

# review of medical microbiology

13th  
EDITION

ERNEST JAWETZ, PhD MD

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# Preface

The authors' intention in preparing this *Review* has been to make available a reasonably comprehensive, accurate, up-to-date presentation of those aspects of medical microbiology which 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 technic and procedure have been excluded.

With the appearance of the Thirteenth Edition the authors are pleased to report that Spanish, German, French, Italian, Portuguese, Turkish, Serbo-Croatian, Japanese, and Polish translations have proved successful.

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, Stephen N. Cohen, John Conte, Margaret Ann Fraher, Moses Grossman, Carlyn Halde, Lavelle Hanna, F. Blaine Hollinger, Kenneth Powell, and Dorothy Purifoy.

Ernest Jawetz  
Joseph L. Melnick  
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San Francisco  
May, 1978

### 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 ( $\mu\text{m}$ ) is  $10^{-6}$  meter (formerly micron,  $\mu$ ); a nanogram (ng) is  $10^{-9}$  gram (formerly millimicrogram,  $\text{m}\mu\text{g}$ ); and a picogram (pg) is  $10^{-12}$  gram (formerly micromicrogram,  $\mu\mu\text{g}$ ). 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,  $40 \text{ A} = 4 \text{ nm}$ ).

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# 1...

## The Microbial World

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 plant-like properties and show strong phylogenetic 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. Members of the kingdom Protista are distinguished from true plants and animals by their simple organization: they are unicellular, or, if multicellular, their tissues show little differentiation. The Protista can be subdivided as follows, based on their fundamental type of cell structure, eukaryotic or prokaryotic. The eukaryotic type of cell structure, which is the more advanced, is shared with the cells of plants and animals; the prokaryotic type of cell structure is the more primitive. The 2 types of cell structure are described in Chapter 2.

- I. Higher protists: (Eukaryotic).
  - A. Algae (except blue-green)
  - B. Protozoa
  - C. Fungi
  - D. Slime molds
- II. Lower protists: (Prokaryotic).
  - A. Bacteria
  - B. Blue-green algae\*

\*In the latest edition of *Bergey's Manual of Determinative Bacteriology* (8th ed. Williams & Wilkins, 1974), the blue-green algae are renamed the Cyanobacteria and are placed with the other bacteria in a new kingdom, Prokaryotae. This kingdom corresponds to the group which we call here the "lower protists."

The bacteria include 2 groups, the chlamydiae (bedsoniae) and the rickettsiae, which differ from other bacteria only in being somewhat smaller (0.2–0.5  $\mu\text{m}$  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 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.

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

### Higher Protists

The higher 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 which are separated, following replication, by an elaborate mitotic apparatus. The nuclear membrane is continuous with the ramifying endoplasmic reticulum. The cytoplasm of the cell contains self-replicating organelles (mitochon-

dria and, in photosynthetic cells, chloroplasts), as well as microtubular elements. Motility organelles (cilia or flagella) are complex multistranded elements.

**A. Algae:** The term "algae" refers in general to chlorophyll-containing higher 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.

**B. Protozoa:** In Smith's classification of algae, several types of photosynthetic, flagellated, unicellular forms are included which 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 which 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 higher protists. From the flagellated forms appear to have evolved the ameboid and the ciliated types; intermediate types are known which 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 page 493):

#### 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 which include a resting or spore stage.
- Class IV: Ciliata. The ciliate protozoa. High degree of internal organization.

**C. Fungi:** Those who argue that fungi have evolved from the algae point to similarities between the most primitive fungi (the phycomycetes) and members of the Chlorophyceae (in the Chlorophyta). However, the latter always store starch as their food reserve, and their motile cells are always multiflagellate; the most primitive fungi generally store glycogen (never starch), and the motile cells in the aquatic forms are usually unflagellate. It thus appears more reasonable to trace their origin from the protozoa. (Note: The fungi show no evolutionary link with the mycelial bacteria called "actinomycetes.")

The fungi are nonphotosynthetic microorganisms

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 differ from bacteria, including the filamentous actinomycetes, in being eukaryotic. They are subdivided as follows:

**Class I:** 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 zygote. *Example:* *Rhizopus nigricans*.

**Class II:** 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*, *Microsporum*, *Blastomyces*.

**Class III:** 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:* *Psalliota campestris* (*Agaricus campestris*), the common mushroom.

