FIFTEENTH EDITION

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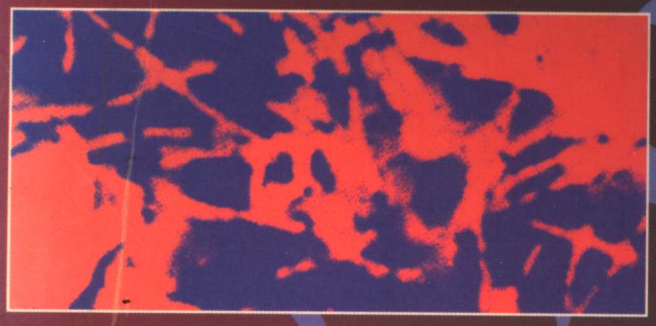
MEDICAL MICROBIOLOGY

医学微生物学

第15版

DAVID GREENWOOD
RICHARD SLACK
JOHN PEUTHERER



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Preface

If T. J. Mackie and J. E. McCartney, the original authors of this book (first published in 1925 as *An Introduction to Practical Bacteriology as Applied to Medicine and Public Health*) were able to see the latest edition, they would be astonished at how the subject has grown. Vastly more infective agents of all kinds – bacteria, viruses, protozoa, helminths and fungi – are recognized. Spectacular advances in molecular genetics have fostered a detailed understanding of microbial physiology, mechanisms of microbial pathogenicity and the host response to microbial invasion. Antimicrobial agents and vaccines beyond the wildest dreams of workers in the 1920s are in common use. Many infectious diseases have been controlled and one scourge, smallpox, eradicated. The subject is now so large that the practical laboratory aspects, once considered essential to a proper knowledge of microbiology, have long been hived off into a companion volume: *Mackie and McCartney: Practical Medical Microbiology*, edited by J. G. Collee, A. G. Fraser, B. P. Marmion and A. Simmons.

Despite our increased understanding of microbes, and the means to control them, infection continues to flourish: one third of the population of the world is estimated to harbour the bacillus of tuberculosis; millions of infants die of bacterial, viral and protozoal infection before they reach their fifth birthday; food-borne disease, even in developed countries, is at an all time high; AIDS continues its inexorable spread; the growth of antimicrobial drug resistance is causing considerable alarm. The lesson is clear. Microbes will not be easily subdued, and medical students, indeed, all health-care professionals, need to understand the principles of infection and its control. The trouble is, that with the subject now so vast, learning is necessarily selective. Moreover, with so many other demands on students' time it is easy to consign the study of infection to a minor place in the curriculum in the mistaken belief that microbial disease has been controlled by antimicrobial drugs and vaccines. Nothing could be further from the truth, and microbiology must retain a high profile in medical schools. In this book we have tried to concentrate on essentials, while providing enough background to help the student to understand the full context of microbial disease, including the often neglected topics of the epidemiology and control of infection. The emphasis is very much on clinical microbiology, but with sufficient explanation of the laboratory aspects of the subject to allow an intelligent use of diagnostic laboratory services. Readers seeking fuller information about laboratory techniques are referred to the excellent companion volume. Rather than provide an exhaustive reference list for each chapter, a few key publications are recommended to the interested reader seeking further information.

For this new edition the text has been brought fully up to date. We are most grateful to our contributors, who have suffered our constant cajoling with equanimity and produced, mostly on time, manuscripts that required very little editorial interference. Unusually among textbooks, we have been able to encompass new developments without increase – in fact, with a modest decrease – in the size of the book. This has been achieved by attention to layout and by some rationalization of the tables, figures and text. Nothing of importance, we believe, has been sacrificed.

Once more we thank our contributing authors and the editorial staff of Churchill Livingstone, who have also endured much badgering during the genesis of this book.

David Greenwood, Richard Slack, John Peutherer
Nottingham and Edinburgh, UK, 1997

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Part 1
MICROBIAL BIOLOGY

1

Microbiology and medicine

D. Greenwood

Applications of microbiology have transformed the diagnosis, prevention and cure of disease. Along with improved nutrition and living conditions, they have – at least in developed communities – revolutionized human health, doubled the average length of life and ensured the safe upbringing of most children born, where before only a minority survived.

