# review of Medical Microbiology

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15th edition

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# Preface

The authors' intention in preparing this *Review* has been to make available a comprehensive, accurate, up-to-date presentation of those aspects of medical microbiology that are of particular significance in the fields of clinical infections and chemotherapy. The book is directed primarily at the medical student, house officer, and practicing physician. However, because the necessity for a clear understanding of microbiologic principles has increased in recent years as a result of important developments in biochemistry, genetics, immunology, virology, chemotherapy, and other fields of direct medical significance, a considerable portion of this *Review* has been devoted to a discussion of the relevant basic science aspects. It is to be expected that the inclusion of these sections will extend the book's usefulness to students in introductory microbiology courses as well. In general, details of technique and procedure have been excluded.

With the appearance of the Fifteenth Edition, the authors are pleased to report that Spanish, German, French, Italian, Portuguese, Serbo-Croatian, Japanese, Polish, Albanian, and Indonesian translations have proved successful. Greek, Chinese, Russian, and Arabic translations are in progress.

The authors wish to reaffirm their gratitude to everyone who assisted them with the preparation of this edition and to all those whose comments and criticisms have helped to keep the biennial revisions of this *Review* accurate and up to date. We are especially grateful to the following for their help: Janet S. Butel, John Conte, Mary Estes, Margaret Ann Fraher, Moses Grossman, Carlyn Halde, Lavelle Hanna, and F. Blaine Hollinger.

Ernest Jawetz
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San Francisco
May, 1982

**SI Units of Measurement in the Biologic Range**

| Prefix | Abbreviation | Magnitude |
|---|---|---|
| kilo- | k | $10^{3}$ |
| deci- | d | $10^{-1}$ |
| centi- | c | $10^{-2}$ |
| milli- | m | $10^{-3}$ |
| micro- | $\mu$ | $10^{-6}$ |
| nano- | n | $10^{-9}$ |
| pico- | p | $10^{-12}$ |

These prefixes are applied to metric and other units. For example, a micrometer ($\mu$m) is $10^{-6}$ meter (formerly micron, $\mu$); a nanogram (ng) is $10^{-9}$ gram (formerly millimicrogram, m$\mu$g); and a picogram (pg) is $10^{-12}$ gram (formerly micromicrogram, $\mu\mu$g). Any of these prefixes may also be applied to seconds, units, mols, equivalents, osmols, etc. The Angstrom (A, $10^{-7}$) is now expressed in nanometers (eg, 40 A = 4 nm).

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# The Microbial World | 1

Before the discovery of microorganisms, all known living things were believed to be either plant or animal; no transitional types were thought to exist. During the 19th century, however, it became clear that the microorganisms combine plant and animal properties in all possible combinations. It is now generally accepted that they have evolved, with relatively little change, from the common ancestors of plants and animals.

The compulsion of biologists to categorize all organisms in one of the 2 "kingdoms," plant or animal, resulted in a number of absurdities. The fungi, for example, were classified as plants because they are largely nonmotile, although they have few other plantlike properties and show strong phylogenic affinities with the protozoa.

In order to avoid the arbitrary assignment of transitional groups to one or the other kingdom, Haeckel proposed in 1866 that microorganisms be placed in a separate kingdom, the **Protista.** As defined by Haeckel, the Protista included algae, protozoa, fungi, and bacteria. In the middle of the current century, however, the new techniques of electron microscopy revealed that the bacteria differ fundamentally from the other 3 groups in their cell architecture. The latter share with the cells of plants and animals the advanced type of structure called **eukaryotic;** the bacteria possess a more primitive type of structure called **prokaryotic.** (The 2 types of cell structure are described in Chapter 2.) The term protist is currently used to refer only to the eukaryotic microorganisms, the assemblage of bacterial groups being referred to collectively as prokaryotes.

The term algae has long been used to refer to all chlorophyll-containing microorganisms that produce gaseous oxygen as a by-product of photosynthesis. Electron microscopy, however, has revealed that one major group—formerly called blue-green algae—are in fact true prokaryotes, and they have thus been renamed **cyanobacteria.***

Three groups of prokaryotes—methanogens, extreme halophiles, and thermoacidophiles—have been found to share a set of properties that distinguish them clearly from all other prokaryotes. It has been proposed that these organisms represent the most primitive cell types and that they should therefore be classified separately as the **archaebacteria.** An analysis of the base sequences of the ribosomal RNA of these and other organisms shows that the archaebacteria are only distantly related to other bacteria; there are also major differences in the composition of their cell walls and membranes and in their metabolism.

