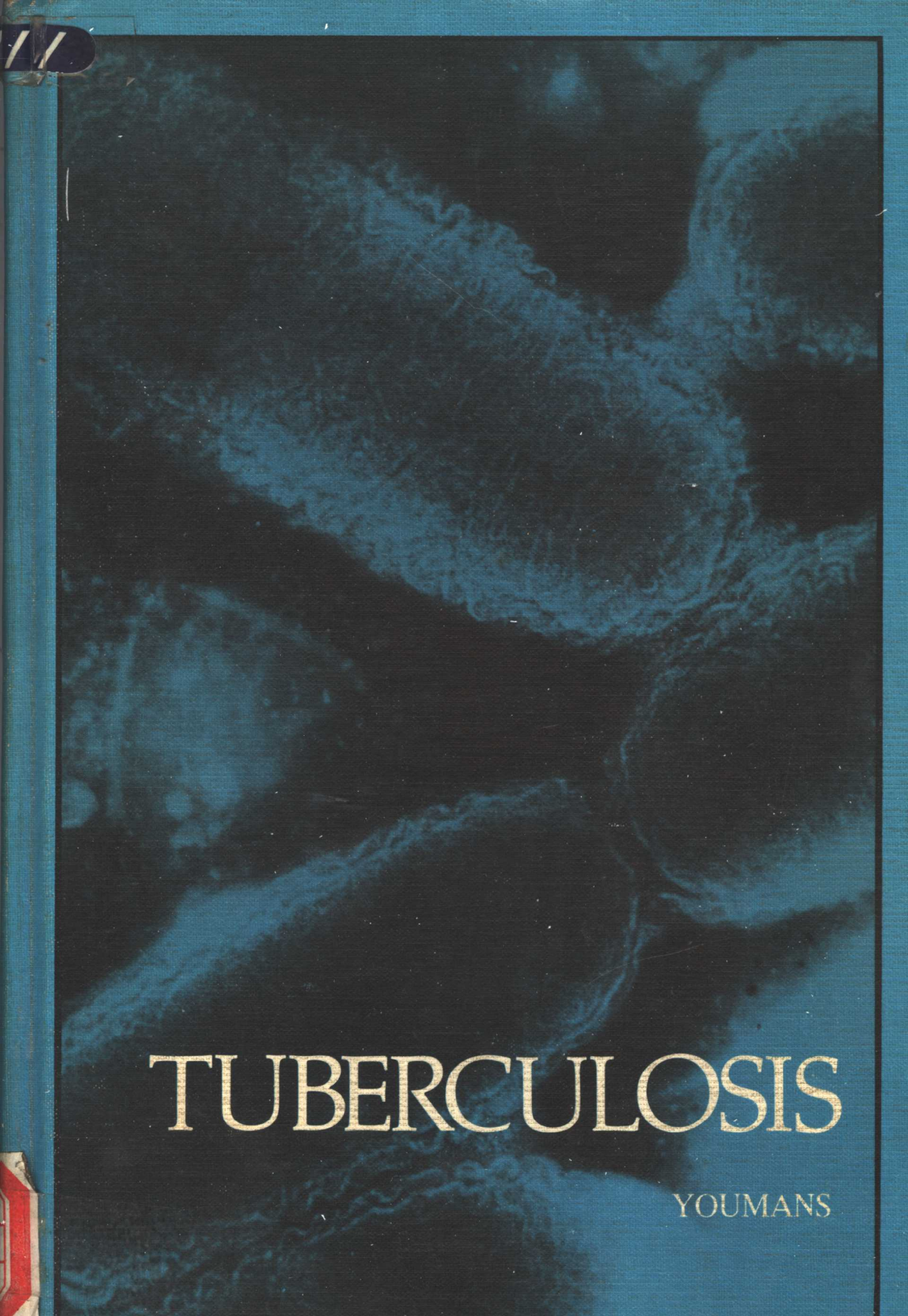
TUBERCULOSIS
YOUMANS

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TO ANNE
Without whose help and encouragement
this book could never have been written

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PREFACE

The following statement appears in the preface to the first edition of the monumental book by Arnold Rich, *The Pathogenesis of Tuberculosis*, published in 1944:

