BACTERIAL AND MYCOTIC INFECTIONS OF MAN

Edited by

RENÉ J. DUBOS, Ph.D.

The Rockefeller Institute

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Preface to the Third Edition

The present volume does not differ in organization or in point of view from the first and the second editions of *Bacterial and Mycotic Infections of Man*. However, while the structure of the book has remained unchanged, the text has been almost completely rewritten. Because of the amount of new knowledge to be described and the large number of new contributors, it has been difficult not to increase the size of the book. This has been achieved by reducing somewhat the length of bibliographies for each chapter. In certain cases, the reader may find it helpful to consult the more extensive list of references printed in the first and the second editions.

A word should be said concerning Chapter 2 (The Evolution and the Ecology of Microbial Diseases). In this new chapter, I have tried to express the view that the ability of microorganisms to produce pathologic changes is under the influence of large biologic forces as yet poorly understood which do not necessarily manifest themselves in the form of recognized immunochemical reactions. Some of the contributors to the book do not entirely share my point of view in this matter, and it is certain indeed that many statements in Chapter 2 cannot be supported by convincing evidence. The responsibility for these statements is entirely mine, and I wish to thank my colleagues for allowing me to preface their factual presentations with speculative concepts.

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New York

Preface to the First Edition

This volume was designed to convey to the medical student—and we hope also to the practitioner of medicine—some knowledge of the bacteria, actinomycetes and molds pathogenic for man, as well as of the phenomena which characterize the infectious process. Infections caused by viruses and rickettsiae are treated in a companion volume edited by Dr. T. M. Rivers.

Medical microbiology is the study of host-parasite relationships and not that of microorganisms alone, considered as independent living agents. It is concerned with those aspects of the structure and the properties of parasites which play a part in their pathogenic behavior, and with the multiple manifestations of the response of the invaded host to their constituents and products. The general chapters of this treatise are therefore devoted to the facts and the problems concerning parasite and host which have a bearing—often immediate, but at times only potential and remote—on infectious disease.

A few words may be necessary to justify the order in which the different pathogenic agents are described in subsequent chapters. This order was adopted to illustrate, by the extensive treatment of a few selected examples, the multiple facets of the problem of infection. Thus, the diphtheria bacillus is discussed first to introduce the concept of toxemia and of antitoxic immunity. As a counterpart, pneumococcus infections are then selected to emphasize the problems of antibacterial immunity. Streptococci, on the other hand, lend themselves to the demonstration that a given microbial agent can exhibit multiple pathogenic potentialities, and that tissues can respond in many different ways to its presence. Tuberculosis illustrates particularly well the acute (exudative) and chronic (proliferative) pathologic processes accompanying infection, and the altered reactivity of the body (allergy) which results from previous exposure to the bacillus. All these aspects of the infectious process appear in more-or-less modified form in the other microbial diseases and give to each of them its peculiar character.

This treatise is the result of the co-operative effort of many experts and naturally reflects their individual outlooks. I wish to thank them all, in particular for their willingness to aim at some measure of uniformity in our common undertaking. The National Foundation for Infantile Paralysis has given generous financial support to the preparation of the book and shares with us the hope that it may contribute something to the understanding of the general problems of infection.

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Contents

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1

A Synopsis of the History of Medical Bacteriology*

The history of bacteriology is brief but crowded with infinitely varied significance. The discoveries and the applications of less than 100 years did more than modify the conceptions and the theories built by the scientific endeavors of preceding centuries; they formed a freshly new branch of biologic science, *bacteriology,* and such great progress was made that there emerged from it the two further highly specialized disciplines of immunology and virology.

