powerful for good may also be potent for evil, as is so agonizingly evident in the case of radiation therapy.

The student must learn that the picture of disease is changing before our very eyes. Old diseases are passing away as the result