> In every field of science, as in all other forms of human endeavor, it is desirable and advantageous periodically to take stock of the state of the endeavor. During the past sixty years, clinicians, pathologists, bacteriologists, immunologists, roentgenologists, epidemiologists and geneticists have devoted an immense amount of work to the attempt to understand the disease tuberculosis and the factors which influence its progression or arrest. Out of this vast effort have come the views and conclusions which are used as guiding principles by those who today have the responsibility of dealing with tuberculosis in the individual patient, in the community or in the laboratory. Everyone knows that many of these views and conclusions, though often dogmatically expressed, are countered by equally dogmatic, contrary opinions. What is the actual evidence upon which these opposing views are based, and how sound is that evidence? Even in the case of views that are more generally agreed upon, it is of value to re-examine the evidence, for it is an old story that opinions supported by little more than the weight of early authority have often remained embedded for years in the corpus of science through the failure to enquire carefully into the validity of the observations upon which the opinions rest.
>
> The purposes of this work are to present, in a clear and orderly manner, the basic factors and principles which influence the occurrence of tuberculous infection or determine its progression or arrest; to examine carefully the evidence relating to those matters and, from that analysis, to attempt to define clearly the present limits of our knowledge regarding the influence of each of those factors upon the pathogenesis of the disease; and, finally, to attempt to accomplish this survey in a manner that will correlate into a unified whole the basic, interdependent, but at present often isolated, facts that have been given to us by bacteriology, immunology, pathology, clinical observation, experimental investigation, epidemiology and genetics.

It is probably even more desirable today to take stock of the situation in tuberculosis. The increase in knowledge and understanding of the pathogenesis of tuberculosis in the years since the publication of Rich's book has probably been greater than in all of the years preceding that event. For example, at that time, the impact of chemotherapy upon tuberculosis had not been felt. Now, this governs our thinking in a number of areas of tuberculosis. In addition, these intervening years have seen the development of almost our entire knowledge of the role of atypical mycobacteria in the production of pulmonary and other disease in human beings. This, in turn, has greatly altered our understanding of the epidemiology of tuberculosis and the factors concerned in its prevention. At the present time, we have a much greater knowledge of the

physiology of the tubercle bacillus and of the biologic activities produced by mycobacterial components. The influence of these on the pathogenesis of the disease in some cases can be reasonably well-defined. Finally, enormous advances have been made in our understanding of the immunologic responses of mammalian hosts. It is clear that immunologic responses are of at least two kinds—humoral and cellular—and that these responses are mediated by different lymphocyte populations. We also know that resistance to infection with facultative intracellular parasites such as *Mycobacterium tuberculosis* is determined primarily, if not exclusively, by cellular factors. At the time of publication of Rich's book, there was still reason to believe that circulating antibody might be involved in immunity to tuberculosis; and the role of lymphocytes in immune responses was hardly even suspected.

For these reasons, and for others too numerous to mention here, we feel that a systematic presentation of some of our knowledge concerning the tubercle bacillus and the host-parasite interaction in tuberculosis, and a critical examination of the significance of these findings, would not only promote a greater understanding of the host-parasite relationship in the disease itself but also would help point the direction for profitable lines of research in the future.

The major focus of this book will be on the host-parasite interaction and, in particular, on host responses. Some of the data to be presented will be that of our own laboratory. The major portion, however, will be provided by the published results of other investigators. Because of the voluminous literature, some selection had to be made. Realizing that many important contributions had to be omitted, we have attempted to include those references which we feel are the most significant. In addition, we have made no attempt to cover, in detail, the literature that appeared before publication of the second edition of *The Pathogenesis of Tuberculosis* by Rich in 1951. Rich more than adequately covers the literature up to that time, and we recommend his book as a source for the earlier literature.

A number of the views expressed in this book are primarily those of the authors and are not necessarily shared by all workers in the field. For any book to achieve the purposes stated by Rich, we feel that it should involve a critical analysis of the available evidence upon which views are based and a re-evaluation of the validity of interpretations. It is our strong feeling that this is the only way in which real progress in science can be made. Uncritical acceptance of the "conventional wisdom" of the day leads too frequently to stagnation rather than to progress.

