# MEDICAL MICROBIOLOGY

## A Guide to The Laboratory Diagnosis and Control of Infection

Edited by

ROBERT CRUICKSHANK

M.D., F.R.C.P., F.R.C.P.E., D.P.H., F.R.S.E.

*Professor of Bacteriology, University of Edinburgh.*
*Adviser in Bacteriology, Scottish Home and Health Department, and S.E. Regional Hospital Board (Scotland).*
*Senior Consultant in Bacteriology, Royal Infirmary, Edinburgh.*

Assistant Editors

J. P. DUGUID

M.D., B.Sc.

*Professor of Bacteriology, Queen's College, Dundee.*

R. H. A. SWAIN

M.A., M.D., M.R.C.P.E., F.C.Path., F.R.S.E.

*Reader in Virology, University of Edinburgh.*

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# LIST OF CONTRIBUTORS

*and the topics for which they have had main or shared responsibility in preparation or revision*

COGHLAN, Joyce D., B.Sc., Ph.D.
Brucella; leptospira; bacteriology of water, food and air.

COLLEE, J. G., M.D., M.C.Path.
Pasteurella; clostridia; use of culture media; tests employed in bacterial identification; biological standardisation and measurement.

CRUICKSHANK, R., M.D., F.R.C.P., F.R.C.P.E., D.P.H., F.R.S.E.
Acquired immunity and prophylactic immunisation; neisseria, corynebacterium; mycobacterium; haemophilus; bordetella; cholera vibrio; spirillum.

DUGUID, J. P., M.D., B.Sc.
Bacterial morphology and classification; bacterial genetics; pathogenic fungi; staining methods; sterilisation.

GILLIES, R. R., M.D., D.P.H., M.C.Path.
Streptococcus; pneumococcus; salmonella; shigella; Escherichia; other enterobacteriaceae; proteus; pseudomonas; loefflerella; bacteroides; donovania; actinomyces; nocardia.

GOULD, J. C., B.Sc., M.D., M.R.C.P.E., M.C.Path., F.R.S.E.[1]
Staphylococcus; phage-typing; protozoa; laboratory diagnosis of common infective syndromes; antimicrobial agents.

HAYWARD, Nancy J., B.Sc., Ph.D.[2]
Culture media.

SLEIGH, J. D., M.B., Ch.B., M.C.Path.
Anthrax; laboratory diagnosis of common infective syndromes; sterilisation.

SWAIN, R. H. A., M.A., M.D., M.R.C.P.E., F.C.Path., F.R.S.E.
Viruses and their cultivation; all chapters on specific viruses and virus infections; psittacosis and lymphogranuloma; rickettsia; bartonella; mycoplasma (PPLO); treponema; borrelia; microscopy; immunological and serological methods; care and use of laboratory animals.

WEIR, D. M., M.D.
Infection and immunity; immunological and serological methods.

WILKINSON, J. F., M.A., Ph.D.
Bacterial physiology; bacteriophage; tests employed in bacterial identification; physical and chemical methods.

[1] Central Microbiological Laboratories, Edinburgh.
[2] Department of Pathology, University of Melbourne.

# PREFACE

It has been agreed that this eleventh edition of what was formerly *A Handbook of Practical Bacteriology* by Mackie and McCartney should now be called *Medical Microbiology* and should cater as much for the needs of medical students and doctors as for bacteriologists and laboratory technicians. Consequently, there has been a rearrangement of the subject-matter into five parts, of which Part I deals with the microbial cell and the general principles of infection and immunity; Parts II and III are concerned with the aetiology, laboratory diagnosis and epidemiology of bacterial infections and of viral and some fungous and protozoal infections; Part IV, on applied microbiology, is aimed particularly at the senior medical student, the house officer and the general practitioner; and Part V is the "methods" section of special interest to microbiologists and technical staff.

Our objective was a comprehensive textbook to cater for the needs of all those concerned with the laboratory diagnosis and control of infection in man. We were particularly conscious of the usefulness, for countries where communicable disease is still the major contributor to sickness and death, of an all-purpose textbook on medical microbiology which could be a vade-mecum for teachers and students alike in the many new Medical Schools in these countries. We were therefore gratified to know that this new edition will be included in the English Language Book Scheme for developing countries.