The stimulus to this phenomenal advance was the establishment of the bacterial cause of infectious disease, and with this elucidation came the introduction of exact diagnosis by etiology, of specific therapy and of preventive medicine, all founded on verifiable fact. The profound reformation of medical thought required by the new knowledge of bacteriology was brought about only by a bitter struggle against almost unbelievable opposition, but out of it arose the beginnings of experimental medicine. Thus, bacteriology did not become merely a useful helping hand but the guiding finger and wrought such changes in human health alone that, if it be a benefit, it must at least equal the contribution to human welfare of any other branch of science. To achieve this it has changed and continues still to change the order of importance of various diseases as the cause of death in different age periods. Diseases such as typhoid fever, diphtheria and pneumonia, as examples, have been reduced from prevalence with a high mortality to almost a rarity. So too the scourge of epidemics has been changed to a threat of danger manifest only if the required precautions are neglected, and the fatal menace of some diseases has been softened. Meanwhile, in the course of the lives of people living today, the marvelous achievement of modern surgery was made possible by lifting it out of the despond of "laudable pus" into the security of asepsis. These are only general instances to give point to greater hope for the future.

Through the ages humanity, of all races, used the products of fermentation in various forms of food and drink or for the making of desirable utilities, without an inkling of the processes involved. The relation of the causes of fermentation and of infectious disease was hardly even suspected for some 2 centuries after bacteria were first definitely seen and figured by Leeuwenhoek (1676), and, though he did describe them in pus, his discoveries stirred interest in heterogenesis rather than disease. Of course, it was recognized that certain diseases were catching and that some conferred immunity from a second attack, but the idea of contagion passing from one indi-

* The names and the dates given relate to the initiation of major trends or developments of medical bacteriology.

vidual to another, made evident by common observation in plague and syphilis, was completely missed in many another disease and was almost certainly exaggerated in leprosy. Fracastoro in his book on contagion (1546) was probably the first to indicate that "infection itself is composed of minute and insensible particles and proceeds from them," and he wondered whether all contagion may not be a putrefaction; he recognized that "the infection is the same for him who has received or has given the infection: also we speak of infection when the same virus has touched one or the other."

Much can be read into the early speculative writings, and it is well to be cautious in interpreting them, for in most instances it seems evident that the words and the phrases used should not be accepted strictly in their modern meaning. Kircher (1658), probably the first to make direct microscopic studies of disease, examined putrefying materials and even blood from plague patients to postulate animated corpuscles which constitute the effluvia and scatter new seeds of contagion. He supposed a tenacity of life in them and that it is difficult to wash them away, so he recommended burning in the fire clothing and household goods infected with the contagion. The immutable specificity of contagious diseases was indicated by the practice of "variolation," but it was forcefully expressed by Thomas Fuller (1654-1734) who said that one could not change into another "any more than a Hen can breed a Duck," and he emphasized it further by saying "consequently one Sort cannot be a Preservative against any other Sort."

Speculation on what might have happened is futile, but Spallanzani (1775) seems to have only barely failed from revealing the science of bacteriology in the course of his efforts to disprove heterogenesis as upheld by Needham. Spallanzani recognized and grew bacteria in sterilized media, he discovered forms which grew when deprived of air and he discovered "germs," which we now call endospores, of a greater resistance to heat than the forms they gave rise to. By his rigid maintenance of conditions of experiment for his intention, he failed to inoculate his media selectively on purpose and to realize the full general significance of his discoveries. It had all to be rediscovered nearly a century later by Pasteur, who also took pains during his studies on fermentation to disprove heterogenesis as maintained by Bastian and by Pouchet without losing sight of the singularly far-reaching importance of his discoveries.

Meanwhile, the empirical method of probing the cause of infectious disease proceeded, with a diversity of observations and experiment too extensive to enumerate. Outstanding among these, because of their subsequent influence, are John Hunter's ill-fated self-inoculation with syphilis (1767) from a case of gonorrhea and Jenner's introduction of vaccination (1796) against smallpox, using material from naturally acquired cowpox. Hunter's experiment was a grave misfortune to himself, and, because he did not recognize a mixed infection, the belief persisted for very many years that syphilis and gonorrhea were the same disease: a warning we cannot ignore today. Jenner's triumphant success, in substantiating a popular belief, resulted in widespread vaccination which reduced an almost world-wide disease to insignificance. The fatal propensity of smallpox is not better illustrated than by its ravages among the Indians of Canada and the United States in 1780, and 1869 and 1870, when whole tribes perished, and others were decimated; these epidemics also provide strong evidence of the efficacy of vaccination when properly done and of its failure when care is insufficient. Of the same order of general importance were the insistence of Holmes (1843) and Semmelweis (1847-1849) and, before them, Charles White* (1773) on practical methods and cleanliness, for the prevention of puerperal sepsis and of blood poisoning from putrid wounds.

