MECHANISMS OF DISEASE

A TEXTBOOK OF COMPARATIVE GENERAL PATHOLOGY

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WILLIAMS & WILKINS
Baltimore/London

Made in the United States of America

Library of Congress Cataloging in Publication Data

Slauson, David O.
Mechanisms of disease.

Includes index.
1. Pathology, Comparative. I. Cooper, Barry J. II. Title. [DNLM: 1. Animal diseases—Pathology. 2. Animal diseases—Physiopathology. SF 769 S631m]
RB114.S58 636.089'607 81-19827
ISBN 0-683-07742-2 AACR2

Composed and printed at the
Waverly Press, Inc.
Mt. Royal and Guilford Aves.
Baltimore, MD 21202, U.S.A.

To our wives, Anne and Lorraine,
and to our children,
Todd, Kurt, Julie, Justine, Michael and Paul.

Preface

Our aim in writing this book is to initiate students into clinical medicine through the study of pathology. As such, our primary focus is to present basic disease mechanisms in a fashion useful to beginning pathology students who will ultimately become clinicians. We are simultaneously hopeful that the book will provide a useful sourcebook of basic material for pathology interns and graduate students, and a compact review of disease mechanisms for persons preparing for pathology board examinations.

The boundary between pathology and the clinical sciences is an increasingly blurred one, and pathology is now widely regarded as a discipline critical to the clinical sciences. We strongly concur with this view, but the blending of pathology and clinical sciences can be a successful marriage only if the material studied in pathology has applicability to a clinical setting. For students of veterinary medicine, memorizing lists of lesions and viewing transparencies of diseased tissue is quite possibly the least useful way to learn pathology. It is not useful because it becomes knowledge out of context which is quickly forgotten. Our emphasis here is on pathogenesis, the mechanisms by which disease occurs, for only through an understanding of **how** and **why** disease states evolve is it possible to deal with the changing dynamics of disease in a clinical setting. We do not wish to downplay the importance of lesions in the teaching of pathology, but in an introductory setting they must be presented as illustrative means of reinforcing the ideas and concepts that emerge from the study of disease mechanisms. In short, it is not our purpose to make pathologists of our readers, but to highlight the ways in which disease occurs in sufficient depth that the basic information becomes applicable to a wide spectrum of disease settings.

The scope of pathology has expanded enormously in the past few decades, and the problem for authors today is not what to include, but what to leave out. We purposely have avoided any attempt to make the coverage encyclopedic, and rather have dealt with critical subject matter in some detail instead of taking a superficial look at a greater variety of material. What is included and what is excluded represent our collective best judgement regarding the needs of contemporary students. We have not hesitated to present material at the ultrastructural and biochemical levels. The greater our level of resolution can be, the greater is our understanding of the disease mechanisms.

The means by which cells become injured and die, thrombi form, inflammatory defenses are mobilized, tissues heal, cells transform to acquire malignant characteristics, and parasites interact with their host form the basis for exciting stories to unfold. No best selling novel possibly could contain more action than is available in most diseases. It seems, however, that the excitement inherent in these various disease dramas often is lost in muddy prose on the printed pages of a deadly boring textbook. Textbooks, we are told, do not have to be interesting, only informative. This is sad. Nothing as interesting

as "biology gone wrong" should become stilted by the way in which it is presented. We have made a concerted effort here to keep the material exciting and the prose readable. History no doubt will tell us how well we have succeeded in that regard. We are hopeful that this book will provide not only a means of acquiring a sound knowledge of the basic mechanisms of disease, but also provide a not unpleasant way to gain that knowledge.