The conquest of epidemic and fatal infections has sometimes seemed so conclusive that the main challenges in medicine are often seen to lie in other fields, such as those of the mental illnesses and degenerative diseases, but a major shift of attention away from the problems of infection could be dangerous. The relative freedom of society from fatal infections depends on the continued, informed deployment of complex countermeasures: on correct diagnosis and treatment of infections, full implementation of immunization programmes, alert epidemiological surveillance and rigorous environmental sanitation. Moreover, on a global scale, infection is far from defeated. In the developing nations of the world, an estimated 10 million young children die each year from the effects of infectious diarrhoeas, measles, malaria, tetanus, diphtheria and whooping cough alone. The tragedy is that we have the means to hand to prevent nearly all these deaths.

Even in the developed world, infection is still extremely common: at least a quarter of all illnesses for which patients consult their doctors are infective; a substantial proportion of patients acquire infection while in hospital, sometimes with multiresistant organisms. Intensive farming methods and a shift in eating habits to pre-prepared 'fast foods' have led to a sharp increase in food-related infection. In hospitals, new approaches to therapy that deplete the competence of the patient's immune system to cope with infection, as well as the increasing use of shunts, intravenous cannulae and prosthetic devices, all provide the ever-resourceful microbes with new opportunities to invade the host. Previously unsuspected links between microbes and diseases such as cancer, peptic ulcer, inflammatory bowel disease and rheumatoid arthritis have been uncovered. Surprisingly, 'new' agents of infectious disease continue to be recognized (Table 1.1). The most notorious of these is undoubtedly the human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome (AIDS). The rise and spread of this condition provides a sobering reminder of the potential impact of microbial disease. It is as essential now as it ever was that health care personnel should be well trained in matters relating to infection.

Table 1.1 Some newly recognized infectious agents, 1975–95

Agent	Disease
Bartonella henselae	Cat scratch disease
Borrelia burgdorferi	Lyme disease
Campylobacter jejuni	Enteritis
Chlamydia pneumoniae	Pneumonia
Clostridium difficile	Pseudomembranous colitis
Cryptosporidium parvum	Diarrhoea
Cyclospora cayetanensis	Diarrhoea
Escherichia coli O157	Haemolytic uraemic syndrome
Helicobacter pylori	Gastritis
Hepatitis C virus	Hepatitis
Hepatitis E virus	Hepatitis
Hepatitis G virus	Hepatitis
Human herpesvirus 6	Exanthem subitum
Human herpesvirus 8	Kaposi's sarcoma
Human immunodeficiency virus	Acquired immune deficiency syndrome (AIDS)
Human T cell lymphotropic virus	Adult T cell leukaemia; tropical spastic paraparesis
Legionella pneumophila	Legionnaires' disease
Microspora (various genera)	Diarrhoea
Mobiluncus spp.	Bacterial vaginosis
Parvovirus B19	Fifth disease
'Small round' viruses	Gastro-enteritis
Tropheryma whippelii	Whipple's disease

DEVELOPMENT OF MICROBIOLOGY

Microbiology is the study of living organisms of microscopic size. The term was introduced by the French chemist Louis Pasteur, whose demonstration that fermentation was caused by the growth of bacteria and yeasts (1857–60) provided a main impetus for the development of the science.

Micro-organisms were first seen about 1675 by the Dutchman Antony van Leeuwenhoek. His microscopes consisted of a single biconvex lens that magnified about ×200 and resolved bodies with diameters down to about 1 μm. He found many micro-organisms in materials such as water, mud, saliva and the intestinal contents of healthy subjects, and he recognized them as living creatures ('animalcules') because they swam about actively. That he saw bacteria as well as the larger microbes is known from his measurements of their size ('one-sixth the diameter of a red blood corpuscle') and his drawings of the forms we now recognize as cocci (spheres), bacilli (rods) and spirochaetes (spiral filaments).