Thus, a current classification of microorganisms might read as follows:

**I. Protists (eukaryotic)**
- A. Algae
- B. Protozoa
- C. Fungi
- D. Slime molds (sometimes included in the fungi)

**II. Prokaryotes**
- A. Bacteria
- B. Cyanobacteria
- C. Archaebacteria

The bacteria include 2 groups, the **chlamydiae (bedsoniae)** and the **rickettsiae,** which differ from other bacteria in being somewhat smaller (0.2–0.5 $\mu$m in diameter) and in being obligate intracellular parasites. The reasons for the obligate nature of their parasitism are not clear; there is some evidence that they depend on their hosts for coenzymes and complex energy-rich metabolites such as ATP, to which their membranes may be permeable.

**Viruses** are also classed as microorganisms, but they are sharply differentiated from all cellular forms of life. A viral particle consists of a nucleic acid molecule, either DNA or RNA, enclosed in a protein coat, or **capsid.** The capsid serves only to protect the nucleic acid and to facilitate attachment and penetration of the virus into the host cell. Viral nucleic acid is the infectious principle; inside the host cell it behaves like host genetic material in that it is replicated by the host's enzymatic machinery and also governs the formation of specific (viral) proteins. Maturation consists of assemblage of newly synthesized nucleic acid and protein subunits into mature viral particles; these are liberated into the extracellular environment.

A number of transmissible plant diseases are caused by **viroids,** small, single-stranded, covalently

**Bergey's Manual of Determinative Bacteriology*, 8th ed. Williams & Wilkins, 1974.

closed circular RNA molecules existing as highly base-paired rodlike structures; they do not possess capsids. Their molecular weights are estimated to fall in the range of 75,000–100,000. It is not known whether they are translated in the host into polypeptides or whether they interfere with host functions directly (as RNA); if the former is true, the largest viroid could only be translated into the equivalent of a single polypeptide containing about 55 amino acids.

Viroid RNA is replicated by the DNA-dependent RNA polymerase of the plant host; preemption of this enzyme may contribute to viroid pathogenicity.

The general properties of animal viruses pathogenic for humans are described in Chapter 27. Bacterial viruses are described in Chapter 9.

## PROTISTS

The protists share with true plants and animals the type of cell construction called eukaryotic ("possessing a true nucleus"). In such cells the nucleus contains a set of chromosomes that are separated, following replication, by an elaborate mitotic apparatus. The nuclear membrane is continuous with a ramifying endoplasmic reticulum. The cytoplasm of the cell contains self-replicating organelles (mitochondria and, in photosynthetic cells, chloroplasts), as well as microtubules and microfilaments. Motility organelles (cilia or flagella) are complex multistranded elements.

### Algae

The term "algae" refers in general to chlorophyll-containing protists. The algae are divided into 6 phylogenetic groups, for descriptions of which the reader is referred to Smith GM: *Cryptogamic Botany*, 2nd ed. Vol 1: *Algae and Fungi*. McGraw-Hill, 1955.

### Protozoa

In Smith's classification of algae, several types of photosynthetic, flagellated, unicellular forms are included that many textbooks class with the protozoa. These include members of Volvocales in Chlorophyta, members of Euglenophyta, the dinoflagellates in Pyrrophyta, and some of the golden browns in Chrysophyta. These have not been classified as algae arbitrarily but because definite phylogenetic series are recognized that link them to typical algal forms.

On the other hand, these photosynthetic flagellates probably represent transitional forms between algae and protozoa; according to this view, the protozoa have evolved from various algae by loss of chloroplasts. They thus have a polyphyletic origin (ancestors in many different groups). Indeed, mutations of flagellates from green to colorless have been observed in the laboratory. The resulting forms are indistinguishable from certain protozoa.

The most primitive protozoa are thus the flagellated forms. "Protozoa" are unicellular, nonphotosynthetic protists. From the flagellated forms appear to have evolved the ameboid and the ciliated types; intermediate types are known that have flagella at one stage in the life cycle and pseudopodia (characteristic of the ameba) at another stage. The simplest classification of protozoa would be the following (see also p 497).

**Phylum:** Protozoa
- **Class I:** Mastigophora. The flagellate protozoa.
- **Class II:** Sarcodina. The ameboid protozoa. (Some also form flagella.)
- **Class III:** Sporozoa. Parasites with complex life cycles that include a resting or spore stage.
- **Class IV:** Ciliata. The ciliate protozoa. High degree of internal organization.

### Fungi

The fungi are nonphotosynthetic protists growing as a mass of branching, interlacing filaments ("hyphae") known as a mycelium. Although the hyphae exhibit cross-walls, the cross-walls are perforated and allow the free passage of nuclei and cytoplasm. The entire organism is thus a coenocyte (a multinucleate mass of continuous cytoplasm) confined within a series of branching tubes. These tubes, made of polysaccharides such as chitin, are homologous with cell walls. The mycelial forms are called **molds;** a few types, **yeasts,** do not form a mycelium but are easily recognized as fungi by the nature of their sexual reproductive processes and by the presence of transitional forms.