**Class IV:** The imperfect fungi. This is not a true phylogenetic group but merely a "taxonomic dumpheap" onto which are thrown all forms in which the sexual process has not yet been observed. Most of them resemble ascomycetes morphologically. *Examples:* *Epidermophyton*, *Sporothrix*, *Cryptococcus*, *Candida*.

The evolution of the ascomycetes from the phycomycetes is seen in the transitional Protoascomycetae, 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.)

**1. Sporangiospores**—Asexual spores borne internally inside a sac known as a sporangium. The sporangium is borne at the tip of a filament called a sporangi-

ophore. These structures are characteristic of the phycomycetes.

**2. Conidia**—Asexual spores borne externally (not enclosed in a sac). The hyphae which bear them are called conidiophores. Conidia are formed by abstriction of the conidiophore; some species of fungi produce 2 types of conidia of differing size, in which case they are designated microconidia and macroconidia.

**3. Thallospores**—This term denotes actively reproducing cells which are formed by segmentation of the mycelium. Once formed, thallospores may reproduce by fission, by budding, or by growth into a new mycelium. There are 2 types: (1) arthrospores (oidia), produced by disarticulation of a filament of a septate mycelium into separate cells, and (2) blastospores, produced by budding from the ends or sides of the mycelial filaments. Blastospores are also known as "yeastlike cells."

**4. Chlamydo spores**—Thick-walled, enlarged, resting spores formed (like thallospores) by segmentation of the mycelium. The chlamydo spores remain as part of the mycelium, surviving after the remainder of the mycelium has died and disintegrated.

**D. 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 which germinate to produce naked unflagellate swarm spores or, in some cases, naked nonflagellated amebae ("myxamoebae"). 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.

### Lower Protists (Bacteria & Blue-Green Algae)

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

The blue-green algae include a variety of prokaryotic forms which overlap bacteria and eukaryotic algae in their range of cellular sizes. They are photosynthetic, possessing the same chlorophylls as the eukaryotic algae and oxidizing  $\text{H}_2\text{O}$  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 blue-green algae 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 blue-green algae.

The blue-green algae exhibit a type of motility called "gliding" or "creeping," the mechanism of which is unknown. Many nonphotosynthetic bacteria

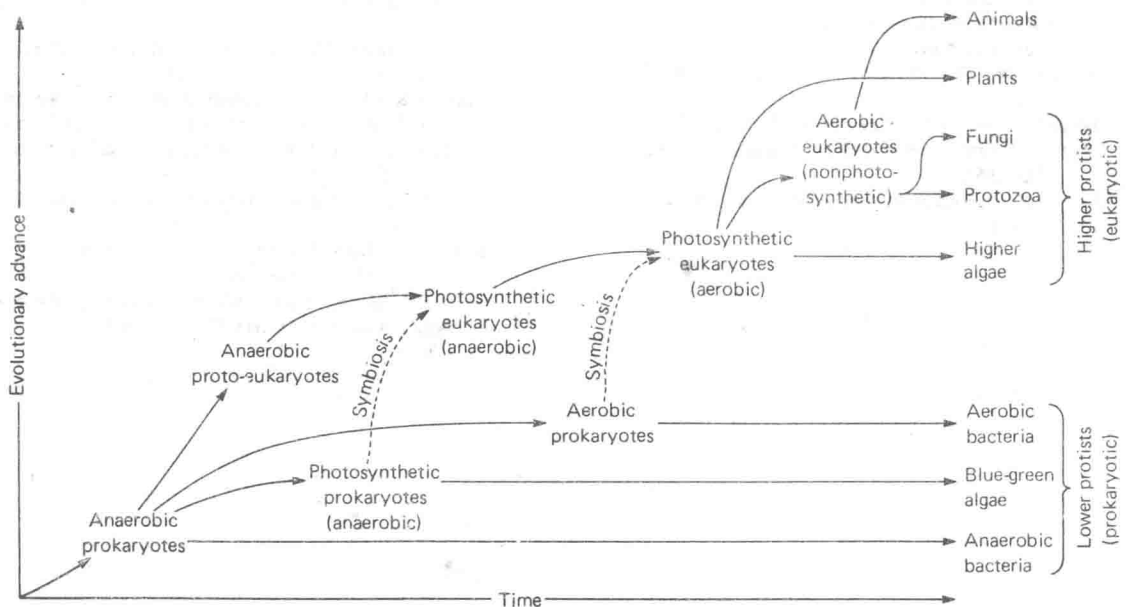


Figure 1-1. Evolutionary relationships of the major groups of microorganisms.

also possess gliding motility; some of these resemble certain blue-green algae 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 lower protists. The reader is referred instead to the descriptions of the various bacterial groups in Chapter 3.