Leeuwenhoek observed that very large numbers of bacteria appeared in watery infusions of animal or vegetable matter which were left to stand for a week or two at room temperature. He believed that these huge populations were the progeny of a few parental organisms, or seeds, that were originally present in the materials of the infusion or had entered it from the air. Other scientists suggested that the organisms arose by spontaneous generation from dead organic matter, and this began a controversy that lasted for 200 years. The prototype of the experiment that ultimately was to settle the matter was first described by the French microscopist Louis Joblot in 1718. Joblot boiled a flask of an infusion of hay for 15 min to kill any microbes originally present, covered it with a parchment cap to prevent the later entry of other microbes from the air and showed that, on subsequent standing, it remained free from microbial growth. Similar experiments, notably those of John Needham (1749), showed, by contrast, that heated, covered infusions gave a growth of organisms and so appeared to demonstrate the occurrence of spontaneous generation. It was not at first realized how exacting were the conditions needed to kill all micro-organisms, and maintain sterility. The necessary techniques were perfected only after much further work, particularly that by Lazzaro Spallanzani (1765, 1776) and Louis Pasteur (1860–64). Pasteur's flasks of infusions, sterilized by autoclaving at 115–120°C, always remained sterile despite the entry of unheated air through a dust-stopping 'swan neck' or cotton-wool stopper, and so finally proved the absence of spontaneous generation.

The controversy over spontaneous generation had the valuable outcome of establishing many of the basic techniques of bacteriology. Convenient nutrient media for preparing cultures of bacteria in the laboratory were derived from meat and vegetable infusions, and reliable methods were developed for the sterilization and maintenance of sterility of culture media and equipment. The mechanism of bacterial reproduction by asexual fission was discovered by De Saussure (1760), and the need for high temperatures for sterilization was explained by Ferdinand Cohn's (1876) discovery that certain bacteria form heat-resistant spores. Other techniques essential for the rapid progress of bacteriology were developed by the German bacteriologist Robert Koch, who in 1877 described methods for the easy microscopical examination of bacteria in dried, fixed films stained with aniline dyes, and in 1881 devised the simple method for isolating pure cultures of bacteria by plating out mixed material on a solid culture medium on which the progeny of single bacteria grow in separate colonies.

MICRO-ORGANISMS AND DISEASE

Few of the micro-organisms that abound in nature are disease-producing, or *pathogenic*, for humans. Most are free-living in soil, water and similar habitats, and are unable to invade the living body. Some free-living micro-organisms obtain their energy from daylight or by the oxidation of inorganic matter, but the majority feed on dead organic matter, and are termed *saprophytes*. In contrast, a parasite lives in or on, and obtains its nourishment from, a living host. In medical usage, the term *parasite* is nowadays usually reserved for parasitic protozoa, helminths and arthropods. The last usually affect the outside of the body, and are termed *ectoparasites*. *Commensal* micro-organisms constitute the normal flora of the healthy body. They live on the skin and on the mucous membranes of the upper respiratory tract, intestines and vagina, and obtain nourishment from the secretions and food residues. They are generally harmless, but under certain circumstances, as when the body's defences are impaired, they may invade the tissues and cause disease, thus acting as *opportunist* pathogens. True pathogens are the micro-organisms 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 (*toxins*), damages the tissues and causes the manifestations of disease. The process of microbial invasion of the body is called *infection*. Those infective diseases that are readily communicable from person to person are called *infectious* or *contagious*.

The germ theory of disease was slow in gaining acceptance, though it was early recognized that epidemic diseases such as smallpox, measles, typhus and syphilis were probably spread from person to person. The Italian scholar Girolamo Fracastoro, in his book *De Contagione* (1546), distinguished three modes of transmission: (1) by direct contact, i.e. touching a patient's body; (2) by contact with clothing and household goods contaminated by a patient; and (3) at a distance through the air. He explained contagion as being due to the transmission of invisible seeds, or germs, different kinds of which were the specific causes of the different diseases. It is unclear whether he regarded the germs as living, but their ability to multiply in successive hosts would certainly be necessary for their continued spread.

Fracastoro's views were largely forgotten by the time Leeuwenhoek discovered micro-organisms, but speculations then began that these organisms might be the cause of certain diseases. The first clear demonstration of a pathogenic role was made by the Italian civil servant Agostino Bassi (1835), who showed that the calcino disease of silkworms was invariably associated with an invasion of their tissues by a fungus and that the disease could be transmitted by the inoculation of material from the tissues of an infected worm into those of a healthy one.