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Acknowledgments

It is a pleasure to be able to record a measure of thanks to the host of individuals who directly or indirectly have contributed to the completion of this text. We are especially grateful to our colleagues at Cornell University who have patiently read and reread various parts of the manuscript. Dr. Gary Cockerell was especially helpful with the chapters on The Inflammatory Process, Immunopathology, and Disorders of Cell Growth. Dr. Ron Minor made a number of helpful suggestions for the chapter on Disease at the Cellular Level. Dr. Bob Lewis, our Department Chairman, was especially helpful on the Immunopathology chapter. We also are grateful for his willingness to pretend not to see that some of our departmental functions suffered a little during the gestation and birth of this book. Dr. Bill Castleman not only provided many excellent electron micrographs, but also was helpful in assisting us in the interpretation of micrographs provided by others. We are grateful to Dr. John King for his willingness to help out on our hospital duties so that we might have more time to pursue the writing of this book. Lastly, we have been fortunate to have the critical input and helpful comments of pathology interns and Fellows such as Drs. John Lay, Roland Gunther, Paul Meunier, Greg Sykes, and Tom Van Winkle. With these and others coming behind us, the future of pathology is secure indeed.

Our own scant collections of electron micrographs have been bolstered substantially by the contributions of others. Dr. Bill Castleman has been to his files many times on our behalf. Dr. Ron Minor and, in particular, Louise Barr, also cheerfully invested some darkroom time producing micrographs for us. Through Dr. Peter Henson of the National Jewish Hospital and Research Center in Denver we were able to secure some of the superb micrographs taken by his wife, Jan. Drs. Donald Dungworth and A. T. Mariassy of the University of California at Davis were willing contributors, as was Dr. J. M. Ward of the National Cancer Institute. Dr. John Cummings of the Anatomy Department here at Cornell was extremely helpful in providing illustrative material. We are grateful to all of these contributors for their cordial willingness to help.

The many line drawings and figures in the book came from the skilled hands of Jane and Bill Jorgensen. The Jorgensen's were a pleasure to work with as well as being highly articulate illustrators. We also are grateful to Kate Church-Winn for making many of the preliminary drawings. Dr. Jay Georgi of the Department of Preventive Medicine was generous enough to allow us to use his superb photomicroscopy unit with which many of the photomicrographs were taken. The Biomedical Communications unit rendered black and white negatives and prints from color slides of gross lesions with especial skill, and were helpful and patient with us in this and many other phases of the work.

We are extremely grateful to Joyce Reyna for the skill and patience with which she typed the manuscript, often beginning with nearly indecipherable handwriting. Lura Marker also skillfully typed drafts of portions of the text and the index.

The Williams & Wilkins Company has been tenacious for excellence from the beginning. We are grateful to the editors Nan Curtis-Tyler and Alan Poulson for their initial encouragement and for their patience with us as we brought the idea to final fruition.

Our own personal support staffs have been most helpful and tolerant of our inconsistent personalities and unusual work schedules during the past 18 months. Our research

technicians Nancy Nielsen, Anita Aluisio and Kate Church-Winn have successfully demonstrated that their capabilities go far beyond the need for much input from us. Our families deserve a special note of praise for their constant encouragement and patience. It is to them that this book is gratefully dedicated.

We also would like to take a moment to acknowledge each other's efforts. In these days of multiple-author textbooks, it is theoretically possible for a single pair of authors to drive each other insane in the process of writing a book together. Happily, this has not occurred. Indeed, we are jointly satisfied with the results of our labor and mutually pleased to have our long-standing friendship not only intact but strengthened. In conclusion, it would be wrong to fail to mention the numerous unseen contributions made by our students of pathology over the years here at Cornell University. In a very real way, it has been their probing questions, effusive spirit, indefatigable good humor, and consistent enthusiasm for pathology that caused this book to be written. Students always think that we are their teachers, but it is we who learn from them.

David O. Slauson
Barry J. Cooper

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Pathology—The Study of Disease

For students of biomedical science the study of pathology is an important and exciting milestone. For them it is an introduction to the study of disease and the mechanisms which underlie it. From the study of pathology should emerge the concepts upon which a satisfying career in medicine can be built. We are firmly committed to the idea that the best medical practice, both diagnostic and therapeutic, is based on a thorough understanding of the mechanisms of disease. Pathology is concerned with these mechanisms.

Students must rationalize and comprehend many apparent conflicts on their route to an understanding of disease. The vital host defenses linked together in the inflammatory response also constitute the major pathways of tissue injury. The same coagulation factors that produce the beautiful and life-saving hemostatic plug are responsible for the ugly and life-threatening thrombus. The injured endothelial cell releases both thromboplastin to start the clot and plasminogen activators to remove it. Macrophages perform phagocytic heroics on our behalf while simultaneously releasing enzymes which degrade our tissues. To understand these things is to understand **how** and **why** diseases are complicated affairs.