The fungi probably represent an evolutionary offshoot of the protozoa; they are unrelated to the actinomycetes, mycelial bacteria which they superficially resemble. Fungi are subdivided as follows:

- **Class I:** Zygomycotina (the phycomycetes). Mycelium usually nonseptate; asexual spores produced in indefinite numbers within a structure called a sporangium. Sexual fusion results in formation of a resting, thick-walled cell termed a zygospore. ***Example:*** *Rhizopus nigricans* (no known pathogens).
- **Class II:** Ascomycotina (the ascomycetes). Sexual fusion results in formation of a sac, or ascus, containing the meiotic products as 4 or 8 spores (ascospores). Asexual spores (conidia) are borne externally at the tips of hyphae. ***Examples:*** *Trichophyton (Arthroderma), Microsporum (Nannizzia), Blastomyces (Ajellomyces).*
- **Class III:** Basidiomycotina (the basidiomycetes). Sexual fusion results in formation of a club-shaped organ called a basidium, on the surface of which are borne the 4 meiotic products (basidiospores). Asexual spores (conidia) are borne externally at the tips of hyphae. ***Example:*** *Cryptococcus neoformans (Filobasidiella neoformans).*

**Class IV:** Deuteromycotina (the imperfect fungi). This is not a true phylogenetic group but rather an artificial class into which are temporarily placed all forms in which the sexual process has not yet been observed. Most of them resemble ascomycetes morphologically. ***Examples:*** *Epidermophyton, Sporothrix, Candida.*

The evolution of the ascomycetes from the phycomycetes is seen in a transitional group, members of which form a zygote but then transform this directly into an ascus. The basidiomycetes are believed to have evolved in turn from the ascomycetes.

Although the fungi are classified on the basis of their sexual processes, the sexual stages are difficult to induce and are rarely observed. Descriptions of species thus deal principally with various asexual structures, including the following: (See Figs 25–1 to 25–9 for drawings of some of these structures.)

**A. Sporangiospores:** Asexual spores borne internally inside a sac known as a sporangium. In terrestrial forms, the sporangium is borne at the tip of a filament called a sporangiophore. These structures are characteristic of the phycomycetes.

**B. Conidia:** Asexual reproductive units that develop along one of 2 basic pathways. "Blastic" conidia develop from an enlargement of some part of the conidiophore (conidiogenous hypha) prior to delimitation by a septum. "Thallic" conidia differentiate from a whole cell after a septum has formed. The blastic type of conidia show many modifications that may be given specific names. When a sexual stage has not been recognized for a given fungus, the form of conidia it produces is used as a basis for classification within the imperfect fungi.

**C. Arthrospores:** Thallic conidia formed by segmentation and disarticulation of a filament of a septate mycelium into separate cells. They are properly called **arthroconidia.**

**D. Chlamydospores:** Thallic conidia formed as enlarged, thick-walled cells within a hypha. They remain a part of the mycelium, surviving after the remainder of the mycelium has died and disintegrated.

**E. Blastospores:** Simple blastic conidia produced as buds that then separate from the parent cell. They are properly called **blastoconidia.**

### Slime Molds

These organisms are characterized by the presence, as a stage in the life cycle, of an ameboid multinucleate mass of cytoplasm called a **plasmodium.** The creeping plasmodium, which reaches macroscopic size, gives rise to walled spores that germinate to produce naked uniflagellate swarm spores or, in some cases, naked nonflagellated amebas ("myxamebae"). These usually undergo sexual fusion before growing into typical plasmodia again.

The plasmodium of a slime mold is analogous to the mycelium of a true fungus. Both are coenocytes; but in the latter, cytoplasmic flow is confined to the branching network of chitinous tubes, whereas in the former the cytoplasm can flow (creep) in all directions.

## PROKARYOTES

The prokaryotes form a heterogeneous group of microorganisms distinguished from protists by the following criteria: size range (0.2–2 $\mu$m for the smallest diameter); cell construction; and unique systems of genetic transfer (see Chapter 4).

Photosynthesis occurs within several subgroups of bacteria, as well as in all cyanobacteria. The cyanobacteria include a variety of prokaryotic forms that overlap bacteria and eukaryotic algae in their range of cellular sizes. They possess the same chlorophylls as the eukaryotic algae and oxidize $H_2O$ to gaseous oxygen in their photosynthesis. By these properties they differ from the photosynthetic bacteria, which have specialized chlorophylls and do not produce gaseous oxygen.