Improvements in the microscope led to more definite discoveries, and micro-organisms became associated with disease processes. The cause of favus found by Schönlein (1839) was used by Remak (1842) to reproduce the disease. Bassi (1837), from his work on disease of silkworms, prophesied that microscopic organisms would be found to be the cause of human disease, and similar suggestions came from many others. Henle (1840), in making

* White's Treatise, published in 1773, went through 5 editions, was translated into French and German and was reprinted in the U.S.A. in 1793.

the same prediction, drew up a statement of the conditions which would have to be satisfied to provide proof of a causal relationship. Similar postulates are ascribed to Robert Koch, but they do not appear in concise form in his writings. The first convincing discovery of microbial disease was the finding by Davaine (1850) of minute "infusoria" in the blood of sheep which had died of anthrax. Stimulated by Pasteur, he returned to this discovery in 1863 and published it finally in 1864. The disease was transferred by inoculation of healthy animals with blood containing the rods he had found, and inoculation remained effective even when the blood was diluted a million times. The subsequent work on anthrax by Koch (1876) and Pasteur (1877) is virtually the starting point of pathogenic bacteriology and was founded on the earlier work of Pasteur from 1857 onward.

The beginnings of the science of bacteriology emanated from Pasteur's interest in fermentation, which was stirred by his discovery (1848) of the selective use of dextrorotatory tartaric acid by a mold which neglected the levorotatory form. His studies of lactic acid fermentation (1857) and of alcoholic fermentation (1860) led him to the necessity of disproving the hypothesis of heterogenesis (1861) in order to substantiate his demonstration of specificity of ferments. The making of wine in France at that time was encountering an enormous reduction in quantity and a deterioration in quality and keeping power, due partly to an *Oidium* disease of the vines and partly to *Phylloxera*. This brought Pasteur to study the "flower of wine" and the "flower of vinegar" (1862) and led to his study of the making, ripening and preserving of wines and beer (1863) and eventually his studies of putrefaction and anaerobiasis. Diseases of silkworms next claimed his attention (1865-1869), and the procedures he instituted not only saved the industry in France, but their wide adoption is still the practice; it is a perfect example of the detection of infected individuals and controlling the spread of disease by isolating them. The war of 1870 stimulated his studies of infected wounds, and he translated his ideas of specificity of fermentations into specificity of infections. From this grew Lister's work and the introduction of antiseptics with the eventual development of aseptic technic as the work of many subsequent investigators. Pasteur went on to work at anthrax (1877), developing his vaccines and proving their worth (1881), then chicken cholera (1880) and swine erysipelas (1882)—to all of which his genius ensured phenomenal results in the recognition of causative agents and specific immunization. Pasteur achieved greatest fame by his work on rabies. Recognizing the site of infection, he obtained a source of vaccine, even though he could not isolate the organism, and he developed a process of attenuation of the virus as well as a procedure for its application which is still used widely and seems only to be surpassed by the recent modification of the Flury strain of virus by egg passage and the use of antirabies serum. Pasteur deserves to be called the father of bacteriology.

Robert Koch, who started his work just when Pasteur had initiated the concept of specificity of infectious disease, contributed enormously and most particularly by his developments of bacteriologic technic. In his studies of anthrax (1876) Koch isolated the bacillus in pure culture and established its infectivity. This was the first purposive isolation of a pure culture. He proceeded then to study traumatic infectious disease (1877) and developed the technic of isolation of pathogenic bacteria in pure culture from mixtures (1878-1881) so effectively that his methods are largely used today. He also used the newly discovered aniline dyes to great advantage in demonstrating bacteria microscopically. After Villemin (1865) had shown that tuberculosis, of both man and animals, could be transmitted by inoculation from man to animals and from one animal to another, Koch (1882) discovered the causative organism of tuberculosis. Later, the differentiation into human type and bovine type was done by Theobald Smith (1896), and Rivalta (1889) and Maffucci (1890) discovered the related organism of avian tuberculosis. Koch went on to the discovery of the cholera vibrio (1883), making important contributions to the knowledge of that devastating disease, but his discovery of tuberculin (1890) was temporarily detracted from by the claim of its being a cure. The greatest of his many contributions was the discovery of methods of isolation and study of bacteria in pure culture and the procedure by which to study their infectivity.

