Medical Microbiology

Volume One: Microbial Infections

MEDICAL MICROBIOLOGY

A GUIDE TO THE LABORATORY DIAGNOSIS
AND CONTROL OF INFECTION

TWELFTH EDITION
VOLUME 1 *MICROBIAL INFECTIONS*

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PREFACE

There are several good reasons for the publication of a new edition of this textbook on Medical Microbiology. The last (11th) edition was first published in 1965; despite numerous reprintings, there has been only one revised reprint, and in a rapidly expanding specialty like microbiology, textbooks soon become outdated. In the last edition, a considerable expansion of the text had given the book a middle-aged spread but a more serious defect from the viewpoint of the medical student and the young doctor was the large amount of space allocated to laboratory procedures of interest mainly to professional and technical staff concerned with the isolation and identification of pathogenic microbes. It may, however, be noted that the English Language Book Society (E.L.B.S.) paperback edition has become popular in many Commonwealth and other English-speaking countries, probably because of its comprehensive coverage of the subject. The time seemed opportune to separate the contents into two volumes—Volume 1 aimed primarily at medical and science students and doctors, and Volume 11 directed to professional and technical laboratory staff—the 'bench book' which will be published within the next few months.

Medical textbooks have not always been popular with the undergraduate student, partly because they tend to be overloaded with scientific and technical details of interest mainly to the specialist. In Volume 1 of this 12th edition of *Medical Microbiology*, we have aimed to present a well-illustrated text which the student would find to be interesting as well as informative—and without too much technical detail. At the same time, recent outgrowths in the broad field of microbiology, e.g., microbial genetics and immunology, have been given additional attention.

Volume 1 is divided into five parts: Part 1 deals with microbial anatomy and physiology and the basic principles of infection and immunity; Parts 2 and 3 are concerned with the common bacterial

and viral infections with emphasis on the pathogenesis of the infection. sources and modes of spread of the pathogen in the community and methods for the diagnosis, control and prevention of the infection; Part 4 is devoted to (a) infections by small microorganisms (chlamydia, rickettsia and mycop'asma) formerly thought to bridge the gap between bacteria and viruses, and (b) to the common protozoal and fungal infections of man. In Part 5, some of the more applied aspects in the laboratory diagnosis and treatment of infective syndromes and in the epidemiology and prevention of community, including hospital, infections are discussed.
Every chapter dealing with specific pathogens has been re-written, a number of new chapters have been added and new contributors co-opted. The editorial staff has been augmented by the inclusion of Professor B. P. Marmion. Although this textbook was born and nurtured in the Department of Bacteriology, Edinburgh University, inevitably some of the contributors have sought new pastures whilst a satellite colony has been formed by Professor J. P. Duguid and his colleagues in the Bacteriology Department of Dundee University.
As in the assessment and preparation of previous editions, we have had most valuable criticisms, comments and constructive suggestions from many colleagues, both in Britain and overseas. To them and to our helpful and patient publishers, we express our sincerest gratitude.

October, 1973. The Editors.

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1. Microbiology and Medicine

Pioneers in Microbiology

Microbiology is, as a biological science, just over a century old. Although its ancestry is rather nebulous, the first productive seed was implanted by a French chemist, Louis Pasteur, who a century ago was persuaded to turn his inquisitive mind from a study of tartrate crystals to the troubles that were affecting the wine industry in France. Pasteur, brooding over the age-old phenomenon of fermentation, which has given us both bread and wine, was not prepared to accept the pontifical pronouncements of the leading chemists of the day that this was a purely chemical reaction. Having satisfied himself that the souring of milk was due to the formation of lactic acid by multiplying bacteria, he proceeded to turn sugar into alcohol with only ammonia and some organic salts as a source of nutrient for the growing yeast cells. He concluded his paper in 1857 with these words: 'Alcoholic fermentation is an act correlated with the life and with the organization of these (yeast) globules, and not with their death or their putrefaction'.

In his early work in microbiology Pasteur also made the fundamental observation that certain bacteria (which he called *anaerobic*) would grow only in the absence of oxygen, a momentous discovery at a time when oxygen was still regarded as the essential elixir for all living creatures. A few years later, his monograph on 'The Study of Wines' and his demonstration of the value of differential heating—or *pasteurization* as we now call it—revolutionized the whole wine and beer industry of Europe and established the importance of microbiology in industry.