### Summary

The concepts presented above are summarized 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 of endosymbiosis between a blue-green alga and an anaerobic proto-eukaryotic cell, the chloroplast evolving from the endosymbiont; and (2) establishment of a second endosymbiont, an aerobic prokaryote, leading to the evolution of the mitochondrion. 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.

Present-day bacteria and blue-green algae, according to this line of reasoning, represent forms which 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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## 2...

# Cell Structure

### OPTICAL METHODS

#### The Light Microscope

The resolving power of the light microscope under ideal conditions is about half the wavelength of the light being used. (Resolving power is the distance that must separate 2 point sources of light if they are to be seen as 2 distinct images.) With yellow light of a wavelength of  $0.4\ \mu\text{m}$ , the smallest separable diameters are thus about  $0.2\ \mu\text{m}$ . The useful magnification of a microscope is that magnification that makes visible the smallest resolvable particles. Microscopes used in bacteriology generally employ a 90-power objective lens with a 10-power ocular lens, thus magnifying the specimen 900 times. Particles  $0.2\ \mu\text{m}$  in diameter are therefore magnified to about  $0.2\ \text{mm}$  and so become clearly visible. Further magnification would give no greater resolution of detail and would reduce the visible area (field).

Further improvement in resolving power can be accomplished only by the use of light of shorter wavelengths. The ultraviolet microscope uses wavelengths of about  $0.2\ \mu\text{m}$ , thus allowing resolution of particles with diameters of  $0.1\ \mu\text{m}$ . Such microscopes, employing quartz lenses and photographic systems, are too expensive and complicated for general use.

#### The Electron Microscope

Using a beam of electrons focused by magnets, the electron microscope can resolve particles  $0.001\ \mu\text{m}$  apart. Viruses, with diameters of  $0.01$ – $0.2\ \mu\text{m}$ , can be easily resolved.

An important advance in electron microscopy is the technic of "shadowing." This involves depositing a thin layer of metal (such as platinum) on the object by placing it in the path of a beam of metal ions in a vacuum. The beam is directed obliquely, so that the object acquires a "shadow" in the form of an uncoated area on the other side. When an electron beam is then passed through the coated preparation in the electron microscope and a positive print made from the "negative" image, a 3-dimensional effect is achieved (eg, Figs 2-24, 2-25, and 2-26).

Other important advances in electron microscopy include the use of ultrathin sections of embedded material and the method of freeze-drying specimens,

which prevents the distortion caused by conventional drying procedures. Another advance has been negative staining with an electron-dense material such as phosphotungstic acid (eg, Fig 27-35).

#### Darkfield Illumination

If the condenser lens system is arranged so that no light reaches the eye unless reflected from an object on the microscope stage, structures that provide insufficient contrast with the surrounding medium can be made visible. This technic is particularly valuable for observing organisms such as the spirochetes, which are difficult to observe by transmitted light.

#### Phase Microscopy

The phase microscope takes advantage of the fact that light waves passing through transparent objects, such as cells, emerge in different phases depending on the properties of the materials through which they pass. A special optical system converts difference in phase into difference in intensity, so that some structures appear darker than others. An important feature is that internal structures are thus differentiated in living cells; with ordinary microscopes, killed and stained preparations must be used.