Disease is a manifestation of physiology gone wrong, and ultimately reflects some structural or functional alteration in the cells of which all living things are made. To understand disease, we must turn our attention toward understanding the changes which occur in living tissues in response to various kinds of stimuli. Students often first encounter pathology with some apprehension feeling that they are poorly prepared to study disease when in fact they are usually well equipped. They are well versed in the normal structure and function of tissues. The typical student, however, generally feels that **finally** all of that basic stuff has been surmounted so that something applicable to medicine can now be learned. Students usually consider pathology a worthwhile pursuit, but all too often no one seems to have told them that understanding normal structure and function is the ultimate basis for understanding disease, and that it is in no sense irrelevant to medicine. Students seem surprised to discover that, in the disease state, there are, with rare exceptions, no new cellular functions and new metabolic pathways at work. Rather, pathways that already exist are accentuated, diminished or lost. The same is largely true for structural changes. Only rarely are truly new structures involved in disease states; rather there are increases, decreases or alterations in structures already present in the normal animal. Even the grossest lesion is produced by the same rigorous, lawful molecular and cellular interactions that govern normalcy. Disease is difficult to understand, but our success or failure at doing so more often lies in the realm of logic than in the realm of application. The Statements of the Obvious in Table 1.1 may help to place this in perspective.

WHAT IS PATHOLOGY?

Broadly speaking, pathology is the study of disease. According to the dictionary, it is the "study of the essential nature of disease, especially the structural and functional consequences thereof." Pathology, however, is different things to different people. To the student it is an introduction to disease, an introduction to the abnormal processes which manifest themselves as signs and symptoms in sick animals. The clinician sees pathology as one of the means by which a diagnosis can be made. To the pathologist it is the study of lesions associated with disease, and the mechanisms which underlie them. These various views of pathology are not incompatible. They simply reflect the varied interests of individuals. Pathology is the study of disease. It is the study of morphologic lesions, that is, structural abnormalities, which characterize particular diseases. Most importantly in the context of this book, it is the study of how and why these lesions develop and their functional consequences.

As a subject for study, pathology bridges the gap between the basic sciences and clinical medicine. It has one foot in the sciences of tissue structure and function, anatomy and histology, physiology and biochemistry. The other foot is in the clinics.

At the simplest level, pathology identifies lesions and often can provide a diagnosis for clinicians. The science of pathology, however, did not grow simply from a need to recognize and name lesions and diseases. It arose from the attempts of practicing clinicians to **understand** disease. The first pathologists were clinicians who studied the structural abnormalities of the tissues in an attempt to explain the illnesses of their patients. Gradually pathology evolved into a specialty, but today it still retains its roots in morphology and in understanding the nature of disease. General pathology, the subject of this book, involves the study of the mechanisms by which tissues are injured. It provides the basic principles which allow us to understand specific diseases, whether they involve the lung, the liver, the kidneys or any other organ system.

The study of disease can be approached in many different ways. We can emphasize the expressions of various disease processes as they lead to the recognizable alterations in tissues which we call lesions. We can emphasize the study and classification of these lesions into recognizable patterns and forms useful to understanding disease and to making definitive diagnoses. We can emphasize the causative agents, the bacteria, viruses, fungi, toxins, and so on, responsible for causing disease. We can emphasize the functional consequences of various kinds of organic diseases, and thus emphasize pathophysiology. All of these are important, but these approaches are by their very nature too often aimed at asking "what is it?" rather than "why is it?" or "how is it?" Students beginning to learn about disease must emphasize the **how** and the **why** over the **what** if they are to become flexible clinicians able to think their way through disease problems encountered in clinical patients. A world of disordered structure and function lies before us in any diseased creature if we can only have the eyes to see it. To enumerate a list of clinical signs and then a list of lesions is not enough, for it is the relation of one to the other that counts. Sometimes this is easy, sometimes difficult, and sometimes impossible to determine. Sometimes our ignorance, however we might try to veil it in attractive phraseology, still sounds like ignorance. But if we try to understand disease as to its **hows** and **whys**, we undertake a persistant endeavor that is the ultimate challenge of medicine. Pathology can never be purely a science; it is made up of too many variables and immeasurables. The dog with verrucose mitral endocardiosis and the cow with viral rhinotracheitis are not internal combustion engines. We can interpret them but we cannot memorize their circuitry and re-