Joseph Lister (1867), an English surgeon working in Scotland, saw in Pasteur's work on fermentation a possible explanation of the tragic fate that befell so many of his patients who after compound fracture or amputation were dying in large numbers from hospital gangrene and 'blood poisoning'. By treating the wound with carbolic acid and covering it with a phenolic dressing, he prevented bacterial growth in the exudate and so satisfied himself that putrefaction or sepsis was caused, like fermentation, by these invisible but living microbes which Leeuwenhoek (1675), two centuries earlier, had called his 'little animals'. Some years before Lister's work, Semmelweis (1848), an obstetric surgeon in Vienna, proved in one of the first controlled trials that disinfection of the hands in chloride of lime by students and surgeons after examination of a patient or the performance of a necropsy reduced the case-fatality from puerperal sepsis from 8·3 to 2·3 per cent in the hospital teaching clinic, that is, to a rate equivalent to that in the midwife clinic or in private practice.

In an era dominated by the physical sciences it required great courage and pertinacity as well as ingenuity and technical skill for these pioneers in microbiology to persuade their fellows of the validity of the new gospel. However, they had strong support from one of the outstanding physicists of the day, John Tyndall (1877), who interested himself in the new biological science and gave us intermittent sterilization (or *tyndallization*) as a method for destroying sporing bacteria; he was, incidentally, one of the first observers to note the antibacterial properties of the mould penicillium. About this time (1876) Robert Koch, a country doctor in Germany, became acutely aware of the havoc which a disease called 'splenic fever', or anthrax, was causing among the sheep and cattle of the farming community. By most ingenious methods devised in a home-made laboratory, Koch was able to prove that a large square-ended sporing rod was constantly present in the blood of animals dying of anthrax, and that the bacilli or spores derived from them could reproduce septicaemic anthrax in mice. Later, after further experience with anthrax and tuberculosis, he formulated the well-known Koch's postulates (1884) which must be fulfilled before a specific microorganism was accepted as the cause of a specific disease. These required, in addition to the constant presence of the microorganism in the tissues of the naturally infected host, that it be grown artificially in *pure culture* (for this he devised boiled potato slices and nutrient gelatin as *solid media*) and after many subcultures should reproduce the specific disease when inoculated into a susceptible animal. And so, by the eighteen eighties, the new science of microbiology was firmly founded and its importance in the economy of men, animals and industry was beginning to be appreciated.

Pasteur was again a pioneer in two early offshoots of this science—immunology and virology. He was the first to extend Jenner's (1794) protective *vaccination* (vacca = cow), a word coined by Pasteur in honour of Jenner's work with cowpox, by the use of living attenuated cultures of pathogenic microbes against important infections like anthrax, swine erysipelas and chicken cholera. Today the *attenuated vaccine* is being used with outstanding success in such diverse diseases as tuberculosis, yellow fever, poliomyelitis, dog distemper and contagious abortion of cattle.

Pasteur's contribution to animal virology was equally fertile. From his boyhood days in the Jura hills, he had known of the horrible deaths that might follow the bite of a wolf or a mad dog, and in due course he turned his attention to the aetiology of rabies. After some false trails, his assistant Roux eventually injected some of the infective material from the brain of a fatal case into the brain of a dog, which fourteen days later developed rabies. Thus the use of selective living tissue for the growth of viruses—which today is practised on an enormous scale—was born in Pasteur's laboratory and this experimental work with rabies led on to the anti-rabies vaccine which was his last great effort in the field of immunology. Later, the demonstration of bacterial toxins by both French and German workers was the precursor of antitoxin therapy through the experimental studies of von Behring who showed that the serum of animals given inoculations of sublethal doses of diphtheria or tetanus toxin could specifically neutralize these toxins *in vitro* and *in vivo*.

Ehrlich who like von Behring was trained in Koch's laboratory later developed an analogous concept of chemotherapy whereby his 'magic bullets' would specifically attack the invading parasite. His success with Hata (1906) in the treatment of syphilis with an organic arsenical, Salvarsan (or 606) was followed in time by the flowering of chemotherapy, pioneered by the discoveries of penicillin by Fleming, a Scot, in 1929 and of prontosil (the prototype of the sulphonamides) by Domagk, a German, in 1930.