The whole text has been thoroughly revised and rearranged and a number of new illustrations have been added. There has been further subdivision of chapters dealing with bacterial and viral infections, and new chapters have been added on the classification and identification of bacteria, laboratory diagnosis of common infective syndromes, biochemical tests in bacterial identification, and biological standardisation and measurement. We were fortunate in having in the department for a year Dr. Nancy Hayward, of Melbourne, who undertook a drastic revision of the chapter on culture media. We have also had most valuable comments, corrections and constructive suggestions from many laboratory colleagues both at home and abroad. Although too numerous to mention individually, we gladly extend our thanks to them collectively.

For this edition, Professor J. P. Duguid and Dr. R. H. A. Swain have acted as Assistant Editors and have taken a large share of the burden of subediting and proof reading. Dr. R. R. Gillies has been responsible for the preparation of the index, and all the contributors, whose responsibilities for new, or the revision of existing, chapters are indicated in the contents page, have in our numerous round-table discussions helped in welding this textbook into what I hope will be a worthy successor to the earlier editions.

I am again greatly indebted to Mr. C. Macmillan and Mr. J. Parker of E. & S. Livingstone Ltd. for much helpful advice and patient tolerance during the long gestation period.

*Edinburgh*, 1965 ROBERT CRUICKSHANK

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# PART I

# MICROBIAL BIOLOGY: INFECTION AND IMMUNITY

## CHAPTER 1

## MICROBIOLOGY AND MEDICINE

MICROBIOLOGY is one of the younger biological sciences. Although its paternity 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 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 nutriment 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 *pasteurisation* as we now call it—revolutionised the whole wine and beer industry of Europe and established the importance of microbiology in industry.

Joseph Lister, 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 injury or amputation were dying like flies of hospital gangrene and "blood poisoning". By placing an antiseptic dressing over the open wound, he prevented bacteria in the environment from getting access to the susceptible tissues and so satisfied himself that putrefaction or sepsis was caused, like fermentation, by thesei nvisible but living microbes which Leeuwenhoek, two centuries earlier, had called his "little animals". A little later, the surgeon Ogston, in Aberdeeen, showed that grape-like clusters of cocci, which he named staphylococci, were the common cause of abscesses.

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, who interested himself in the new biological science and gave us intermittent sterilisation (or *tyndallisation*); he was, incidentally, one of the first observers to note the antibacterial properties of the mould penicillium. About this time Robert Koch, a country doctor in Germany, became painfully aware of the havoc which a disease called "splenic fever" 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 rod was constantly present in the blood of animals dying of splenic fever, that this microbe could be grown and purified from contaminants on nutrient jelly, and when injected into laboratory animals could reproduce an infection identical with that which killed the cow and the sheep. This was the first wholly satisfying evidence that a specific germ, the anthrax bacillus, was the cause of a specific disease. And so, by 1880, the new science of microbiology was firmly founded and its importance in the economy of men, animals and industry was beginning to be appreciated.

Mention may be made here of two early offshoots of this science—immunology and virology—in which Pasteur was involved. He was the first to extend Jenner's protective *vaccination*, 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, and 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 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 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 by von Behring, leading on to Ehrlich's concept of "magic bullets" and so to our modern chemotherapy.

This brief historical sketch illustrates the importance of microbiology as an applied science, particularly in fermentation processes and in infectious diseases. The term *microbiology* (as originally used by Pasteur) 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; most of the microorganisms present on the skin and mucous membranes are non-pathogenic and are often referred to as *commensals* (table companions), or if they live on food residues, as in the intestine, they may be called *saprophytes*. The term saprophyte is, however, commonly used in a wider sense to denote free-living bacteria in soil, water and decaying matter. In contrast, a *parasite* may be defined as a microorganism or some larger species (*e.g.* worms) that lives in or on, and obtains its nourishment from, a living host, and is potentially pathogenic. Some of the commensal bacteria which constitute the resident flora of the skin and mucous membranes may also be potentially pathogenic in the sense that they may initiate infection under certain circumstances, as when coliform bacilli from the gut set up infection in the urinary tract or when mouth streptococci become attached to diseased heart valves and cause endocarditis.