Both the cyanobacteria and the photosynthetic bacteria contain their photosynthetic pigments in a series of lamellae just under the cell membrane. In some photosynthetic bacteria, these lamellae differentiate under certain environmental conditions into ovoid or spherical bodies called chromatophores. In contrast, the eukaryotic algae always contain their photosynthetic pigments in autonomous cytoplasmic organelles (chloroplasts). There is strong evidence to support the hypothesis that the chloroplasts of eukaryotic algae and plants evolved from endosymbiotic cyanobacteria.

The cyanobacteria exhibit a type of motility called "gliding" or "creeping," the mechanism of which is unknown. Many nonphotosynthetic bacteria also possess gliding motility; some of these resemble certain cyanobacteria so closely that they are believed to be "colorless blue-greens" that have lost their photosynthetic pigments in the course of evolution.

No further generalizations can be made about the prokaryotes. The reader is referred instead to the descriptions of the various bacterial groups in Chapter 3.

## SUMMARY

A theory of evolutionary relationships between the above groups is diagrammatically presented in Fig 1–1. Listed at the right are the major groups of present-day microorganisms; the horizontal scale indicates time, and the vertical scale indicates relative evolutionary advance. Thus, the earliest cell type to emerge on earth was presumably anaerobic and prokaryotic. From this ancestral type, 3 parallel lines of evolution diverged, leading to (1) photosynthesis; (2) aerobic respiration; and (3) such eukaryotic structural features as microtubular systems and nuclear complexity ("proto-eukaryotes").

The contemporary eukaryotes are pictured as arising by a sequence of further events: (1) establishment

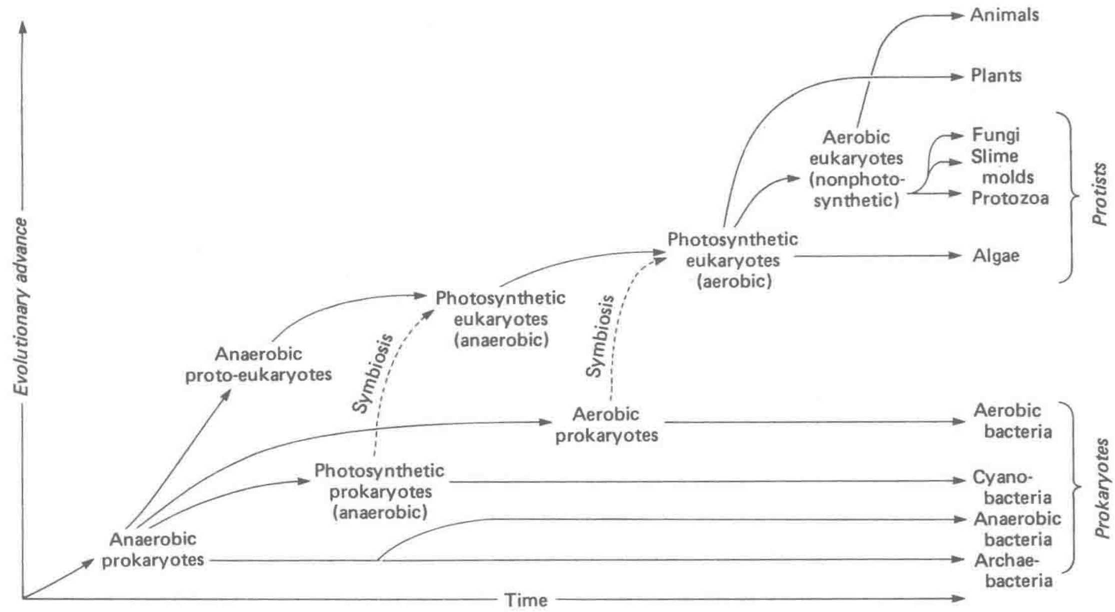


**Figure 1–1.** Evolutionary relationships of the major groups of microorganisms.

of endosymbiosis between a cyanobacterium and an anaerobic proto-eukaryotic cell, the chloroplast evolving from the endosymbiont; and (2) evolution of the mitochondrion, either from an endosymbiotic aerobic prokaryote or by segregation of part of the eukaryotic nucleus. Although mitochondria share many properties with bacteria, their DNA more closely resembles that of the eukaryotic nucleus in possessing highly reiterated sequences as well as introns; thus, both theories are at this time equally tenable.

These 2 events would have produced an aerobic photosynthetic eukaryote comparable to present-day higher algae. Loss of the chloroplast would account for the appearance of protozoa and ultimately of fungi and slime molds.

Anaerobic bacteria and archaebacteria, according to this line of reasoning, represent forms that have evolved with relatively little change from the earliest prokaryotic groups. The evolutionary origin of present-day viruses, on the other hand, is obscure. A reasonable hypothesis is that they have evolved from their respective host cell genomes, escaping the normal control mechanisms of the cell and acquiring capsids.

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