Table 1.1
Statements of the Obvious*

The proportions and organization of both the cellular and extracellular constituents of a tissue determine the structural and functional characteristics of the tissue.
The structural and functional characteristics determine the adaptability of each tissue. Tissue adaptability decreases with aging, and in many disease states.
Any agent or condition that exceeds a tissue's capacity to adapt results in an injury or disease process.
Understanding the mechanism and site of action of a disease-producing agent or condition should allow one to be able to predict the effects of this perturbance on the host.
Knowing the structural and functional changes occurring in the tissues allows one to predict the clinical presentation.
The clinical presentation, conversely, allows us to draw conclusions about the structural and functional changes that have occurred in the tissue. These conclusions can then be used to decide on a differential list of causes for each disease process.

* Courtesy of Dr. R. R. Minor.

place their spark plugs. Our best effort is to try to understand **why** their systems failed by knowing **how** such systems fail. In other words, knowing **what** disease they have is ultimately less useful than understanding the mechanisms by which that disease came to be. The former approach gives a name to the disease to help us communicate among ourselves, but the latter forces a reconstruction of the moving series of events involved in the disease process itself.

WHAT DO PATHOLOGISTS DO?

Clearly, not all of the many people who study disease would call themselves pathologists. Traditionally, pathologists have been regarded as those who study the morphologic manifestations of disease. To some extent this is still true. Most pathologists today are trained to study the morphologic manifestations of disease but also are vitally interested in the functional changes with which such lesions are associated. Most also are interested in **why** such lesions develop.

Many pathologists have particular interests and a number of subspecialties have developed within the field of pathology. **Medical pathology** deals with the diseases of man, and **veterinary pathology** with the diseases of other animals. Many veterinary pathologists would regard themselves as **comparative pathologists** as their interests encompass the diseases of all species, including man. The study of the pathogenesis of animal diseases often allows considerable insight into similar disease processes in man. **Diagnostic pathologists** study tissue abnormalities, using either gross pathology or microscopic pathology, in order to identify the nature of the disease. They may study the whole animal, in the case of the postmortem examination (necropsy) or they may study samples of tissue taken from the living patient as a diagnostic procedure (biopsy). **Surgical pathologists** specialize in the study of biopsy material. **Specialty pathologists** have a specific interest in particular organ systems and might, for example, be pulmonary pathologists, neuropathologists, or renal pathologists. Such specialization is a natural outcome of the virtual explosion of information available about disease and disease mechanisms. It is a tough chore for even a specialist to keep up with his field in today's world, and any pathologist who believes he knows all of the answers probably does not understand all of the questions. One beneficial outgrowth of specialization is consultation. The renal pathologist asks the neuropathologist to examine the brain

lesions in a case awaiting a final diagnosis, and the neuropathologist seeks the opinion of the renal pathologist on a difficult kidney case. Both individuals profit from the knowledge of the other. Most pathologists try to keep up with the entire field of pathology in a broad sense, and most have recognized the necessity for specialization. **Immunopathologists** are particularly interested in tissue injury that is associated with or caused by the immune system. **Clinical pathologists** are especially important to clinicians in providing tests and helping to interpret them to support or deny diagnoses. They utilize hematology, cytology, serum chemistry, clinical endocrinology and similar tests to help make specific diagnoses. **Experimental pathologists** manipulate, analyze and sometimes recreate abnormalities of structure and function so that we may better understand the mechanisms which underlie disease. Of course, there is some overlap in these interests. Diagnostic pathologists may utilize the techniques of immunopathology, for instance, and experimental pathologists also may be diagnostic pathologists.