Largely as the result of the work of Pasteur and Koch the isolation and the identification of causative organisms of disease by many investigators proceeded apace. Long lists could be made of pathogenic micro-organisms with the date of discovery and even longer lists of bacteria important or unimportant to other human interests. These dates and authors can be found in manuals of determinative bacteriology, and the exciting history of their discovery is in the original papers or special chapters of books.

The isolation of the diphtheria bacillus by Letzerich and Klebs (1881) and by Klebs and Loeffler (1883-1884) and of the tetanus bacillus by Kitasato (1889), after it was seen by Nicolaier (1884), opened the way for one of the most important chapters in bacteriology, the discovery of toxin and antitoxin. Loeffler (1887) supposed the production of a poison to explain the results of his inoculation experiments, using cultures of the diphtheria bacillus, and Roux and Yersin (1888) demonstrated the toxin in filtrates of cultures. This was followed by Knud Faber (1890) showing that the tetanus bacillus also secreted a toxin. These various discoveries stimulated tremendous work on diphtheria, resulting in the discovery of antitoxin by Behring (1890) for diphtheria and by Behring and Kitasato (1890) for tetanus. The brilliant confirmation of this by Roux and Martin (1894), who first immunized horses, and gave notoriety to serum therapy, resulted in the spectacular drop in the mortality rate of diphtheria. The first serum treatment in man was instigated by Behring and Wernicke and actually was done on Dec. 25, 1891. Ehrlich (1896) introduced standardization of toxin and antitoxin, thereby contributing greatly to their successful use in the treatment of disease and to the knowledge of their working.

In recent years, through the work of Ramon (1925), active immunization with formalin-treated diphtheria toxin (Anatoxine or Toxoid) has all but eliminated, where it is used, the incidence of diphtheria in children. Before this, immunization had a measure of success using toxin-antitoxin mixtures which Babes (1895) had proved on guinea pigs and Behring (1913) first used on humans. It was forwarded most effectively by Park (1913-1918) and controlled by the intradermal test of immunity introduced by Schick (1913) on the basis of the intracutaneous test used in animals by Roemer (1909). But the immediate influence of the early discoveries was to overemphasize the possibilities and the hopes of the humoral immunity, and toxins and antitoxins were sought for everything, often in vain. However, this search and interest occasioned the mixing of cultures, filtrates of cultures and immune serum, and the frequently unforeseen results introduced entirely new procedures and concepts into medicine. Thus Buchner (1889) found complement (alexin), Fodor (1886) the bactericidal action of normal rabbit serum for anthrax bacilli, Nuttall (1888) the dependence of bactericidin on complement, and Richard Pfeiffer (1894) showed that with cholera vibrios immunization greatly intensified bactericidal activity.

Between 1870 and 1877 independent observations by Hayem, Klebs, von Recklinghausen, Waldeyer, Koch and others suggested that the leukocytes in pus, in which bacteria could be seen, were a suitable lodgement or a site of predilection for the microbes. Metchnikoff (1883), from a study of the activity of the ameboid (mesodermal) cells of invertebrates and vertebrates, called them phagocytes and ascribed to them a protective activity by virtue of their destruction of ingested microbes. He conceived these scavenging microphages and macrophages to be the principal defense mechanism against infection, and a polemic arose and lasted several years between the Cellular Defense protagonists and those for Humoral Defense. Experiments to prove or disprove either hypothesis resulted in many interesting observations, and the recognition of immunity reactions and responses not suspected until then. Thus Denys and Leclef (1895) showed that immunization greatly increased phagocytosis, and the work of Almroth Wright and his colleagues (1903) advanced knowledge of it and gave the name opsonin to this activity.

Charrin and Roger (1889) observed that *B. pyocyaneus* grown in immune rabbit serum first lost its motility and then grew in agglomerated masses, contrasting with the diffuse growth of motile organisms in normal serum. This was confirmed by many others for several different organisms, and Bordet showed that