Our aims in writing this book, then, remain much the same as those expressed by Rich in the preface to the first edition of *The Pathogenesis of Tuberculosis* (1944) and quoted here.

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GUY P. YOUMANS, M.D., PH.D.

CONTENTS

1

Introduction

TUBERCULOSIS IN THE WORLD TODAY

Of all the infectious diseases that have plagued man, tuberculosis has probably been responsible for the greatest morbidity and mortality. It has apparently plagued man ever since human beings emerged as a species on this planet. Its depredations, especially over the last several hundred years, have earned it the epithet, "The captain of all the men of death."[7] Readers interested in the history of tuberculosis, and how it has ravaged successive generations of human beings beginning with the early years of the Industrial Revolution, should consult the beautifully written and descriptive book entitled *The White Plague*, by René and Jean Dubos.[7] (See also Chapter 16.)

Even today, when the incidence of tuberculosis in the Western nations has markedly decreased and the mortality is less than ten per hundred thousand population, tuberculosis still remains one of the world's most prevalent infectious diseases. It is found, at the present time, primarily in the developing areas of the world.[19] The World Health Organization estimates that there are probably as many as 20 million active cases, which annually infect from 50 to 100 million people in the areas of highest prevalence.[17] It has been estimated that on a world-wide basis approximately 3 million people die every year of tuberculosis and, of this total, 80 percent or more are in the developing nations.[17] As a cause of death among human beings, tuberculosis is still at the forefront of infectious diseases. Thus, on a world-wide basis, tuberculosis remains one of the important infectious diseases with which human beings have to cope.

In spite of the enormous amount of research that has been done since Koch first reported the isolation of the etiologic agent in 1882,[13] we still have a very incomplete understanding of the nature of the virulence of the tubercle bacillus and the nature of the host response to the tuberculous infection. Nor do we have a very clear un-

derstanding of the reason for the rise and fall in the number of cases of tuberculosis, nor is there a general appreciation of the inadequacies of the public health control methods that have been used to combat the disease. However, in recent years there has been great improvement in our understanding of the host-parasite interaction in tuberculosis. It is hoped that in the not-too-distant future, continued research will point the way toward better methods for the control and treatment of tuberculosis. Our present knowledge and the implications for future control of the disease will be brought out in detail in subsequent chapters in this book.

There are those who feel that tuberculosis may eventually be eradicated as an infectious disease of human beings.[10, 12] This ideal conclusion to the war between the parasite *Mycobacterium tuberculosis* and its human host is indeed a very unlikely prospect, as we will demonstrate later on in the text (see especially Chapters 16 and 17). Nevertheless, we must always harbor the hope that our increasing knowledge and understanding of both parasite and host reaction will eventually put us in a position to completely control this infectious disease.

THE MYCOBACTERIAL WORLD

As far as disease in human beings is concerned, *Mycobacterium tuberculosis* is by far the most important of the mycobacterial pathogens, and the one that has been responsible over the centuries for most of the mycobacteria-caused morbidity and mortality among human beings. However, readers should be aware that *M. tuberculosis* is only one member of a microbial family that includes many microorganisms with certain common properties. For example, all mycobacteria are acid-fast; to the best of our knowledge, they are all obligate aerobes; they all grow and metabolize rather slowly; and all share the property of being appreciably more resistant to a variety of deleterious influences than most other bacteria. However, the mycobacteria vary markedly in their metabolic activities and are found in widely different habitats. For example, *M. tuberculosis* is an obligate parasite of human beings and certain other warm-blooded animals and grows best at 37° C. On the other hand, *M. avium,* which is a parasite of fowl, has an optimum growth temperature of 42° C; thus, it is able to grow and produce disease in fowl, which have a higher body temperature than human beings. Disease is seldom produced in man by *M. avium,* although a related microorganism, *M. intracellulare,* frequently does so. (More will be said about *M. intracellulare* in Chapter 18.) There are other mycobacteria, such as *M. leprae, M. marinum,* and *M. ulcerans,* which have lower optimal growth temperatures. In fact, *M. marinum* and *M. ulcerans* will not grow in temperatures over 35° C. This does not prevent them from producing disease in man, but it does limit the tissues that will be affected. In addition, there is a large group of mycobacteria usually referred to as saprophytes. These are found widely distributed in nature — in soil, in water, and so forth — and do not produce disease in man or other animals except under the most abnormal conditions.