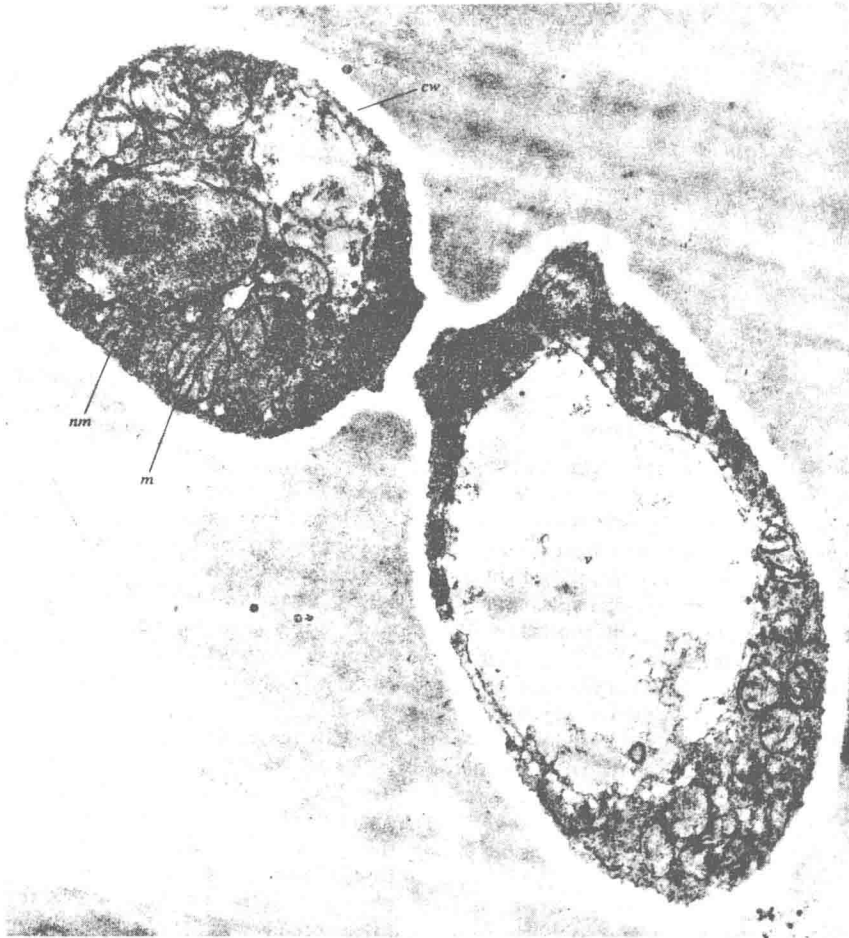
#### Autoradiography

If cells which have incorporated radioactive atoms are fixed on a slide, covered with a photographic emulsion, and stored in the dark for a suitable period of time, tracks appear in the developed film emanating from the sites of radioactive disintegration. If the cells are labeled with a weak emitter such as tritium, the tracks are sufficiently short to reveal the position in the cell of the radioactive label. This procedure, called autoradiography, has been particularly useful in following the replication of DNA, using tritium-labeled thymidine as a specific tracer (Fig 4-1).

### EUKARYOTIC CELL STRUCTURE

The principal features of the eukaryotic cell are shown in the electron micrograph in Fig 2-1. Note the following structures:





**Figure 2-1.** Thin section of a eukaryotic cell. A dividing cell of the unicellular yeast *Lipomyces* (17,500 X). *n* = nucleus; *nm* = nuclear membrane; *v* = vacuole; *m* = mitochondrion; *cw* = cell wall. Electron micrograph taken by Dr CF Robinow. (From Stanier RY, Doudoroff M, Adelberg EA: *The Microbial World*, 2nd ed. Copyright © 1963. By permission of Prentice-Hall, Inc, Englewood Cliffs, NJ.)

### Nucleus

The nucleus is bounded by a membrane (*nm*) which is continuous with the endoplasmic reticulum. The chromosomes, embedded in the nuclear matrix, are not distinguishable. The mitotic apparatus is not present at this stage in the division cycle.

### Cytoplasmic Structures

The cytoplasm of eukaryotic cells is characterized by the presence of an **endoplasmic reticulum**, **vacuoles**, and self-reproducing **plastids**. The plastids include the **mitochondria**, which contain the electron transport system of oxidative phosphorylation, and the **chloroplasts** (in photosynthetic organisms), which contain the chlorophylls and other photosynthetic components. The plastids contain their own DNA and multiply by binary fission.

### Surface Layers

The cytoplasm is enclosed within a lipoprotein

cell membrane. Most animal cells have no other surface layers; many eukaryotic microorganisms, however, have an outer **cell wall** which may be composed of a polysaccharide such as cellulose or chitin, or may be inorganic, as in the silica wall of diatoms.