Despite Bassi's work, the germ theory of disease did not become firmly established until 1876, when Robert Koch, a country doctor in East Prussia, reported his observations on anthrax. Ten years earlier, C. J. Davaine had shown that the blood of sheep dying from anthrax contained numerous non-motile filaments and that its inoculation into healthy sheep caused them to develop anthrax. These findings, however, did not exclude the possibility that the filaments were inanimate products of the disease rather than its cause. Koch began his work by transmitting anthrax from infected sheep and cattle to the mouse, an unnatural but convenient laboratory host. He observed filaments in the blood and tissues of the infected mouse, and proved that they were living bacteria by watching them grow and form spores in drops of sterile ox serum or aqueous humour seeded with fragments of infected tissue. He showed that the bacteria alone were the cause of the disease by growing them in a series of eight pure cultures in aqueous humour, each seeded with a small proportion of the preceding one, and then reproducing the disease by inoculation of the final culture into a mouse. He thus provided the evidence, now described as *Koch's postulates*, which Jacob Henle had earlier stated would be needed to prove that the particular micro-organism was the cause of a particular disease, namely: that the microbe be found in the body in all cases of the disease; that it be isolated from a case and grown in a series of pure cultures in vitro; and that it reproduce the disease on the inoculation of a late pure culture into a susceptible animal.

Koch obtained a research appointment in Berlin and there built up a successful school of bacteriology. He demonstrated the pathogenic roles of the tubercle bacillus (1882) and cholera vibrio (1883), and established the general principle that specific micro-organisms cause different kinds of disease. This principle is not absolute, and in 1883 some exceptions were demonstrated by the Scottish surgeon Alexander Ogston, who showed that *Staphylococcus aureus* and *Streptococcus pyogenes* could each cause various suppurative infections, such as abscesses and wound sepsis.

Alongside the discovery of the pathogenic role of bacteria the involvement of protozoa, helminths and fungi was soon established. Worms visible to the naked eye had, of course, been recognized in antiquity, but great strides were made in the 19th century. Among notable events were: the discovery by James Paget (while a first-year medical student at St Bartholomew's Hospital, London) of the larvae of *Trichinella spiralis* in muscle during an autopsy (1835); the observation by Alfred Donné of *Trichomonas vaginalis* in vaginal secretions (1836); the discovery of adult worms of *Schistosoma haematobium* by Theodor Bilharz in Cairo (1851); demonstration of the fungal nature of thrush by Langenbeck (1859); and the recognition of the parasites of malaria in human blood by the French Army surgeon Alphonse Laveran (1880). The complex life cycles of many of the parasitic worms and protozoa were later worked out by painstaking studies by numerous workers, of whom Patrick Manson, Ronald Ross and David Bruce are among the most celebrated.

The viruses were more difficult to demonstrate, for most were too small to be seen with the light microscope and none could be grown on an inanimate culture medium. At first they could be demonstrated only by observation of the disease they produced when infected tissue was inoculated into a susceptible animal. Thus, in studies of rabies, Pasteur and his colleagues in 1881 failed to isolate any micro-organism capable of causing the disease. They were able to

reproduce the disease in dogs and rabbits by the intracerebral injection of brain tissue or saliva from a fatal case, and they suggested that the causal agent was an organism too small to be seen. Their experiments, however, did not exclude the possibility that the agent might be a bacterium, or a larger microbe which was present but undetected in the inoculum. The means of excluding such a possibility was devised by Ivanowski (1892) in experiments with the viral mosaic disease of tobacco; he transmitted the disease to healthy plants by the inoculation of juice from a diseased plant after it had been filtered through a porcelain filter fine enough to prevent the passage of bacteria. Filter-passing viruses were soon similarly demonstrated in foot-and-mouth disease of cattle by Loeffler and Frosch (1898), in yellow fever by Reed, Carroll, Agramonte and Lazear (1900), who had to test their inoculations in human volunteers, and in other diseases. Virology did not progress rapidly, however, until after the Second World War, when the availability of the electron microscope enabled viruses to be visualized and the use of living human and animal tissue cells for the in-vitro culture of viruses was developed by John Enders (1949) and others from the earlier work of pioneers such as Alexis Carrel.

IMMUNITY AND IMMUNIZATION

It was known from ancient times that persons who had suffered from a distinctive disease, such as smallpox or measles, resisted it on subsequent exposures and rarely contracted it a second time. Such an acquired immunity is generally effective only against the same type of infection as that previously suffered.