The pathogenic properties of mycobacteria range from those of the saprophytes, which ordinarily do not produce disease, to those of the obligate intracellular parasites (such as *M. leprae* and *M. lepraemurium*), which will not grow at all except in a suitable host or, under certain conditions, in cells in tissue cultures. In between these two extremes are microorganisms, such as *M. tuberculosis,* which are facultative intracellular parasites; that is, they can grow within cells or outside of cells, depending upon the conditions that

prevail in the host. There also are species of mycobacteria that produce disease in a variety of lower animals. *M. bovis*, for example, produces disease primarily in cattle and other domestic animals but can and will infect human beings if the opportunity arises.

The mycobacterial world, therefore, is a large one containing diverse species of mycobacteria with greatly differing potentials for producing disease.

THE CLASSIFICATION OF THE MYCOBACTERIA

In this section, a brief classification of the mycobacteria will be presented. This is done primarily to indicate some of the characteristics of the major mycobacterial species. The names and the disease-producing potential of a much wider number of species, which do on occasion produce disease in man, can be found in Chapters 18 and 19.

Included in this section for purposes of orientation are some of the species of mycobacteria listed in *Bergey's Manual of Determinative Bacteriology*,[6] together with their important characteristics and disease-producing potential. This list emphasizes the variety of species of mycobacteria and the considerable differences in their characteristics.

1. *Mycobacterium tuberculosis.* Type species. We will say relatively little about this microorganism here, since the major portion of the subsequent chapters of this book will be devoted to the characteristics and disease-producing potential of *M. tuberculosis* and the host reaction to infection with this parasite.

2. *Mycobacterium microti.* Common name: Vole bacillus. Slow-growing facultative intracellular parasite, with an optimal growth temperature of 37° C. Produces disease in rodents, such as the vole and guinea pig, in rabbits, and sometimes in calves.

3. *Mycobacterium bovis.* Optimal growth temperature of 37° C. Facultative intracellular parasite. Produces tuberculous disease in cattle and in other domestic and wild ruminants. Pathogenic in man and other primates, in carnivores (including dogs and cats), in swine, in parrots (and possibly other birds), and in hamsters and mice.

4. *Mycobacterium africanum.* Occasionally causes pulmonary tuberculosis in human beings in tropical Africa. Optimal growth temperature apparently 37° C.

5. *Mycobacterium kansasii.* Optimal growth temperature 37° C. Produces pulmonary disease in human beings (see Chapter 18).

6. *Mycobacterium marinum.* Found in swimming pools, aquaria, and other water sources. May produce disease in fish. Grows only in temperature range of 25° to 35° C. In human beings, causes cutaneous granulomas ("swimming pool granulomas"). Lesions found on the elbows, knees, feet, fingers, and toes; heals spontaneously.

7. *Mycobacterium gastri.* Grows in the temperature range of 25° to 40° C. Found originally in gastric contents of human beings. Not considered to be pathogenic.

8. *Mycobacterium nonchromogenicum.* Saprophyte.

9. *Mycobacterium terrae.* Also found in gastric contents. Not considered to be pathogenic.

10. *Mycobacterium triviale.* Found in sputum. Thought to be a saprophyte.

11. *Mycobacterium gordonae.* Common name: Tap water scotochromogen (see Chapter 18). Found in human sputum and gastric lavage specimens. Also found in water and soil. Rarely, if ever, implicated in disease processes.

12. *Mycobacterium scrofulaceum.* Causes cervical lymphadenitis in children. Not particularly pathogenic for experimental animals. (See Chapter 18.)

13. *Mycobacterium intracellulare.* An

important pathogen, which may produce pulmonary disease in man (see Chapter 18).

14. *Mycobacterium avium.* Causes tuberculosis in fowl.

15. *Mycobacterium xenopi.* Mostly a saprophyte. Has occasionally been isolated from human excretions and from disease of the genitourinary tract.