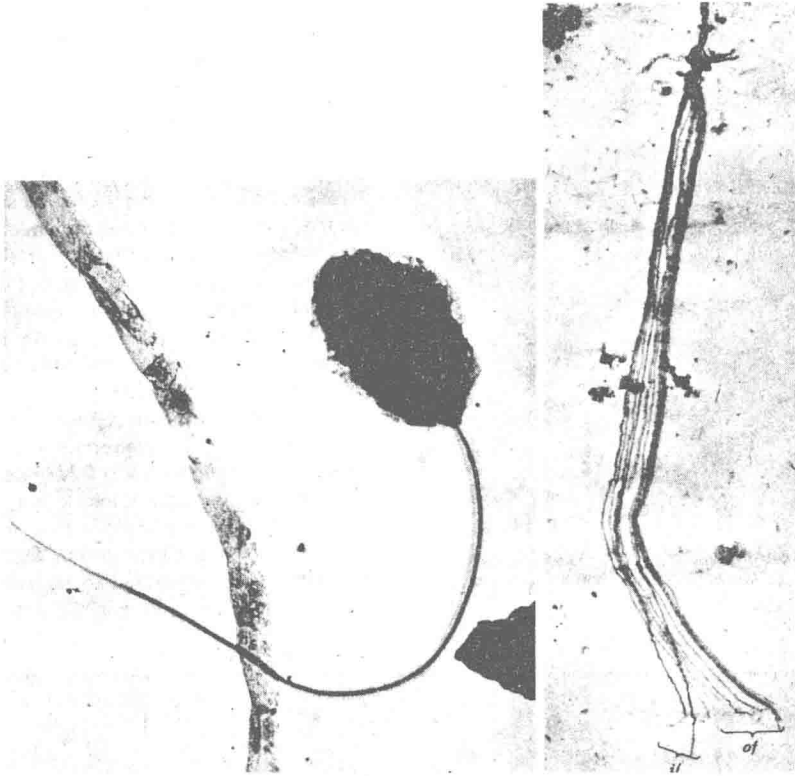
### Motility Organelles

Many eukaryotic cells propel themselves through water by means of protein appendages called **cilia** or **flagella** (cilia are short; flagella are long). In every case the organelle consists of a bundle of 9 fibrils surrounding 2 central fibrils (Figs 2-2 and 2-3). The fibrils are assembled from small units called microtubules.

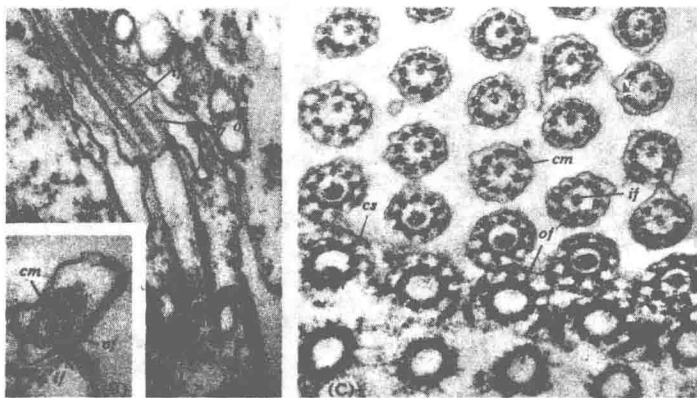
## PROKARYOTIC CELL STRUCTURE

The prokaryotic cell is simpler than the eukaryotic cell at every level, with one exception: the cell





**Figure 2-2.** Eukaryotic flagella (3000 X). *Left:* A zoospore of the fungus *Allomyces*, with a single flagellum. *Right:* A partially disintegrated flagellum of *Allomyces*, showing the 2 inner fibrils (*if*) and 9 outer fibrils (*of*). (Courtesy of Manton I & others: J Exp Bot 3:204, 1952.)



**Figure 2-3.** Fine structure of eukaryotic flagella and cilia (31,500 X). (A) Longitudinal section of a flagellum of *Bodo*, a protozoon, showing kinetoplast (*k*) from which extend the outer fibrils (*of*). Note the origin of the inner fibrils (*if*) at the cell surface. (B) Cross section of same flagellum near the surface of the cell, showing outer fibrils (*of*), inner fibrils (*if*), and extension of cell membrane (*cm*). (C) Cross section through surface layer of the ciliate protozoon *Glaucoma*, which cuts across a field of cilia just within the cell membrane (lower half) as well as outside the cell membrane (upper half). *cs* = cell surface. Electron micrographs taken by Dr D Pitelka. (From Stanier RY, Doudoroff M, Adelberg EA: *The Microbial World*, 2nd ed. Copyright © 1963. By permission of Prentice-Hall, Inc, Englewood Cliffs, NJ.)