Medical microbiology is concerned with the aetiology, *pathogenesis* (mode of infection), laboratory diagnosis and treatment of infection in the individual and with the *epidemiology* (study of mass disease) and control 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 recognised 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 (hepatisation) 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 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. Certain infections are not ordinarily transmissible from one person to another, *e.g.* the urinary tract infections or subacute bacterial endocarditis, and for these the term *endogenous* (or *autogenous*) infection may be used although an autogenous infection, for example, a boil resulting from infection with a staphylococcus on the victim's skin or nose may be *infectious* in the sense of being transmissible to another person. Most of the common fevers—measles, whooping-cough, chicken pox, etc.—are *infectious* or *communicable* diseases. However, certain infections that are transmissible from animal hosts to man, called the *zoonoses*, are not ordinarily communicable from man to man, *e.g.* bubonic plague, brucellosis, rabies.

The doctor engaged in the care of sick patients, be he general practitioner, surgeon or other medical specialist, will often be able to identify the pathogenic microorganism from the special clinical features of an infection and will accordingly prescribe the appropriate treatment. Sometimes 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 (P.U.O.) will require laboratory help to elucidate the cause of the fever. Even when the doctor identifies the infection 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, viruses and protozoa. Moreover, some of these pathogenic bacteria which are ordinarily sensitive to certain anti-microbial drugs, may acquire drug-resistance. Therefore with modern selective *chemotherapy* the effective treatment of the patient with a clinical infection requires the early isolation and identification of the infecting microorganism. 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 neutralising antibodies against the pathogenic agent (either specially prepared in animals like the horse or derived from human blood *i.e.* gamma globulin) may be used either to treat the patient as in diphtheria or to give temporary protection to a person exposed to the risk of infection as in measles.

Microbiology is closely concerned with the *epidemiology* and control of infection in any community where the transmission and disease-producing capacity of the infecting microorganisms is 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 is concerned with the study of any community disease or disability and in recent years we have seen the application of epidemiological methods to many non-infective conditions. As a medical science it is particularly concerned with aetiological factors and it has had remarkable successes in their elucidation among both infectious and non-infectious 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, 20 years or more before the aetiological agents were identified, pellegra 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.

In the study of the sources and modes of spread of infectious diseases, microbiology has demonstrated the importance of *carriers*; that is, individuals who while not showing any clinical symptoms of infection, carry and disperse a pathogenic microorganism and so contribute to the dissemination of infection in a community. Again, tests for the presence of antibodies to specific pathogens or their toxins have shown that latent or inapparent infections may play a large 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 immunisation, the microbiologist has been a most valuable partner.

Most of the major pestilences—typhus and typhoid fever, plague, cholera, smallpox and yellow fever—that used to decimate armies and beleaguered cities or spread like wild-fire round the world are now being controlled by good environmental sanitation, by the destruction of insect vectors such as louse, flea and mosquito, or by prophylactic vaccination. However, some of these great plagues, together with other global infections like malaria, tuberculosis and leprosy, the diarrhoeal diseases and the pneumonias, still take a heavy toll of life and health in most of the developing countries. Pandemics of influenza still occur and respiratory infections are still the major cause of sickness in most countries.

A community infection of a special kind still occurs among patients congregated in hospitals. Although the consequences of hospital cross-infection are much less serious than they were in Lister's day, we are reminded of the aphorisms of two great hospital reformers of the nineteenth century—Florence Nightingale's pungent comment that "the first requirement of any hospital (is) that it do the sick no harm" and Sir James Y. Simpson's conclusions after a most remarkable epidemiological survey of deaths from infection following amputations that "in treatment of the sick, there is ever danger in their aggregation and safety only in their segregation; and our hospitals should be constructed so as to avoid . . . the former and secure . . . the latter condition". We are still far from achieving these worthy objectives. It is pertinent in these days when teaching hospitals are becoming the repositories of ageing patients with degenerative diseases to remind medical students and doctors that acute and chronic infections are still responsible for more than a third of all the illnesses requiring medical care and that in the most susceptible group of children under 5 years of age, infections account for over 80 per cent. of the total sickness.