Artificial immunization against smallpox was practised in various communities by the unsafe method of inoculating smallpox exudate through the skin (*variolation*), until, in 1796, the safer method of inoculating cowpox exudate (*vaccination*) was discovered by the Gloucestershire doctor Edward Jenner. Present-day vaccinia virus has been shown to be different from cowpox virus, and its origin is obscure. Nevertheless, it is highly effective and has been instrumental in the world eradication of natural smallpox, the last case of which occurred in Somalia in 1977. The natural existence of a safe immunizing agent such as vaccinia virus is exceptional, and we owe to Pasteur the development of immunizing strains of pathogenic microbes which are artificially *attenuated* (reduced in virulence) by prolonged or repeated culture under laboratory conditions. Pasteur derived such attenuated live *vaccines* for fowl cholera, anthrax, swine erysipelas and rabies, and called them *vaccines* in honour of Jenner's work with cowpox, or vaccinia (Latin *vacca* = cow). In 1881 he made a convincing controlled trial of his anthrax vaccine, in which a vaccinated group of cows and sheep survived a later challenge by the inoculation of virulent anthrax bacilli, while a control group of unvaccinated animals perished from the same challenge. Today, attenuated live vaccines are used with outstanding success against such diseases as tuberculosis, poliomyelitis, measles and yellow fever.

The efficacy of vaccines consisting of killed bacteria was discovered by Salmon and Smith in 1886 in experiments on salmonellosis in pigeons, and today killed vaccines are used against, for example, typhoid fever, whooping cough and influenza. About 1900, Loewenstein in Vienna and Glenny in London discovered that bacterial toxins rendered non-poisonous by treatment with formaldehyde were effective in immunizing against diphtheria and tetanus, diseases in which the serious effects are due to the toxin. The *toxoids* are now used routinely for immunization.

The first step in elucidating the mechanisms of acquired immunity was the discovery of *antibodies* by Behring and Kitasato in 1890. They found that the injection of sublethal doses of diphtheria or tetanus toxin into guinea-pigs rendered the animals immune to the later injection of large doses of the same toxin. The immunity was associated with the appearance in the animal's blood of a substance, *antitoxin*, that specifically neutralized the toxin. These diphtheria and tetanus antitoxins were the first known antibodies, but protective antibodies which reacted directly with bacteria and viruses were soon demonstrated by other workers. Antibodies have a highly specific affinity for the microbial substances, or *antigens*, that have induced their formation, and this property is exploited in the common use of blood serum containing antibodies (*antiserum*) in laboratory tests for the precise identification of microorganisms. Discovery of the means of perpetuating the growth of single antibody-producing cells has enabled these techniques to be further refined by the use of *monoclonal antibodies* that exhibit absolute specificity for the target antigens.

SEROTHERAPY AND CHEMOTHERAPY

The work of Behring and Kitasato led to the successful use of antisera raised in animals for the treatment of patients with diphtheria, tetanus, pneumonia and other diseases. Because, however, the antisera con-

tained animal proteins foreign to the human body, and were given by injection, serotherapy often caused unpleasant allergic responses, called *serum sickness*. For this reason, and also because serotherapy was unsuccessful against many kinds of infection, further progress depended on the development of drugs that exhibited *selective toxicity* – the ability to inhibit or kill the microbe without harming the patient.

Although agents active against bacteria now form the most abundant group of antimicrobial drugs, the earliest therapeutic successes were achieved with antiprotozoal and anthelminthic compounds. Indeed, effective treatment for malaria (cinchona bark), amoebic dysentery (ipecacuanha root), tapeworm (male fern) and roundworm (wormseed) have been known for centuries. In contrast, effective therapy for systemic bacterial disease was unknown before the use of hexamine (methenamine) at the turn of the 20th century and Paul Ehrlich's development of the arsenical Salvarsan (arsphenamine) for spirochaetal disease in 1909. Even these discoveries were of limited value. The true beginning of the therapeutic revolution in infection dates from Gerhard Domagk's description of Prontosil (the forerunner of sulphonamides) in 1935, the development of Alexander Fleming's penicillin by Howard Florey and his colleagues in 1940, and Selman Waksman's exploitation of the potential for antibiotic production among soil micro-organisms in the 1940s. Within 25 years of these discoveries, most of the major groups of antimicrobial agents had been recognized and more recent developments have chiefly involved chemical alteration of existing molecules.