This brief historical sketch illustrates the importance of microbiology as an applied science, particularly in fermentation processes and in infectious diseases. The term *microbiology*, 'biology of the small organisms', is preferred to *bacteriology* since it includes in the present context viruses, fungi and protozoa in addition to bacteria. Only a small proportion of the myriads of microorganisms that abound in nature are disease-producing or *pathogenic* for man. The majority of microorganisms are *free living* in soil, water and similar natural habitats, and are unable to invade the living human or animal body. Some free-living microorganisms obtain their energy from daylight or by oxidation of inorganic matter, but most feed on dead organic matter; these last microorganisms are termed *saprophytes* ('grow on dead matter'). In contrast, a *parasite* is defined as a microorganism or a larger species (e.g. helminth) that lives in or on, and obtains nourishment from, a living host. Parasitic microorganisms are either commensal or pathogenic. *Commensals* (table companions) constitute the normal flora of the healthy body. They live on the skin and on the mucous membranes of the upper respiratory tract, the intestinal and female genital canals, and obtain nourishment from the secretions and food residues. Since normally they do not invade the tissues, they are generally harmless, though under certain circumstances, usually when the body's defences are impaired, they may invade the tissues and cause disease, thus acting as *opportunistic pathogens*. True pathogens are the parasitic microorganisms that are adapted to overcoming the normal defences of the body and invading the tissues; their growth in the tissues, or their production of poisonous substances, or *toxins*, often causes damage to the tissues and thus the manifestations of disease.

MICROBIOLOGY AND THE PATIENT

Medical microbiology is concerned with the *aetiology* (causation), *pathogenesis* (mechanism of attack on tissues), laboratory diagnosis and treatment of infection in the individual and with the *epidemiology* (study of mass disease among the people) and control or prevention of infection in the community. It therefore, has close links with several other disciplines into which the training of the doctor has been divided to form the medical curriculum, e.g. pathology, clinical medicine and surgery, pharmacology and therapeutics, and preventive medicine.

The changes that occur in the host's tissues as the result of infection are often recognized by the pathologist as specific or pathognomonic of a particular pathogenic microorganism, e.g. the circumscribed boil of the staphylococcus, the spreading cellulitis of the streptococcus, the red liver-like appearance (hepatization) of the lung in pneumococcal pneumonia, the tubercles and the subsequent necrotic changes (called caseation) of tuberculosis, the aortic disease and granulomata (gummata) of syphilis, and the typical intestinal ulcerations of typhoid fever and the dysenteries. But the prudent pathologist will usually seek to confirm his diagnosis of the cause of these macroscopic changes by taking smears and preparing cultures from the lesions to demonstrate the microscopic germ. The pathology of infection provides a fascinating but relatively unexplored field of study since it includes the affinity of pathogens for particular tissues and the initiation of infection as well as the characteristic tissue reactions.

Microbiology has a close link with curative medicine in regard to the precise diagnosis and the rational treatment of microbial diseases. The doctor engaged in the care of sick patients will often be able to identify the pathogenic microorganisms from the typical clinical features of an infection and will accordingly prescribe the appropriate treatment. Sometimes, however, the patient presents with a fever but no characteristic signs or symptoms that will allow the doctor to make a precise diagnosis; this pyrexia of unknown—or uncertain—origin (PUO) will require laboratory help to elucidate the cause of the fever. Even when the doctor identifies the disease from the patient's signs or symptoms—sore throat, acute diarrhoea, pneumonia, meningitis—he will still need laboratory help since many of these syndromes are caused by different kinds of microorganisms, e.g. acute diarrhoea may be due to a wide range of pathogenic bacteria, protozoa and possibly viruses. Therefore with modern selective *chemotherapy* the effective treatment of the patient with a clinical infection requires the early isolation and identification of the infecting microorganisms and tests for its drug-sensitivities. In other words, the doctor has to identify and treat specific infections rather than clinical syndromes. When an infection is not amenable to chemotherapy as is the case with the toxic infections and most virus infections, *antisera* containing neutralizing antibodies against the pathogenic agent (either specially prepared in animals like the horse or derived from human blood containing the specific antibodies, called immunoglobulins), may be used either to treat the patient as in diphtheria or to give temporary (passive) protection to a person exposed to the risk of infection as in measles or tetanus.