16. *Mycobacterium ulcerans.* Temperature growth range between 30° and 33° C. In man, causes skin ulcers that may be severe. Found in Australia, Mexico, New Guinea, Malaysia, and Africa.

17. *Mycobacterium phlei.* Saprophyte found in soil and water.

18. *Mycobacterium vaccae.* Occasionally seen in skin lesions in cattle. Widely distributed in nature; found in water and soil. Mostly a saprophyte.

19. *Mycobacterium diernhoferi.* Isolated from water and found in environments where there are domestic cattle. Apparently not pathogenic.

20. *Mycobacterium smegmatis.* Found in soil, in water, and in the smegma of man. Not pathogenic.

21. *Mycobacterium thamnopheos.* Has a temperature growth range of 10° to 35° C. Produces generalized disease in snakes, frogs, lizards, and fish, but not pathogenic for guinea pigs, rabbits, or fowl.

22. *Mycobacterium flavescens.* A rapidly growing saprophyte.

23. *Mycobacterium fortuitum.* Produces disease in man, in cattle, and even in the frog. Found in soil and in some cold-blooded animals.

24. *Mycobacterium peregrinum.* Isolated from the sputum of man, though its possible role as a pathogen is obscure.

25. *Mycobacterium chelonei.* Rarely produces infection in man. Growth temperature range of 22° to 40° C.

26. *Mycobacterium paratuberculosis.* Common name: Johne's bacillus. Facultative intracellular parasite that produces disease primarily in cattle and sheep. Lesion produced is a regional ileitis. Disease is serious in cattle and sheep, and mortality can be high. Does not produce disease in man.

27. *Mycobacterium leprae.* Produces leprosy (Hansen's disease) in man. An important obligate intracellular parasite. Has an optimal growth temperature that is apparently lower than 37° C. Lesions produced in skin and in other organs, such as the testes, where temperature is lower; internal organs not affected.

28. *Mycobacterium lepraemurium.* Obligate intracellular parasite that produces leprosy in rodents, such as rats and mice. Serves as an important experimental model for the study of leprosy.

For a detailed consideration of the very complicated problems involved in the classification of mycobacterial species, the following references should be consulted: Barksdale and Kim;[2] Bradley and Bond;[5] Juhlin;[11] Kubica;[14] Ratledge;[20] Runyon et al.;[22] Tsukamura and Mizuno;[32] and Tsukamura et al.[33]

MYCOBACTERIAL DISEASES OF MAN

From the descriptions given in the preceding list of species, it should be clear that there are many nonpathogenic as well as disease-producing mycobacteria. Some mycobacteria are capable of producing disease in certain lower animals; other species, besides *M. tuberculosis,* can and do produce disease in human beings.

Tuberculosis in human beings is, by definition, disease caused by *M. tuberculosis.* However, it is now clear that a number of mycobacteria can produce pulmonary or other disease in man that is indistinguishable from that produced by *M. tuberculosis.* In particular, these include *M. kansasii* and *M. intracellulare.* More will be said about these pathogens and the disease they cause in Chapter 18. We wish to emphasize

here that tuberculosis can no longer be regarded simply as a disease caused by *M. tuberculosis*. In fact, in certain areas of the country (see Chapters 16 and 18), as many as 10 to 15 percent of the pulmonary disease cases diagnosed as tuberculosis may be caused by *M. kansasii*. Thus, even though in this book we are concerned primarily with disease produced by *M. tuberculosis* and with the particular host-parasite relationship involved when *M. tuberculosis* is the etiologic agent, we must always keep in mind that certain other mycobacteria produce disease that is similar in every respect to that produced by *M. tuberculosis*. Fortunately, insofar as we can determine, the major features of the host-parasite relationship are the same for all of these species.

No mention of human mycobacterial disease would be complete without some reference to *M. leprae* and leprosy (Hansen's disease).[3, 21] A disease that is probably as old as tuberculosis, leprosy over the centuries has afflicted tens of millions of human beings. It was more prevalent at one time, since the disease has now almost disappeared from Western Countries; nevertheless, a few cases of leprosy are detected each year in the United States. In many of the developing countries, leprosy is still a major infectious disease affecting a high proportion of the population.

