BLACK AND WAGNER

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Preface

As teachers of pathology, we feel that we have a twofold responsibility in regard to medical education. On the one hand are the sophomore students who come to us with the vocabulary and, to some extent, the concepts derived from such courses as anatomy, biochemistry, and physiology. On the other hand are the more advanced students and the practicing physicians who are fluent in the vocabulary of disease but often lack insight into the dynamic continuity of function and dysfunction. It is, therefore, our particular responsibility not only to impart the vocabulary of disease to the former, but also to integrate and make meaningful for both that which has gone before as a basis for that which is to come. We believe that pathology should be presented as an extension of normal structure and function. It should seek to define the nature and consequences of those structural and functional aberrations which we term pathological and which commonly have their clinical expression in overt disease. Such knowledge is basic to any rational approach to the diagnosis, treatment, and prevention of disease.

However, it is important that the presentation of details should not obscure the dynamic continuity of biological function in health and disease. It is the dynamic orientation which gives meaning to the details. Such an orientation reveals medicine as the ultimate "who-done-it," whose amazing plot and cast of characters can provide a never-ending source of interest and satisfaction. This book was written in order to emphasize the thread of continuity which runs throughout medicine in general and pathology in particular. It is not intended to be a substitute for a formal course in pathology.

For this reason, we have not included extensive photomicrographs. Neither have we listed extensive bibliographical references. The references cited were

chosen to document concepts and illustrate the significance of pathology to clinical medicine. In keeping with this latter aim, we have been partial to reports appearing in general medical publications. We believe that such a selection will emphasize that pathology is not just a hurdle in the medical curriculum but rather the foundation of medical investigation and practice.

We are aware that this book often reflects our personal orientation and that different interpretations might be preferred by others. However, a presentation can be just as severely emasculated by an attempt to do justice to all hypotheses as it can be hampered by a slavish adherence to articles of faith. One of the pleasures and prerogatives of teachers is to disagree with other teachers and authors. Although we have sought to keep such pleasures among our colleagues to a minimum, we have no doubts but that some remain.

It has been said that we see what we know. It is our hope that this book will aid both the student and physician in becoming more knowledgeable and more receptive to what is to be seen in the laboratory and clinic. Above all, we would hope that this presentation will help impart the sense of beauty and excitement which should be engendered by the study and practice of medicine.

Each of us is the recipient of a rich legacy of fact and concept which, in a small measure, we acknowledge by the citation of references. Such citations are but token recognition of our indebtedness to countless predecessors and colleagues. We should also like to acknowledge particular indebtedness to our more immediate mentors.

One of us (M. M. B.) acknowledges with pleasure his indebtedness to the late Professor Robert Chambers for training in cellular physiology, to Dr. Benjamin W. Zweifach for revealing the wonders of homeostatic systems, to Dr. Israel S. Kleiner for his generosity and proficiency as a teacher, and to Dr. Francis D. Speer whose encyclopedic knowledge of pathology has always been at the disposal of his students and colleagues. The other author (B. M. W.) extends thanks to Dr. Paul Klemperer for his training and for exemplifying the role of the pathologist in scholarship, service, and investigation. Both of us wish to acknowledge the critical comments of Dr. Hudson R. Ansley and the assistance of Dr. Ada Chabon in the preparation of this book.

Maurice M. Black
Bernard M. Wagner

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PART ONE

Homeostatic mechanisms

There is no simple way to approach the study of pathology; however, it would seem desirable to orient such study in terms of a common phenomenon that should provide continuity between the biological activities at different levels of organization. For this purpose we have chosen to consider homeostasis as the thread of reference.

Homeostasis may be defined as the constellation of activities that serves to maintain the functional integrity of the biological system under consideration. Such control is known to operate on varying levels from the ultrastructural to the multicellular organismal level. To a large extent, therapeutic rationale depends on our knowledge of the chemical basis of homeostatic defects.

It should be emphasized that biological systems are open systems; therefore, biological homeostasis refers to a steady state in a dynamic system. According to Drabkin, there are two pertinent characteristics of open systems: "(1) they are inseparable from the external environment . . .; (2) they are not obliged to maintain unique stationary levels. . . . In other words, there may be more than one, perhaps an infinite number of possible homeostatic levels. . . . [Thus] the open system exhibits only the *constancy of constant change. When change ceases, life ceases.*"*

Because of these features, defects on one level may produce alterations in succeeding, and sometimes in preceding, levels of organization. The precision with which we are able to define the dimensions of defective function will depend not only on the nature of the primary defect, but also on the secondary effects and on our analytical tools. For this reason, pathology is concerned with and employs a variety of methods. Sometimes these are arbitrarily divided into such groupings as morbid anatomy, clinical pathology, histochemistry, ultrastructure, cytochemistry, cytology, etc. It should be emphasized that these are but particular levels of inquiry and not separate entities.

