CLINICAL CONCEPTS OF INFECTIOUS DISEASES

THIRD EDITION

Edited by
Leighton E. Cluff, M.D.
and
Joseph E. Johnson, III, M.D.

CLINICAL CONCEPTS OF INFECTIOUS DISEASES

THIRD EDITION

Edited by

Leighton E. Cluff, M.D.

Executive Vice President
The Robert Wood Johnson Foundation
Princeton, New Jersey
Adjunct Professor of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Joseph E. Johnson, III, M.D.

Professor of Medicine
Chairman, Department of Medicine
The Bowman Gray School of Medicine
of Wake Forest University
Winston-Salem, North Carolina

WILLIAMS & WILKINS
Baltimore/London

Made in the United States of America

First edition, 1972
Reprinted 1974
Second edition, 1978
Reprinted November 1978
Reprinted November 1979

Library of Congress Cataloging in Publication Data

Main entry under title:

Clinical concepts of infectious diseases.
Bibliography: p.
Includes index.
1. Communicable diseases. I. Cluff, Leighton E. II. Johnson, Joseph Eggleston, 1930– . [DNLM: 1. Communicable diseases. WC 100 C6415]
RC111.C56 1982 616.9 81-19654
ISBN 0-683-01656-3 AACR2

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

CLINICAL CONCEPTS OF INFECTIOUS DISEASES

THIRD EDITION

PREFACE

Infectious diseases account for about 20% of all acute and chronic clinical problems seen in ambulatory care settings. Of the acute illnesses, approximately 70% are acute respiratory infections. Between 30 and 50% of hospitalized patients are given at least one antimicrobial drug during hospitalization. Finally, in recent years the increasing use of immunosuppressive and cytotoxic chemotherapy along with the introduction of new surgical and technological advances have led to a proliferation of infectious complications in compromised hosts.

Textbooks of medicine invariably include chapters or sections on infectious diseases and immunology. Usually, comprehensive coverage is attempted, including presentations on almost all microbial diseases, whether esoteric or common, clinically important or unimportant, in the United States. Therefore, a proportion of the material covered has limited relevance to training of students and housestaff, and practicing physicians. They serve as essential reference sources but are not prepared for easy reading and perspective.

Involvement with preclinical education, student clerkships, house staff, and postdoctoral clinical and research fellowship training over several years convinced us that a collection of selected essays emphasizing concepts of infectious diseases could serve a useful purpose. Therefore, we arbitrarily have chosen to cover aspects of host resistance which have clear clinical implications. We have selected a few clinical problems with broad ramifications, particularly important to general medical care. The principles of the treatment and prevention of the infectious diseases are presented to emphasize an approach to clinical management. Each section is preceded by an introduction to set the stage for the reader.

This third edition of *Clinical Concepts*, justified we believe by the acceptance and reported usefulness of its predecessors, represents an updated revision of the entire volume plus additional new material.

Chapters on the phagocytic system, humoral immunity, and nonspecific resistance to infection have been revised significantly to reflect new and current information. New and expanded chapters have been written also on the systemic mycoses, viral hepatitis and antiviral chemotherapy. Finally, the tabulation of infectious diseases has been revised and simplified.

Our hope is that those reading this book will attain a perspective of the approaches important for thinking about problems in infectious diseases and caring for patients.

To serve as an entry to consideration of infectious diseases not covered fully in

the text, we have provided a selected list of references directing the interested reader to some of the important sources of information. The table preceding that section can serve to refresh the reader's memory or orient his thinking about other infectious diseases.

Leighton E. Cluff, M.D.
Joseph E. Johnson, III, M.D.

CONTRIBUTORS

Adair, Norman E., Assistant Professor of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapter 21*)

Ayoub, Elia M., Professor of Pediatrics, University of Florida College of Medicine, Gainesville, Florida. (*Chapter 17*)

Bennett, John E., Head, Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland. (*Chapter 22*)

Brachman, Philip S., Director, Bureau of Epidemiology, Center for Disease Control, Atlanta, Georgia (*Chapter 2*)

Carpenter, Charles C. J., Professor and Chairman of Medicine, Case Western Reserve School of Medicine, Cleveland, Ohio. (*Chapter 23*)

Cluff, Leighton E., Executive Vice President, The Robert Wood Johnson Foundation, Princeton, New Jersey; Adjunct Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. (*Chapters 3, 8, 10, 13, 14, 15, 28, 35, 36*)

Corey, Lawrence, Head, Virology Division, University of Washington School of Medicine, Seattle, Washington. (*Chapter 26*)

