An Introduction to THE PRINCIPLES OF DISEASE

WALTER

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To Elizabeth

PREFACE

The aim of *An Introduction to the Principles of Disease* is to initiate the student into clinical medicine via the study of pathology. In the past such an approach has been successful in the training of physicians; recently, attempts to deviate from this course have not been particularly popular or successful. Although pathology has often been likened to the basis or roots of medicine, efforts to make students study it in great detail before venturing into clinical medicine have also been unpopular. This lack of enthusiasm for an in-depth study of pathology is quite understandable: Does any tree develop a full root system before embarking on the exciting experiment of sending a shoot toward the sky? Pathology and clinical medicine must be closely associated: This introduction to disease is intended to be no more than a primer in the study of medicine. No prior knowledge of medicine is assumed, but the reader should have had some instruction in biology, chemistry, human anatomy, and physiology.

Part I of this book describes the general principles of disease and the disorders that affect the body as a whole. Part II concentrates on diseases of individual organs. The objective has been to describe important mechanisms of diseases in considerable detail and to omit any reference to rare conditions. This book is not a synopsis of pathology; consequently, readers who are aiming for a degree in medicine will have to graduate to the larger texts of clinical medicine and pathology before attaining their objective.

The complexity and ever-increasing cost of providing medical care has led to a reappraisal of the role of the medical doctor. In the past, it was expected that physicians would assume absolute responsibility for the diagnosis and treatment of their patients. No longer can this view be upheld. Physicians must now rely on the competence of coworkers not trained as medical practitioners, but whose specialized knowledge is of vital importance in the diagnosis and treatment of patients. Nurses, midwives, physical therapists, pharmacists, and medical technologists are among this group of workers in the allied health sciences for whom this book has been written.

When studying medicine for the first time, the student meets many new words and concepts. An attempt has been made in this book to define these items when they are first introduced so that learning can proceed by a series of progressive steps. Little attempt has been made to avoid the specialized

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terminology of medicine, because this technical language is widely used in medical practice. If used correctly, it acts as a type of shorthand by which medical personnel can express their ideas by either the spoken or the written word. Without learning the language of medicine, one finds it difficult to converse with a physician or to comprehend the medical literature. The medical student and allied health worker must be able to do both. In an effort to encourage independent thought by the reader, each chapter ends with a list of selected readings in which further details or different views can be found.

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I owe special gratitude to those who have given me pictorial material or who have allowed me to modify their original published work. The source of material is detailed in the caption of each figure. I am particularly grateful to the following: Dr. Y. C. Bedard, for providing many electron micrographs; Dr. J. B. Cullen, for his help in providing pictures of autopsy and surgical material from the Toronto General Hospital; Dr. P. Stuart, for pictures of intestinal parasites; Dr. N. B. Rewcastle, for many of the illustrations in the chapter on the nervous system; and Micheline Fauvel, for her excellent electron micrographs of viruses.

A number of figures (also appearing in *General Pathology*) are of specimens from the Welcome Museum of Pathology, Royal College of Surgeons of England, London; I am grateful to the President and the Council of the Royal College of Surgeons of England for permission to reproduce these illustrations. In accordance with the wishes of the council, each specimen is acknowledged at the end of the caption and the catalogue number of each is indicated. Some specimens are from the Boyd Museum, University of Toronto, and I thank Dr. E. Farber of that institution for permission to use these.

I am indebted to a number of colleagues for providing valuable criticism and for assisting in the areas of their particular expertise: Dr. G. T. Simone (electron microscopy), Dr. Agnes Reicher (diseases of the skin), Dr. Susan Ritchie (diseases of the kidney and liver), Dr. J. S. Speakman (diseases of the eye), and Dr. A. W. P. Van Nostrand (diseases of the ear).