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*From Drabkin, D. L.: Imperfection: biochemical phobias and metabolic ambivalence, Perspect. Biol. & Med. 2:476-477, 1959.

Chapter 1

Concepts and terminology

INTRODUCTION

It is no longer valid to limit the field of pathology to an examination of alterations in the gross structure and microscopic appearance of tissues. This is not to deny the historical and continuing significance of careful microscopic analysis in the diagnosis and investigation of disease. However, the neophyte in pathology should keep in mind that the microscopic section is but one level of experience contributing to our knowledge of biological events. In some instances, there may be excellent correlation between the microscopic picture and the etiology, pathogenesis, and prognosis of a disease. On the other hand, the microscopic appearance may give little or no evidence of the nature of the illness or cause of death.

Unless these features are appreciated, the student will fall into the error of some clinicians who are chagrined and feel cheated when the pathologist states that the microscopic examination failed to reveal the cause of death. Toxicological, biochemical, or microbiological studies performed during the illness may provide the requisite information to establish the cause of death. Although the microscope is, and will probably long remain, the hallmark of the pathologist, it is hoped that this book will emphasize the dynamic scope and dimension of modern pathology.

It should be emphasized that pathology and medicine are biological sciences. One should not construe the application of biophysical techniques to

biological problems as a denial of the distinction between life and nonlife. On the contrary,

> "Analysis of living systems, based on modern physical and chemical theory, leads to the conclusion that life is unique and that it cannot be reduced to the property of a single substance or of a system less complex than a living cell."*

This thought, from an article by Commoner, provides a most valuable perspective to the student of medicine. From this concept, there stems the awareness that:

> "Too often, we are prepared to expose miles of countryside to substances known chiefly for their power to kill. By the time we have dispersed insecticides, herbicides, fungicides, nematocides, pesticides, and other assorted agents, the adaptive latitude of the ecological environment, which is so vital to the success of plant, beast, and man, may have been fatally restricted. I sometimes think that the difficulties we now face in controlling water, air, and soil pollution, and the undue dissemination of radioactive materials, are the result of a common impression that 'the boundary between life and non-life has all but disappeared.' In fact, if we do not mend our ways, the statement may, after all, turn out to be true."†

CONCEPTS OF CELLULAR AND HUMORAL BASIS OF DISEASE

Correlation between structure and disease

The tissues of man, like those of all higher forms, are made up of aggregates of cells. Therefore, it is not surprising that many diseases are associated with structural changes in cells and tissues. Of particular interest is the empirical finding that particular patterns of microscopic changes may often be correlated with the type of disease or causative agent. This correlation between structural changes and disease is the basis of microscopic diagnosis. It permits the pathologist to render such diagnoses as cancer, tuberculosis, acute infectious disease, glomerulonephritis, etc. on the basis of the gross and microscopic features of tissue obtained surgically or at autopsy. The efficiency of this method of diagnosis is generally greater than that of any other diagnostic procedure. The commonly employed term "biopsy-proved diagnosis" is a testament to the general reliability of microscopic diagnosis.

Nevertheless, it must be emphasized that lightning and thunder do not accompany the pathologists' reports. Recognizable structural changes do not accompany all types of illness, nor does each etiological agent leave an absolutely distinctive fingerprint on the tissues. In addition, it should be remembered that individual pathologists may provide different interpretations of the same tissue section, based on their personal experience with the particular lesion and the available knowledge in the field. Despite these limitations, which must always be kept in mind, structural alterations in tissues provide one of the most powerful tools currently available for the diagnosis and understanding of disease.

The pathologist utilizes both gross and microscopic observations of a speci-

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*From Commoner, Barry: In defense of biology, Science 133:1747, June 2, 1961.
†From Commoner, Barry: In defense of biology, Science 133:1748, June 2, 1961.

men in order to arrive at a diagnosis. With both types of study the approach is essentially the same, that is, from the general architectural features to the particular detailed alterations. In many instances the gross appearance will be characteristic. Thus, cancer tissue can usually be recognized by its gross characteristics, a feature equally as important to the surgeon as to the pathologist. Through the medium of microscopic study, the pathologist seeks answers to the following questions: (1) Is there structural evidence of abnormality in the specimen? (2) What is the nature of the abnormality, for example, degenerative, inflammatory, or neoplastic? (3) What specific diagnosis is compatible with the observed findings? At the same time, he also seeks answers to ancillary questions regarding prognosis and therapy.