General pathology is a traditional academic subdivision of pathology which remains in use to distinguish it from **special pathology**, or the pathology of specific diseases as they affect specific organs and organ systems. As such, general pathology deals with common denominators of disease and the mechanisms of disease production. The topics of general pathology include cellular degeneration and death, circulatory disorders common to many tissues, inflammation and repair, immunopathology, growth disturbances and neoplasia, and the nature and causes of disease. These are the subjects of general pathology because they have common mechanistic features useful to a general understanding of specific disease states. All tumors have some features in common. Inflammation, whether it affects the heart or the lungs or the kidneys, has a large number of common features. Hence, what is learned in general pathology is applicable to disease problems involving any organ system. As such, it is a mechanism-oriented discipline.

THE TOOLS OF PATHOLOGY

The wide range of interests covered by pathology necessitates the use of a wide variety of tools, or techniques, to study lesions. The **light microscope** is still the basic tool of the pathologist. It is most commonly used to study sections of tissues taken from animals. Sections are simply very thin slices of tissue prepared from larger pieces of tissue preserved in formaldehyde or other fixative and embedded in paraffin wax. The sections are stained with dyes which allow the various components of the tissue to be visualized. The usual stains for routine sections are **hematoxylin** and **eosin** (H&E) (Fig. 1.1), but a wide variety of special stains may be used to illustrate special components of the tissue. For example, the periodic acid-Schiff (PAS) stain is used to demonstrate carbohydrate substances such as glycogen. Toluidine blue stain can be used to illustrate mast cell granules and so distinguish these cells from others. A number of different stains can illustrate organisms in tissues. There are far too many special stains to list them all here but these few examples indicate their usefulness to the pathologist. **Histochemical stains** are those which react with known specific chemical groups or substances in the tissue. For instance, stains are available which can identify iron in tissues and distinguish it from other substances. Enzyme histochemical stains identify the presence of specific enzymes in the tissue. These are widely used, for example, in the study of muscle lesions to distinguish different types of muscle fibers (Fig. 1.2). For some of these techniques, sections cut from fresh, frozen (rather than fixed) tissue are required.

Other special techniques utilizing the

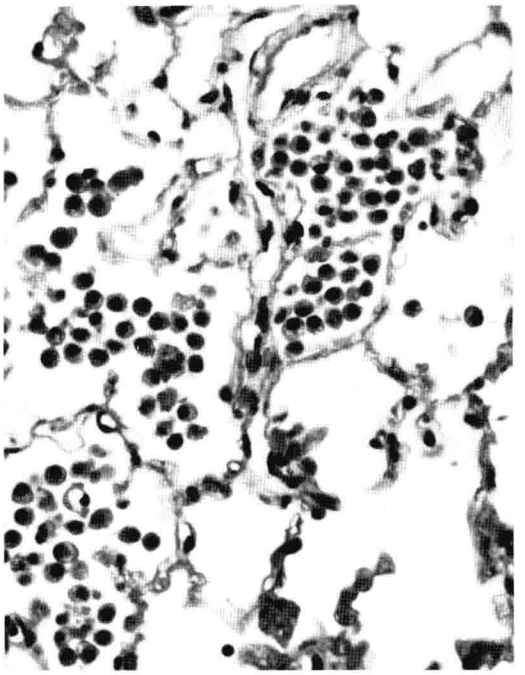

Figure 1.1. Tissue section stained with hematoxylin and eosin (H&E). In this routine preparation, nuclei stain dark with the hematoxylin while cytoplasmic and extracellular elements stain light with the eosin. This section of lung from a dog contains many alveolar macrophages.

light microscope are **darkfield, phase contrast** and **fluorescence** microscopy. The latter technique is especially useful in immunopathology where deposits of immunoglobulin, complement or other substances can be detected. If, for example, we wanted to illustrate deposits of IgG in the glomeruli of a horse with glomerulonephritis, we would stain renal tissue with a specific antiserum against equine IgG (Fig. 1.3). The antiserum is conjugated to a dye such as fluorescein which is fluorescent under ultraviolet (UV) light. The suspect tissue is examined in a microscope fitted with UV illumination and the deposits, if present, are revealed by fluorescence against a dark background. This technique has been modified by labeling antisera with the enzyme horseradish peroxidase so that instead of fluorescence, colored reaction product of the enzyme is detected, and can be seen in the ordinary light microscope. Any substance against which an antiserum can be raised can be detected by these techniques and they are now widely used in pathology.