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Part I.
GENERAL PATHOLOGY

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INTRODUCTION

Chapter 1

Chapter Outline

After studying this chapter the student should be able to:

- Define the terms *sign, symptom, lesion, etiology, pathogenesis, syndrome, idiopathic, biopsy, thoracotomy,* and *laparotomy.*
- List the units of measurement used in microscopy.
- Compare and contrast the techniques and value of light microscopy with those of electron microscopy with respect to (a) resolution, (b) magnification, (c) ease of studying living cells, (d) thickness of tissue sections used, and (e) methods of staining.
- Describe the major steps in the preparation of a paraffin-wax section and the appearance of cells when stained with hematoxylin and eosin (H & E).
- Describe the main uses in pathology of phase contrast and dark ground illumination in microscopy.
- Discuss the advantages that the frozen section technique has over the paraffin-wax technique.
- Give examples of the use of radioactive isotopes in clinical medicine and in experimental pathology.
- Distinguish between cell culture and organ culture.

INTRODUCTION

Introduction

The majority of persons seeking medical help do so because of some abnormality causing them distress. Often such *symptoms* can be dispelled by simple remedies—quite often by reassurance. Much of medicine is an art, which its practitioners—whether they be doctors, dentists, nurses, or physical therapists—must learn. Nevertheless, there have always been individuals who were not content simply to observe disease and the effects of time-honored remedies upon it. They have attempted to describe and record the abnormalities in their patients in an objective manner; by introducing measurements, they initiated the science called *pathology*.

Disease itself is as difficult to define as is the normal, from which it is a departure. As generally used, the term "disease" is employed to describe a state in which there is a sufficient departure from the normal for *signs* or *symptoms* to be produced. A symptom is an abnormality noted by the patient. A sign is one noted by another observer. The objective variations from the normal are called *lesions*, and although the term generally refers to structural changes, it may also be used to describe functional abnormalities, such as biochemical lesions (see Chapter 4). The theory of the cause of a disease is its *etiology*, and the development of the lesions is its *pathogenesis*. When used strictly, these two terms are quite separate entities, but in practice they are often used interchangeably. Thus, it is commonly said that the cause of a heart attack is blockage of a diseased coronary artery (arteriosclerosis). Nevertheless, the cause of this may be some genetic defect or an abnormality in the diet. Thus, the coronary disease is merely part of the pathogenesis of the whole picture.

The great advances in bacteriology that started at the end of the nineteenth century fostered the concept that each disease had a single cause. To state that the common wart is always caused by a particular virus is true; nevertheless, this is an incomplete statement. It is known that some patients with multiple warts have a deficient immunity that either can be inherited or can be acquired by administration of drugs. Which is the cause of the warts—the virus or the impaired immunity? Present doctrine would still favor the organism, but the genetic or acquired immunological deficiency would be labeled a major predisposing factor. Multiple causes are probably much more common than we think. The doctrine of one cause for one disease has certainly failed to be a profitable concept in the search for the etiology of many common diseases such as cancer, arteriosclerosis, emphysema, and chronic bronchitis. Nevertheless, the concept that each disease is an entity implies a specific cause for each.

To avoid the difficulty of defining disease the term *syndrome* has been introduced. A syndrome is a condition having a defined collection of lesions,

signs, or symptoms that are not necessarily always due to the same agent. Thus, Raynaud's syndrome is a condition in which the hands are unduly susceptible to cold, and on exposure become pale and finally blue and painful. This syndrome can be found in patients with systemic lupus erythematosus (see Chapter 27), it may be seen in workers who use pneumatic hammers, and finally it can occur for no apparent reason. When the cause is unknown, the condition is said to be *idiopathic*. Clearly, those conditions that are commonly labeled "diseases," and in which the cause is not known, are difficult to distinguish from syndromes. Indeed, the terms "syndrome" and "disease" are frequently used quite indiscriminately and interchangeably.

Pathology is thus the scientific study of disease. It describes the cause, course, and termination of disease as well as the nature of its lesions. In almost all diseases the lesions are of varying nature and may be morphological, chemical, or functional. Nevertheless, anything that can be measured is within the domain of pathology. The height of the blood pressure, the rate of the heart beat, and the temperature of the patient are all valued measurements. If they are accurately recorded, they are as scientific as measurements of the size of a nucleus or of the amount of DNA that it contains. The remainder of this chapter is devoted to a brief account of the methods of investigation that can be employed.

Microscopy

THE LIGHT MICROSCOPE

The application of the compound light microscope to the examination of biological material was one of the most important steps ever taken in scientific medicine. From it stemmed the concept that all living organisms are composed of cells and cell products. The light microscope is now routinely used in the examination of diseased tissue; *histopathology* is the study of changes in diseased tissue.