Microbiology developed originally as an applied science of particular importance in medicine, agriculture and industry. But it soon became obvious that the bacterial cell and its products had many attractions for the general biologist, the chemist, the physicist, the geneticist, the pharmacologist and other specialists as well as the bacteriologist, immunologist and pathologist. In its free living form, the bacterial cell with its simple food requirements, rapid growth and remarkable hardiness, and its great range of enzymes and diffusible products has become very acceptable for detailed study and, in the past few decades, bacterial physiology (sometimes called microbial chemistry) has made many contributions to advances in our knowledge of cellular and molecular biology. Together with bacteriophage (its own particular parasite) the bacterial cell has been specially useful in advancing the science of genetics while the biochemist interested in enzymology finds it a most valuable granary. Although many of the developments in general microbiology are not immediately relevant to medicine, it is essential that the medical student should have some understanding of the anatomy and physiology of the bacterial cell and this aspect of microbiology is discussed in the chapters that follow.

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CHAPTER 2

# MORPHOLOGY OF BACTERIA

**Microorganisms** may be defined as living creatures that are microscopical in size and relatively simple, often unicellular in structure. The diameter of the smallest body that can be resolved and seen clearly with the naked eye is about 100 $\mu$ (1 $\mu$, or micron = 0·001 millimetres). All but a few of the microorganisms are smaller than this and a microscope is therefore necessary for their observation. The light microscope under optimal conditions can resolve bodies down to 0·2 $\mu$ in diameter, and this includes all microbes except the viruses, most of which are even smaller. The electron microscope has a limit of resolution better than 0·0005 $\mu$ (*i.e.* 0·5 m$\mu$ or millimicron = 5 Angström Units), and can resolve even the smallest viruses (0·01 $\mu$ diam.). It should be noted, however, that when bacteria or fungi are allowed to grow undisturbed on a solid or semi-solid substrate, their numerous progeny accumulate locally to form masses, or *colonies*, which are readily visible to the naked eye.

Living material, or protoplasm, is organised in units known as *cells*. Each cell consists of a body of protoplasm, the *protoplast*, enclosed by a thin semipermeable membrane, the *plasma membrane* or *cytoplasmic membrane*, and also, in most cases, by an outer, relatively rigid *cell wall*. The protoplast is differentiated into a major part, the *cytoplasm*, and an inner body, the *nucleus*, which contains the hereditary determinants of character, the *genes*, borne on thread-like *chromosomes*.

The bodies of higher plants and animals are multicellular, with interdependence and specialisation of function among the cells, the different kinds of cells being segregated in separate tissues. Many microorganisms, on the other hand, are unicellular, existing as single self-sufficient cells, unattached to their fellows. Other microorganisms grow as aggregates of cells joined together by their cell walls in clusters, chains, rods, filaments (hyphae) or mycelia (*i.e.* meshworks of branching filaments), and some grow as a *plasmodium*, *i.e.* a multinucleate mass of cytoplasm. Generally, these morphologically multicellular microbes are physiologically unicellular, each cell being self-sufficient and, if isolated artificially, being able to nourish itself, grow and reproduce the species. Some specialisation of cell function, approaching that of true multicellular organisms, is encountered in colonies of moulds and higher bacteria; thus, certain cells, which form an aerial mycelium, are specialised for the formation and dissemination of spores, and are dependent for their nutrition on the activities of other cells comprising a vegetative mycelium.

The majority of microorganisms may be classified in the following large biological groups: (1) Algae, (2) Protozoa, (3) Slime moulds, (4) Fungi proper, or *Eumycetes*, including the moulds and the yeasts, (5) Bacteria, or *Schizomycetes* ("fission fungi"), (6) *Rickettsiales*, (7) *Mycoplasmatales*, and (8) Viruses, or *Virales*. The algae (except the blue-green algae), the protozoa, slime moulds and fungi include the larger and more highly developed microorganisms; their cells have the same general type of structure and organisation, described as *eucaryotic*, that is found in the cells of higher plants and animals. The bacteria and the closely related blue-green algae, the organisms of the mycoplasma and rickettsia groups and the so-called "viruses" of the psittacosis-lymphogranuloma-trachoma group include the smaller microorganisms having a simpler form of cellular organisation described as *procaryotic* (Stanier & van Niel, 1962). The viruses are the smallest of the microorganisms; the infectious virus particles, or *virions*, have a relatively simple structure that is not comparable with that of a cell, and their mode of reproduction is fundamentally different from that of cellular organisms.