Electron microscopy is also a major method of examining the morphologic changes in diseased tissues. Its advantage is high resolution, which far exceeds that of light microscopy. Structures far too small to be seen in the light microscope can be detected in the electron microscope (Fig. 1.4). For **transmission** electron microscopy, small pieces of fixed tissue are embedded in special plastics and extremely thin sections are cut. Stains are used which are electron dense, and the image formed by the beam of electrons is recorded on photographic film. **Scanning** electron microscopy is used to study the three-dimensional structure of tissue (Fig. 1.5). It is particu-

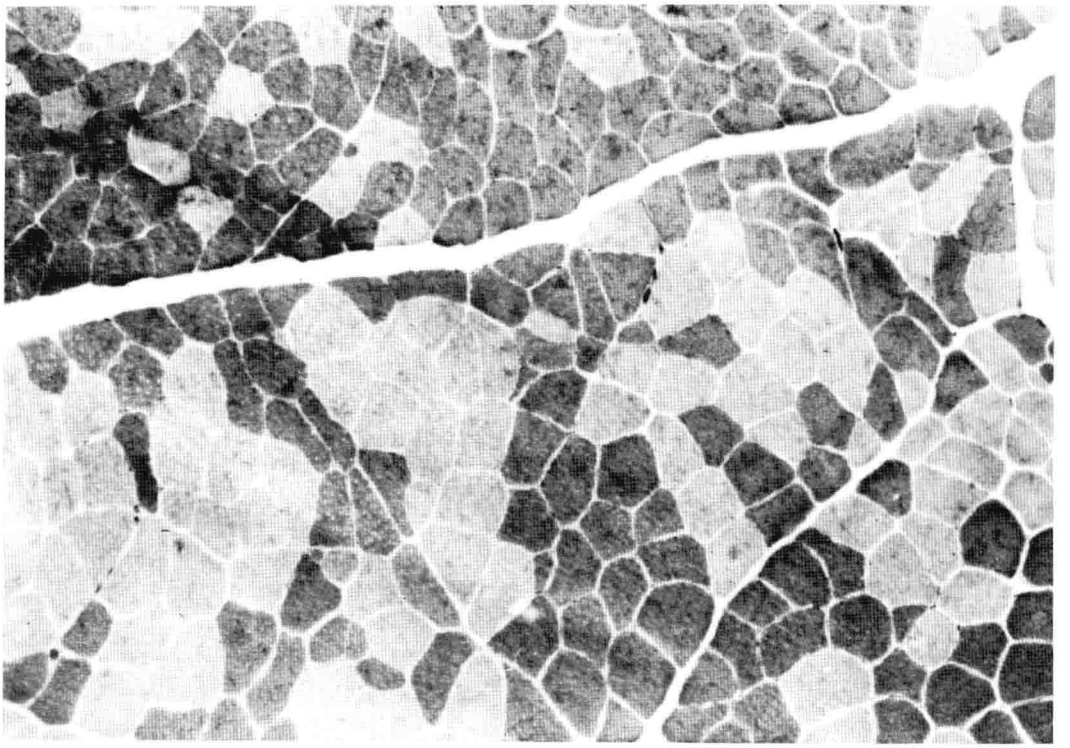

Figure 1.2. Enzyme histochemistry of muscle. ATPase stain differentiates Type I fibers (light) from Type II fibers (dark). In this case there is abnormal grouping of fiber types typical of denervation followed by reinnervation. The lesion in this dog could not be appreciated without enzyme histochemistry.

larly useful in demonstrating surface microanatomic changes which cannot be appreciated with the transmission electron microscope. Finally, special methods of preparation can be used for electron microscopy. Deposition of substances such as immunoglobulins can be demonstrated using antisera linked to electron-dense substances or to enzymes using methods which produce an electron-dense product. These techniques are similar to those used at the light microscopic level but provide much higher resolution.

Tissues embedded in plastic also can be used for high resolution light microscopy. Because sections can be cut from plastic which are much thinner than the 4–5 μm usually provided by paraffin-embedding techniques, a much better level of resolution is provided (Fig. 1.6).