The ability to distinguish two closely placed points is called the *resolving power* of the microscope. When light is used, it is limited by the wavelength of the light beam used. With the light microscopes currently available, the resolving power is about 250 nm.* One of the great advantages of the electron microscope is that its resolution is much greater; in fact, it is about 0.5 nm. The maximum magnification obtainable with light microscopes of current design is about 1200. Further magnification is useless, since it merely produces a large but indistinct image that is due to the limited resolution obtainable.

Living tissue is transparent, and the homogeneity in optical density of its components hides its detailed structure. Staining techniques must therefore be employed. Unfortunately, staining almost invariably means that the cells must be dead. Nevertheless, there are two special techniques, having limited specific uses, which can be employed to visualize living cells.

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*1 mm = 1000 μm (micrometers or microns); 1 μm = 1000 nm; 1 nm = 10Å (Ångström units). The present tendency is to dispense with the Ångström unit and use the nanometers (nm) instead. It is useful to remember that most cocci (*e.g., Staphylococcus aureus*) are about 1 μm in diameter, a normal red cell is about 7 μm in diameter, and most nuclei are 5 to 10 μm in diameter.

Dark ground illumination relies upon the fact that objects placed in a beam of light may be seen by the light they reflect in much the same way that dust particles are rendered visible by a shaft of sunlight. Using a special substage condenser, this method finds particular application in the demonstration of the organism responsible for syphilis, *Treponema pallidum*, which is regularly demonstrated in venereal disease clinics by this method.

Phase contrast microscopy takes advantage of the different refractive indices of various parts of the cell. These differences are converted into differences in optical density. In this way, living cells can be examined, and the method may be applied in virology where thin sheets of cells in culture can be seen and the effect of viruses on them examined (Figs. 12–4, 12–7, and 12–8).

For the routine examination of tissue, the material must be processed and then sectioned into thin slices. The two methods available, the paraffin section technique and the frozen section technique, are described later in this chapter. Human tissue for histopathological studies is obtained in three ways:

1. SIMPLE BIOPSY. This entails the removal of a small piece of living tissue for examination. With skin lesions, this can be done easily under the anesthesia produced by the local injection of 1 or 2 per cent Xylocaine solution. Biopsy through an endoscope is an extension of this method, *e.g.*, bronchoscopy for lung lesions, and cystoscopy for bladder lesions. Solid tissues like liver, spleen, and tumors can be examined by needle biopsy; a core of tissue is obtained with this technique.

2. BIOPSY AT OPERATION. An operation is occasionally performed specifically to obtain a biopsy. Thus *thoracotomy* (opening the chest wall) is used to diagnose some diffuse lung lesions not readily examined by needle biopsy. *Laparotomy* (opening the peritoneal cavity) is a necessary prelude to the biopsy of abdominal lesions and is generally followed by some definitive treatment.

3. NECROPSY. Necropsy provides abundant tissue for histopathological study, but unfortunately postmortem autolysis (Chapter 4) often limits detailed examination.

Paraffin Section Technique. This is the most commonly used routine method of examination. Fresh tissue is placed as soon as possible in *fixative*, generally a 10 per cent solution of formalin. It can remain in this solution for many months without deteriorating. Fixation renders many cell constituents insoluble, and it also inhibits enzymatic action. Blocks no thicker than 2 mm are prepared, *dehydrated* in graded alcohol, *cleared* in xylol, chloroform, or some other solvent that is miscible in both alcohol and wax, *impregnated* with molten paraffin wax, and finally when cooled, are blocked out or *embedded* in paraffin wax. From the block obtained in this way 5-μm sections are *cut* on a microtome (Fig. 1–1).

When mounted on glass slides the sections must be stained to render tissue components visible. The commonly used stains are *hematoxylin and eosin* (H & E). Hematoxylin is a blue basic dye obtained from the bark of a South American tree. It is taken up by acidic substances in the cell. Hence, the nucleus with its nucleic acid content is stained blue. Eosin is a red synthetic acidic dye that binds to basic proteins found for the most part in cytoplasm. H & E stained sections are used routinely for diagnostic purposes.

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