Since the algae and slime moulds contain no species of medical or veterinary importance, they will not be dealt with in this book. The main differential characters of the other groups are as follows:

**Protozoa.**—These are non-photosynthetic unicellular organisms (a few are colonial) with protoplasm clearly differentiated into nucleus and cytoplasm. They are relatively large microorganisms, with transverse diameters mainly in the range 2–100 $\mu$. Their surface membranes vary in complexity and rigidity from a thin, flexible membrane in amoebae, which allows major changes in cell shape and the protrusion of pseudopodia in the movements of locomotion and ingestion, to a relatively stiff pellicle in ciliate protozoa, which preserves a characteristic shape to the cell. Most free-living, and some parasitic species have the mode of nutrition typical of animals, that called *holozoic*: they capture, ingest and digest internally solid masses or particles of food material. Many protozoa, for instance, feed on bacteria. Protozoa, therefore, are generally regarded as the lowest forms of animal life, though certain flagellate protozoa are very closely related in their morphology and mode of development to photosynthetic flagellate algae in the plant kingdom. Some free-living protozoa are *saprophytic*, absorbing soluble nutrient substances derived from dead plant or animal material, or from the excretions of plants and animals. Many protozoa are *parasitic* and live in and derive their nourishment from the body of an animal host; some of these parasites ingest masses of solid material whilst others absorb soluble nutrients through their cell surface. Malaria parasites, for instance, both absorb soluble nutrients from the host and ingest masses of host-cell cytoplasm. Protozoa reproduce asexually by binary fission or multiple fission (schizogony), and some also by a sexual mechanism. Some species exhibit a definite life cycle with both sexual and asexual phases, and some form round, thick-walled resting cells, or "cysts", which are important for the persistence and spread of the organism through the environment, where conditions may be unfavourable to survival of the vegetative forms.

**Fungi.**—These are non-photosynthetic microorganisms possessing relatively rigid cell walls. They are saprophytic or parasitic, and take in soluble nutrient substances by diffusion through their cell surfaces. When solid food materials are utilised, these are first broken

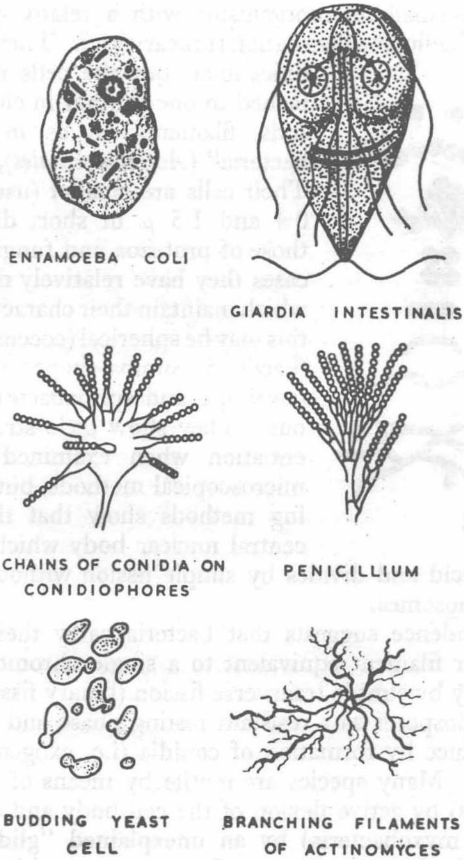


FIG. 1

down to soluble products by enzymes secreted extracellularly by the fungus. Except for the flagellate spores and gametes of the primitive aquatic species, fungi are non-motile. *Moulds* grow as branching filaments (hyphae), usually between 2 and 10 $\mu$ in width, which interlace to form a meshwork (mycelium). The hyphae are *coenocytic* (*i.e.* have a continuous multinucleate protoplasm), being non-septate or else septate with a central pore in each cross-wall. Moulds reproduce by the formation of various kinds of sexual and asexual spores that develop from the vegetative (feeding) mycelium or from an aerial mycelium that effects their airborne dissemination. *Yeasts* are ovoid or spherical cells that reproduce asexually by budding and also, in many cases, sexually with the formation of sexual spores. They do not form a mycelium, although the intermediate *yeast-like fungi* may form a pseudomycelium consisting of chains of elongated cells. The higher fungi of the class *Basidiomycetes* (mushrooms), which produce large fruiting structures for aerial dissemination of spores, play no part in infection of man or animals, though some species, e.g. *Amanita phalloides*, are poisonous when eaten.