Ganguly, Rama, Associate Professor of Medicine and Microbiology, West Virginia University School of Medicine, Morgantown, West Virginia. (*Chapter 18*)

Gates, Robert H., Fellow in Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapter 19*)

Grizzard, Michael B., Staff Physician, Department of Pediatrics and Clinical Research; Chairman, Department of Clinical Investigation, Lovelace Medical Center, Albuquerque, New Mexico. (*Chapter 17*)

Hayden, Frederick G., Associate Professor of Medicine and Pathology, University of Virginia School of Medicine, Charlottesville, Virginia. (*Chapter 31*)

Holmes, King K., Associate Professor of Medicine, University of Washington School of Medicine, United States Public Health Service Hospital, Seattle, Washington. (*Chapter 26*)

Johnson, Joseph E., III, Professor and Chairman of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapters 1, 7, 15, 16, 20, 21, 25, 28, 29, 36*)

Keene, Willis R., formerly Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida; private practice, Folkston, Georgia. (*Chapter 12*)

Khakoo, Rashida, Assistant Professor of Medicine, West Virginia University School of Medicine, Morgantown, West Virginia. (*Chapter 11*)

Kluge, Ronica M., Professor of Medicine, University of Texas Medical Branch, Galveston, Texas. (*Chapter 34*)

Kolts, Byron E., Associate Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida. (*Chapter 24*)

McCall, Charles E., Professor of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapters 4, 7, 19*)

McLees, Byron D., Professor of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapter 21*)

Myrvik, Quentin N., Professor of Microbiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapter 6*)

Noyes, Ward D., Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida. (*Chapter 12*)

Pegram, P. Samuel, Jr., Assistant Professor of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapters 16, 26, 37*)

Philp, James R., Professor of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. (*Chapters 32, 37*)

Sanders, W. Eugene, Jr., Professor of Medical Microbiology and Medicine, Creighton University School of Medicine, Omaha, Nebraska. (*Chapters 9, 10, 27, 30*)

Streiff, Richard R., Professor of Medicine, University of Florida College of Medicine, Veterans Administration Hospital, Gainesville, Florida. (*Chapter 12*)

Waldman, Robert H., Professor and Chairman of Medicine, West Virginia University School of Medicine, Morgantown, West Virginia. (*Chapters 5, 11, 18, 33*)

CONTENTS

SECTION THREE

SPECIFIC PROBLEMS OF INFECTIOUS DISEASES

SECTION FOUR

MANAGEMENT AND PREVENTION OF INFECTIOUS DISEASE

SECTION FIVE

TABULATION AND OTHER REFERENCES OF INFECTIOUS DISEASE

SECTION

ONE

EPIDEMIOLOGY AND PATHOGENESIS OF INFECTIOUS DISEASE

Chapter
1

INTRODUCTION

Joseph E. Johnson III

Man lives in a sea of microorganisms. Intermittently seeding the air he breathes are viruses, bacteria, and spores. Growing on the surfaces of his body, in the hair follicles and cavities of the integument are still other organisms. The food and drink he ingests are virtually never sterile, as the teeming flora of his gastrointestinal tract attest. In the deeper tissues of the body, even within the cells themselves, microbial forms lie dormant. . . .

And yet serious infection is a relatively rare event. Although minor skirmishes occur with considerable frequency, the body's defenses easily repulse or at least come to terms with the majority of microbial invaders. Although it was popular in the past to view man's posture with respect to the microbial world in terms of "nature, red in tooth and claw," in actual fact for much of the time the body's ecologic relationship with this sea of microbes is one of commensalism and even occasionally a mutually beneficial symbiosis.

What then are the circumstances in which this happy state of truce collapses? What determines the events which result in tissue invasion, destruction or disease?

It is convenient to conceive of microorganisms as possessing a hierarchy of virulence. Among the flora common to the microenvironment of man are bacteria, for example, which almost never produce significant disease. It is clear that such organisms are easily susceptible to normally present antibacterial mechanisms. *Micrococcus luteus* is readily inactived by lysozyme, and *Bacillus subtilis* by β-lysin. *Staphylococcus epidermidis*, part of the "normal flora" of the skin surface, is readily ingested by the phagocyte without a requirement for specific antibodies. Still other organisms such as the pneumococcus are ordinarily dealt with quite effectively with the assistance of opsonizing antibodies which facilitate phagocytic ingestion. A third order of virulent organisms, including tubercle bacilli, listeria, and histoplasma, are capable of intracellular survival following ingestion by polymorphonuclear leukocytes. When the polymorph dies, the surviving microorganism may even withstand the intracellular assault of the immature mononuclear phagocyte and only succumb after activation produces an "angry macrophage."