In some instances, the microscopic alterations may not allow for a specific diagnosis but may indicate the need for special types of biochemical, serological, or microbiological studies which, in combination with the pathological lesion, would allow a definitive diagnosis to be made. In short, the pathologist uses his knowledge of the normal structural features as a baseline to determine whether or not a tissue in question is the seat of a histopathological change. The nature of the change is determined by discerning the type of cellular and tissue alteration that is present, whereas the final diagnosis is dependent upon the degree of empirical correlation that exists between the histopathological alterations and known diseases.

Alterations of blood in disease

Since the cells of the body are bathed in a liquid medium (extravascular, extracellular fluid) that is in equilibrium with the blood, pathological changes in tissues are commonly associated with changes in blood constituents. Abnormal constituents or altered concentrations of normal constituents may be found in response to the pathological tissue or as a consequence of the disease. Such changes may be biochemical and/or cellular. Therefore, measurements of the chemical and cellular components of the body may provide important diagnostic or prognostic information in addition to, or sometimes without, specific microscopically demonstrable changes in tissue structure; for example, elevations in blood glucose or glucosuria readily suggest the presence of diabetes mellitus, whereas the tissue changes in this disease are often of minimal degree or lack diagnostic specificity.

It is also pertinent to note that some blood chemical abnormalities arising in disease may have pathological consequences of their own. Thus, the rise of acid metabolites and the fall of fixed base in the course of diabetes lead to acidosis with concomitant malfunction of the central nervous system, defective albumin synthesis in liver disease may accentuate edema formation, impairment in antibody synthesis in lymphoid tissues predisposes to recurrent bacterial infection, etc. These few examples illustrate that significant alteration of the internal milieu is not only of diagnostic significance but may also lead to secondary alterations that are of themselves deleterious. The phase of pathology concerned with measurements of body fluids and wastes in relation to diagnosis and prognosis of disease is called clinical pathology. It embraces

such diverse disciplines as biochemistry, serology, microbiology, hematology, and parasitology. It is evident that this is a distinction of convenience and in no way implies a separate area of study.

THE MIRAGE OF HEALTH

Dubos used the phrase "mirage of health" as the title of a provocative monograph on host-parasite interactions. Therein he emphasized that health is not synonymous with the absence of infection, for infection by potential pathogens is usual despite the apparent health of the host. Disease is thus viewed as a consequence of a loss of equilibrium between the host and parasite.

This concept may be extended to include other potentially deleterious factors as well; for example, potentially toxic agents of exogenous or endogenous origin may cause no demonstrable effect provided detoxification or sufficiently rapid excretion occurs. Even cancer may remain quiescent in some patients for months or years. The clinical manifestations of cancer may be as much due to failure of host factors as to the presence of a focus of cancer cells. Such observations emphasize the importance of the dynamic aspects of disease, which include both the host and the causative agent.

An appreciation of the dynamic reactivity of biological systems allows disease processes to be viewed as experiments of nature. Such experiments are doubly interesting since they provide information concerning the functional consequences of the agent or disease in question and also demonstrate individual variations in the host-agent relationship. Individuality is the basis of such concepts as the LD_{50}. The latter refers to the dose of a potentially lethal agent that will kill 50% of the exposed population. Such a value takes into account the remarkable variability that may be encountered in the biological response to deleterious stimuli. Actually the concept may be broadened to include responses to a variety of stimuli other than those that are potentially lethal.

The recognition and study of those individuals who survive what should have been a lethal exposure to drugs, radiation, cancer, infectious disease, etc. may disclose factors whose control might provide protection for the great majority of the currently susceptible population. In fact, the field of protective immunization developed from just such types of observation. Conversely, the recognition and study of those individuals who exhibit unusual sensitivity to drugs that are innocuous to most people have provided valuable data on the genetic control of cellular metabolism.

BASIC TERMINOLOGY OF DISEASE

An understanding of conceptual terms is of prime importance in any systemic study. It is, therefore, important that such terms be defined early and that the phenomena to which they refer be recognized in the course of subsequent studies.

Etiology refers to the agent or cause of a disease or pathological process in a **susceptible** host. The latter phrase is included to emphasize the contribu-