Pathologists, especially experimental pathologists, use many other techniques to measure the functional consequences of lesions. These include essentially all the techniques of biology. The data they generate is important for it provides the basis on which we eventually are able to predict the clinical consequences of particular morphologic lesions.

LANGUAGE OF PATHOLOGY

The study of pathology will introduce the student to an extensive new vocabulary. Many of these terms will become evident

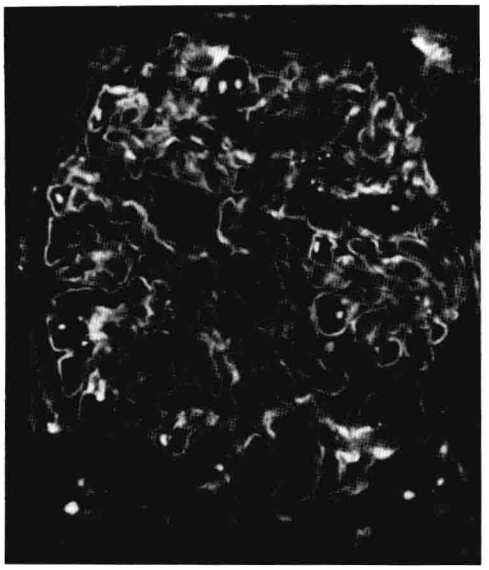

Figure 1.3. Fluorescence microscopy. This section of kidney has been stained with fluorescein-labeled antibody against equine IgG. It demonstrates linear deposition of host IgG in the glomerulus. (Micrograph courtesy of Dr. R. M. Lewis).

throughout this book. Here we will limit ourselves to a few particular terms which are of general importance. A **lesion** is an abnormality in a tissue. Generally when we use this term we are referring to a structural abnormality, but sometimes the word is used in reference to a functional abnormality. We might, for instance, use the term "biochemical lesion" to describe a functional abnormality. Such a lesion may or may not have a morphologic counterpart. **Pathogenesis** is the term used to describe the way in which a disease or lesion develops. That is, it is the sequence of events and mechanisms which underlie a disease process. The lesion itself is an observation, its pathogenesis is the explanation of how and why it developed.

Disease itself is hard to define. What does it mean to be sick? It is the culmination of those various defects, abnormalities, excesses, deficiencies and injuries as they occur at the cell and tissue level which ultimately result in clinically apparent dysfunction. Disease may sometimes go undetected at the clinical level even though the lesions underlying the disease have been present in the tissues for a long time. Most of us can recall from our experience some situation where a person "suddenly" became ill, but the underlying lesions had in fact been present for months. Cancer often presents in this way.

Diseases, and indeed lesions, are often difficult to categorize and the terminology can be confusing. Let us take the specific example of leptospirosis in a dog. Leptospirosis names the disease and as such it is the **definitive diagnosis**. The dog probably had subacute nonsuppurative interstitial nephritis which names the lesion and gives us a **morphologic diagnosis**. As the **etiology**, or cause, in our example was *Leptospira canicola*, the **etiologic diagnosis** for the renal lesions would be leptospiral nephritis. Other examples can be given. *Escherichia coli* (the etiology) results in colibacillosis (the disease) which is basically an acute to subacute catarrhal enteritis (the morphologic diagnosis). *Mycobacterium paratuberculosis* (the etiology) produces a chronic granulomatous enterocolitis (the morphologic diagnosis) in cattle which have Johne's disease (the name of the disease and the definitive diagnosis). One of the important jobs of diagnostic pathologists is to find, interpret and name such changes in order to reach a diagnosis. In some situations, particularly with surgical biopsies, this information will allow the pathologist to offer a **prognosis**, or estimate of the future behavior of any lesion or change in tissue.

AN APPROACH TO THE STUDY OF PATHOLOGY

Pathology, and in fact medicine as a whole, can be approached in two ways. We can learn to **recognize** disease entities and to treat them by certain set maneuvers.