We have no intention here of discussing leprosy to any great extent, but we would like to point out that the host-parasite relationship in leprosy is apparently very similar to that found in tuberculosis. The lesions of leprosy occur primarily in the skin, peripheral nerves, and mucous membranes of the upper respiratory tract. It is assumed that this localization occurs because the causative organism requires lower temperatures for growth. *M. leprae* has never been isolated and cultured in vitro. Experimental infections with *M. leprae* can be induced in the footpad of the mouse[23-26] and more recently, in a cold-blooded animal — the nine-banded armadillo.[27-31]

For many years it has been assumed that *M. leprae* is strictly a parasite of human beings and that the disease is transmitted only from human to human by close contact. However, very recently, a natural disease caused by a microorganism that cannot be distinguished in any way from *M. leprae* has been detected in the nine-banded armadillo.[4, 18, 34, 35] This raises the important question of whether there is, by chance, a reservoir of infection with *M. leprae* in cold-blooded animals such as the armadillo, thereby explaining some of the peculiar epidemiologic features of leprosy. With tuberculous disease, it has also been assumed that it is only transmitted from human to human and that there is no reservoir of infection with *M. tuberculosis* except in man. We now may have cause to wonder, or at least to keep in mind, the possibility that eventually an animal reservoir of tuberculous infection might be found. It is well known that domestic animals, particularly pets, may become infected with *M. tuberculosis* and serve as sources of infection for human beings; however, to date, no natural infection with *M. tuberculosis* in wild animals has been detected.

Other mycobacterial infections of man that should be mentioned are those caused by *M. marinum* and *M. ulcerans*. *M. marinum* infections can occur epidemically from either natural waters, such as ocean beaches, or from swimming pools.[1, 15] *M. ulcerans* infections are limited geographically, as previously indicated.[8, 9, 16] Other bacteria that occasionally produce disease in man, such as *M. scrofulaceum* and *M. fortuitum* and some of the others, will be covered to a greater extent in Chapter 18.

Thus, while *M. tuberculosis* is still the major culprit for the production of human disease, increasingly, we are finding that other mycobacteria found in nature can also cause troublesome

clinical problems in man. In this book our emphasis will be on *M. tuberculosis*, because most of our knowledge about the mycobacteria and the host-parasite relationship in mycobacterial disease has been derived from studying this microorganism. However, most of what we will have to say, particularly about host-parasite interaction, can be applied to infection produced in man by the other mycobacteria as well.

THE HOST-PARASITE RELATIONSHIP IN MYCOBACTERIAL DISEASE

A good part of the book will be devoted to the host-parasite relationship in tuberculosis. In this chapter, we only wish to emphasize two points that readers should always keep in mind. First, the pathogenicity of *M. tuberculosis* and the other mycobacteria depends primarily upon the capacity of these microorganisms to resist the natural defensive mechanisms of the infected host. Second, in view of the insusceptibility of these mycobacteria to normal defense mechanisms, the host has developed a special and rather unique way of responding to the presence of these parasites, so that it has the power to inhibit the multiplication of the infecting mycobacteria. This unique defense mechanism is known as cellular immunity to infection and is invoked by the body primarily against facultative or obligate intracellular parasites. As we will see, it is a potent antimicrobial immunologic response. Yet the mechanism is a very inadequate one because it does not readily bring about destruction of all of the infecting mycobacterial cells.

Cellular immunity to infection not only is the major immunologic defense reaction to infection of man and lower animals with *M. tuberculosis* or other mycobacteria but also is a major immunologic defense reaction against a variety of other bacterial parasites and viruses. We need only mention such diseases as histoplasmosis, coccidioidomycosis, pasteurellosis, brucellosis, and Listeria infection. Most of our knowledge of cellular immunity to infection has come from study, under experimental conditions, of host-parasite relationships in tuberculosis. Apparently, the same general mechanisms that operate in defense against tuberculosis also operate in defense against these other parasites. Thus, knowledge of the nature of the host-parasite relationship in tuberculosis is important for students interested in cellular immune responses to many other infectious diseases. It is very likely that when the exact nature of acquired cellular immunity to infection is determined, the knowledge will have been derived from a study of the host-parasite relationship in tuberculosis.

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