Thus some infectious diseases, especially those due to the microflora indigenous to man, ordinarily result when there is a breakdown in the normal defenses of the host. Others, said to have primary virulence, such as measles and smallpox viruses, and the plague and tularemia bacilli, produce disease in virtually all human hosts on initial exposure. Immunity (i.e., resistance acquired either through previous disease or vaccination) is required for protection against these agents.

The external and environmental forces which govern the occurrence of infection in individuals and their patterns in groups of people are discussed in Chapter 2, which deals with the epidemiology of infection. The particular characteristics of microor-

ganisms which determine how and where they produce infection in the host are described in Chapter 3.

Although all host defense ultimately derives from the cells of the body, it is customary to consider two basic systems: the *humoral* and the *cellular*. Each system will be seen to have a "*natural*" or normally present component as well as an "acquired" or *immune* component. Normally present humoral components include substances such as lysozyme, β-lysin, the "natural antibodies" and the complement system, while the cellular "first line of defense" is the phagocytic system composed of polymorphonuclear leukocytes (Chapter 4) and of the mononuclear phagocytic system (formerly the "reticuloendothelial system"). Polymorphs are mature cells which come equipped with a full set of antibacterial enzymes and digestive factors; while the mononuclear phagocytes tend to be immature and require time and an appropriate stimulus for full activation.

The immune system also is conveniently thought of as having a humoral component—the immunoglobulins (antibodies), and a cellular component—cell-mediated immunity. Because certain of the immunoglobulins (IgA and IgE) appear to function predominantly on body surfaces (the respiratory, gastrointestinal, and genital tracts), while the classic antibody systems (especially IgG and IgM) are predominantly intravascular or interstitial, it seems justifiable to separate the humoral system (Chapter 5) into circulatory and secretory subsystems. *Cellular immunity* (Chapter 6) is a term which perhaps properly should be used to designate the circumstance in which cells (e.g., activated macrophages) act as the principal effector agents of immunity, showing enhanced capacity for intracellular killing of organisms such as the tubercle bacillus. *Cell-mediated immunity* is the term designated to describe the possession by certain cells (e.g., the immunologically committed lymphocytes) of surface molecular-recognition sites which react with specific antigens.

There is considerable interaction between all the components of these systems. Various complement components, for example, may function directly against certain gram-negative bacilli, may act as chemotactic factors for polymorphs, or may collaborate with antibodies in phagocytosis. The polymorph which may serve as the first line of defense against a pneumococcus is capable of ingesting the microorganism without the aid of specific opsonizing antibodies by the process of "surface phagocytosis," but ingestion is greatly facilitated by the collaboration of type specific antipneumococcal opsonins. Mononuclear phagocytes may be "activated" nonspecifically to mature into "angry macrophages" or they may be stimulated by the interaction of immunologically committed lymphocytes and specific microbial antigens (Chapter 6).

The body in its teleological wisdom fortunately seems to have available a variety of "back-up" systems such that, if one line of resistance fails, another is capable of filling the breach. This seems to hold true, for example, for the bactericidal mechanisms of the polymorph. Certain types of myeloperoxidase-deficient cells, although partially defective, nevertheless can kill many kinds of bacteria intracellularly and little difficulty is experienced by the host. It is only when more profound deficiency (probably of NADPH oxidase) occurs that the cells' antibacterial mechanisms are markedly impaired and chronic granulomatous disease results (Chapter 4). Even these cells, however, are capable of killing certain bacteria. Similarly, the host can at least partially compensate for deficiencies of a particular immunoglobulin, whose functions may be assumed by another. Defects in either the humoral or cellular systems individually may be partially compensated for by the remaining system. Catastrophic results ensue, however, when both systems are deficient.

Much of our knowledge about the biological functions of the various components of the immune defense mechanisms has been derived from observations of illnesses in which particular systems or substances are deficient or impaired. Defective polymorphs in chronic granulomatous disease result in chronic recurrent infections with staphylococci and certain gram-negative bacilli. Pneumococcal and group A streptococcal infections, however, are not increased nor are viral infections a particular problem. These observations helped direct investigations which delineated the mechanisms by which these organisms are inactivated. Studies of the consequences of de-

ficiencies of particular immunoglobulins in the hypogammaglobulinemia syndromes or in multiple myeloma have indicated the roles played by these substances. Similarly, disorders of cell-mediated immunity have helped to clarify the biological role of this system. Common viral infections such as measles, for example, are handled without great difficulty by hypogammaglobulinemic children, pointing to a major role for cell-mediated immunity in these disorders. Modern therapeutic techniques which alter polymorph function or immune defenses at particular levels also add to understanding of biologic functions.