MICROBIOLOGY AND THE COMMUNITY

Microbiology is closely concerned with the epidemiology and the control of infection in any community where the transmission and disease-producing capacity of the infecting microorganisms may be facilitated by environmental or host factors, e.g. overcrowding, contaminated food, drink or air, malnutrition, tissue damage. The term epidemiology has in the past been applied particularly to the study of the factors contributing to the endemic or epidemic prevalence of an infectious or communicable disease; but, as the name implies, it may be concerned with the distribution and determinants of any disease or disability in the community and in recent years epidemiological methods have been applied to many noninfective conditions. As a medical science, epidemiology is particularly concerned with aetiological factors and it has had remarkable successes in their elucidation among both infectious and noninfectious diseases. Thus, the evidence that cholera and typhoid fever were due to living agents spread by water was produced from epidemiological data collected respectively by John Snow, a London anaesthetist and William Budd, a West Country doctor, 30 to 40 years before the aetiological agents were identified. Pellagra was shown by Goldberger to be a deficiency disease long before vitamins were defined. While in our own time, heavy cigarette smoking has been proved to be causally related to lung cancer although the carcinogenic agent has not yet been identified.

Certain infections are not ordinarily transmissible from one person to another because they are due to opportunistic invasion of tissues by commensal microorganisms previously resident elsewhere in the body, e.g. urinary tract infections or subacute bacterial endocarditis, and for these the term *endogenous* (originating from within) infection may be used. Most of the common fevers—measles, whooping-cough, chickenpox, etc., are *infectious* or *communicable* diseases in the sense that they are transmissible from one person to another and are therefore called *exogenous* (originating from without) infections. Other infections that are transmissible from vertebrate animal hosts to man, called the *zoonoses*, are not ordinarily communicable from man to man, e.g. bubonic plague, brucellosis, rabies; the same is true of some infections derived from microbes in the soil, e.g. tetanus.

In the study of the sources and modes of spread of infectious diseases, the importance of *carriers* was first demonstrated when on Koch's recommendation 'bacteriological stations' were established around 1900 in typhoid-ridden parts of Germany. Combined bacteriological and epidemiological studies brought to light convalescent and more persistent stool excreters of typhoid bacilli, and these findings with other data confirmed Koch's hypothesis that in typhoid fever the acute or convalescent patient was a common source for further infection. Later it was shown that carriers, that is, individuals who while not showing any clinical symptoms of infection, carry and disperse a pathogenic microorganism, were important links in the chain of dissemination of various infections in a community. Again, tests for the presence of antibodies to specific pathogens or their toxins have shown that inapparent infections may play an important part in raising the resistance of a community to epidemic outbursts of disease. With a good knowledge of the epidemiology of a specific communicable disease, the Health Officer concerned with preventive medicine, knows what measures for its control are most likely to be effective and here again, in the field of prophylactic immunization, the microbiologist has been a most valuable partner.

Mortality and Morbidity Rates

In the economically more developed countries the past century has seen a phenomenal decrease in the death rate from infections. Some examples may be taken from Scotland, a small but representative country, where the population has increased from approximately 2·5 millions in 1865 to 5·0 millions in 1965. Deaths from the principal infectious diseases contributed, at a rate of 1 167 per 100 000 population, more than half the total deaths in the quinquennium to 1865 whereas in the corresponding five years to 1965 they were reduced to one tenth (111 per 100 000) of the earlier death rate, and constituted less than one tenth of the total deaths. The main causes of death among the infections a century ago were tuberculosis, pneumonia and bronchitis, diarrhoeal diseases (including typhoid fever) and scarlet fever whereas in the period 1961–65 only pneumonia and bronchitis took a heavy toll of life; the death rates from tuberculosis (8·2 per 100 000) and the diarrhoeal diseases (2·3 per 100 000) have fallen precipitously and scarlet fever has become a mild non-hospitalized infection although rheumatic heart

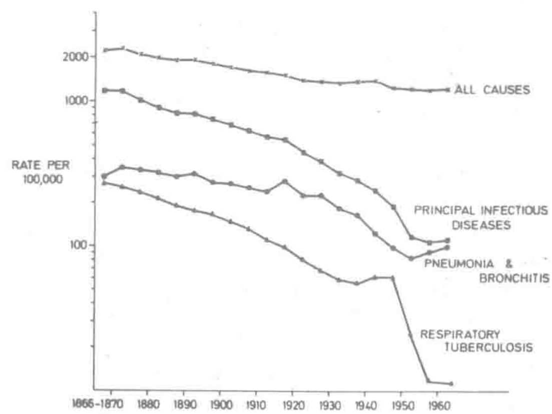

FIG. 1.1. Crude death rates in Scotland per 100 000 population for all causes, principal infectious diseases, pneumonia and bronchitis, and respiratory tuberculosis. Five year averages 1866–1965.