Progress in the development of antiviral, antifungal and antiparasitic compounds has been much slower and therapeutic options in non-bacterial infection consequently remain severely limited. Meanwhile, the explosion of knowledge in immunology has renewed hopes that it may be possible to manipulate immunological processes triggered by infection to the benefit of the host.

SOURCES AND SPREAD OF INFECTION

Sources of infection are the habitats in which the pathogenic microbes ordinarily grow and from which they are disseminated to susceptible hosts. Inanimate objects may act as passive vehicles of infection, while some pathogens are derived from healthy persons, known as *carriers*, in whom infection may be unsuspected. Some infections,such as rabies, bubonic plague, brucellosis and leptospirosis, have their sources in animals, which are the natural hosts of the pathogen, and are called *zoonoses*. They are transmissible from animals to humans, but not ordinarily from person to person, so that prevention depends on the control of human contact with the infected animals.

As well as these kinds of *exogenous* infections from external sources, there are also many infections, termed *endogenous*, which are due to the invasion of tissues by a commensal organism that hitherto grew harmlessly elsewhere in the body, e.g. infections of the lung with pneumococci previously resident in the throat. The prevention of endogenous infections depends on the avoidance of predisposing conditions that impair the tissue defences.

Epidemiological observations may suggest the mechanism by which an infection is transmitted and so lead to the formulation of preventive measures even when the causal micro-organism is still unknown. In 1846, for instance, in a maternity clinic in Vienna, Ignaz Semmelweis deduced that puerperal fever was caused by a putrefactive agent which doctors picked up on their hands when attending patients or performing necropsies and then transferred into the birth canal when assisting women at childbirth. He reduced the number of maternal deaths from nearly 10% to about 3.5% by requiring staff to wash their hands in chloride of lime before attending the birth.

In a comparable study in London, John Snow (1849, 1854) showed that the geographical distribution of cholera was related to the sources of the supplies of drinking water, and concluded that the 'peculiar poison of the disease' was spread in patients' faeces, which contaminated water later drunk by other persons (*faecal–oral transmission*). Measures subsequently taken to ensure the purity of drinking water by protection, filtration and chlorination have led to the decline of cholera, typhoid fever and other water-borne infections.

The development of the techniques of antiseptic and aseptic surgery for the prevention of wound sepsis had its origin in the conception by Joseph Lister (1867) that if, as shown by Pasteur, bacteria were the cause of the fermentation and putrefaction of dead organic matter, they might well also be the cause of suppuration in living tissues. By covering operation wounds with dressings soaked in carbolic acid to kill any bacteria present in them and to exclude others from entry, and by disinfecting his hands and instruments, he greatly reduced the incidence of sepsis in his patients.

The discovery that blood-sucking arthropods spread certain diseases led to prevention by measures for the control of these vectors. In 1893, Theobald Smith

and F. L. Kilborne first showed that Texas fever of cattle was spread by ticks that bite an infected cow and transmit its blood to another animal. Subsequently, it was shown that malaria was transmitted by anopheles mosquitoes (Ronald Ross, 1898), yellow fever by aedes mosquitoes (Walter Reed and co-workers, 1900), bubonic plague by the rat flea (W. G. Liston and co-workers, 1905) and typhus fever by lice (Charles Nicolle, 1909). Campaigns of vector control by the use of insecticides and other means have since been conducted for the prevention of these diseases.

A major group of infections that have proved largely insusceptible to control by environmental sanitation are those of the respiratory tract, e.g. common colds, sore throats, influenza, whooping cough, pneumonia, tuberculosis, measles and chickenpox. Organisms that enter and leave the body via the respiratory tract may be transmitted by a variety of means, including contact and air-borne secretion droplets. It is probably this versatility in their means of spread, as well as the frequency with which urban dwellers share and breathe indoor air polluted by others, that explains the continuing high prevalence of respiratory infections.

Although infective illness has remained common during the last 100 years, industrialized countries have seen a phenomenal decrease in the death rate from the classic infections. Since the steep decline began more than a century before preventive and curative medicine became significantly effective, the earlier reduction in deaths must have been due to improvements in nutrition and living conditions which increased the resistance of individuals to the point that they generally recovered from their many infections. Subsequently, and particularly with the introduction of immunization programmes and antimicrobial therapy in the last 50 years, medicine has made a more substantial contribution to the saving of life, but let no-one imagine that microbial disease has been conquered!

RECOMMENDED READING

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