While the immune responses of the host are clearly beneficial in many of their aspects, nevertheless, adverse consequences of the immune response to microbial agents also account for a number of untoward reactions and disease states. Cell-mediated immunity in tuberculosis is of great assistance in resistance to this disease—in major part, it appears, through activation of macrophages—while at the same time the consequent "delayed hypersensitivity" reaction to tuberculoprotein contributes significantly to tissue destruction and many of the clinical manifestations of tuberculous disease (Chapter 7). Immune (allergic) responses to inhaled thermophillic actinomycetes present in moldly hay result in the disease, "farmer's lung," probably as a consequence of tissue damage from immune complexes formed in the pulmonary interstitium by precipitating antibodies and fungal antigens (Chapter 7). Immune responses to group A streptococcal infections are clearly operative in the pathogenesis of rheumatic fever, probably through cross reactions between microbial antigens and components of heart tissue. Post-streptococcal glomerulonephritis appears to result from the deposition of immune complexes in renal tissue.

Thus the defense mechanism may at times act as a "double-edged sword." Even the helpful polymorphonuclear phagocyte can be shown to participate actively in the production of tissue damage in "immune complex" disease.

The section that follows attempts to assemble in a useful way information about key components of man's defense mechanisms against microbial infection and to illustrate the biological roles of these components by relating a variety of important disease states resulting from disorders of these systems. It is our knowledge of the mechanisms of defense which permit rational efforts to augment, reinforce or bolster the host in his continuing effort to maintain the truce with his ecological microflora. Manipulation of the immune response allows us to supplement man's defensive armamentarium by active or passive immunization, circumventing the natural requirement for suffering the disease itself. Finally, the detailed understanding of the intricate mechanisms by which an immune process may turn into a "double-edged sword" point to ways in which these adverse consequences may be lessened or avoided.

Chapter
2

CLINICAL EPIDEMIOLOGY

Philip S. Brachman

Epidemiology is the study of the relationship between disease (or health) and the population at risk; or as Stallones has said, "the occurrence of disease (and by inference health) in groups of people." It is a science of rates, with a numerator that specifies the number of cases and a denominator that defines the population among whom the cases are occurring.

The numerator alone does not provide enough information on which to judge whether or not there is a problem. The epidemiologist must know something about the population in which the disease occurs, that is, the denominator. The epidemiologist also needs information about the past history of the disease in that population to be able to determine whether the situation is abnormal or not.

The clinician is the patient's diagnostician and the epidemiologist is the community's diagnostician. The epidemiologist is concerned both with the diagnosis of individual patients and groups of patients. The epidemiologist uses the laboratory to confirm clinical diagnoses and define the extent of disease. He organizes the data on the basis of time, place, and person to identify the source of infection, the mode of spread, and duration of occurrence. The clinician makes a prognosis concerning the patient; the epidemiologist predicts the trend of the disease in a community. The clinician prescribes therapy leading to a cure; the epidemiologist suggests measures leading to control of the outbreak and prevention of further cases. Thus, the clinician deals with a single case, while the epidemiologist deals with cases in a defined population. The clinician asks what illness the patient has and prescribes treatment. The epidemiologist asks why people become ill and why others did not and prescribes control measures.

The patient takes the initiative in seeking a physician; the epidemiologist takes the initiative and seeks the patient. There is a direct relationship of physician to patient; the epidemiologist may have to contact many patients in order to help a few. On the other hand, by diagnosing what is happening to a few people, the epidemiologist can extrapolate the diagnosis to many. For example if the presence of influenze A/Bankok/1/79 like virus has been confirmed in a community, the diagnosis can be extrapolated to other cases of the same clinical disease in the same community. Epidemiologists may have to treat (for example vaccinate) a group of patients to help an individual.

Epidemiologic Methods

There are three kinds of epidemiologic methods: descriptive, analytic, and experimental. Descriptive epidemiology is essentially observational. Analytic defines disease determinants. Experimental deals with hypothesis testing. They may be used individually or in any combination in the same investigation.

Descriptive Epidemiology

Descriptive epidemiology is the study of the occurrence and distribution of disease. It is an extension of the discipline of de-