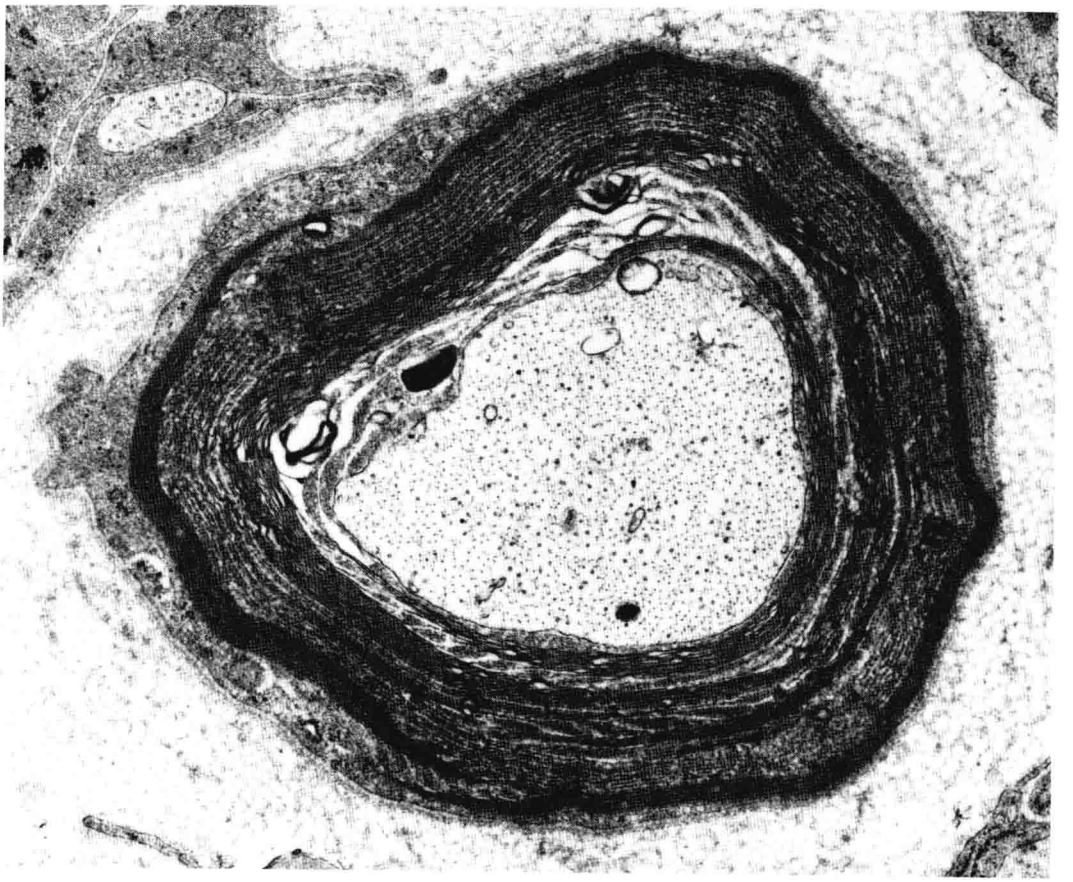

Figure 1.4. Transmission electron micrograph. In this peripheral nerve from a dog with inherited neuropathy there is abnormal compaction of myelin lamellae. The increased resolution provided by electron microscopy allows such lesions to be visualized.

Unfortunately, disease varies in its manifestations and such an approach is bound to fail frequently. Alternatively, we can try to **understand** the disease process and to make logical diagnoses and formulate treatments based on the functional abnormalities which we have shown to be present. In practice, we utilize both methods, but it is essential that we understand, as well as we can, the biologic processes which underlie disease. If we understand basic mechanisms we can dissect our way through new or unfamiliar disease syndromes. If we understand we can generate rational, rather than empirical, methods to treat disease. We need only to look at the recent history of medicine to see that our attempts to understand disease have led to much more effective means to control it.

We can appreciate disease at any one of a variety of levels, ranging from the whole animal, or organismal level, to the molecular level. Between these extremes we might understand any particular disease process at the level of the organs, the tissues, the cells, or the subcellular organelles involved. Consider, for example, a dog which is presented with the disease diabetes mellitus (Fig. 1.7). At the crudest level of understanding we have a sick or possibly even a dead dog. If we look at the organ level we find that the animal has a large, yellow