ESSENTIALS OF

Medical Microbiology

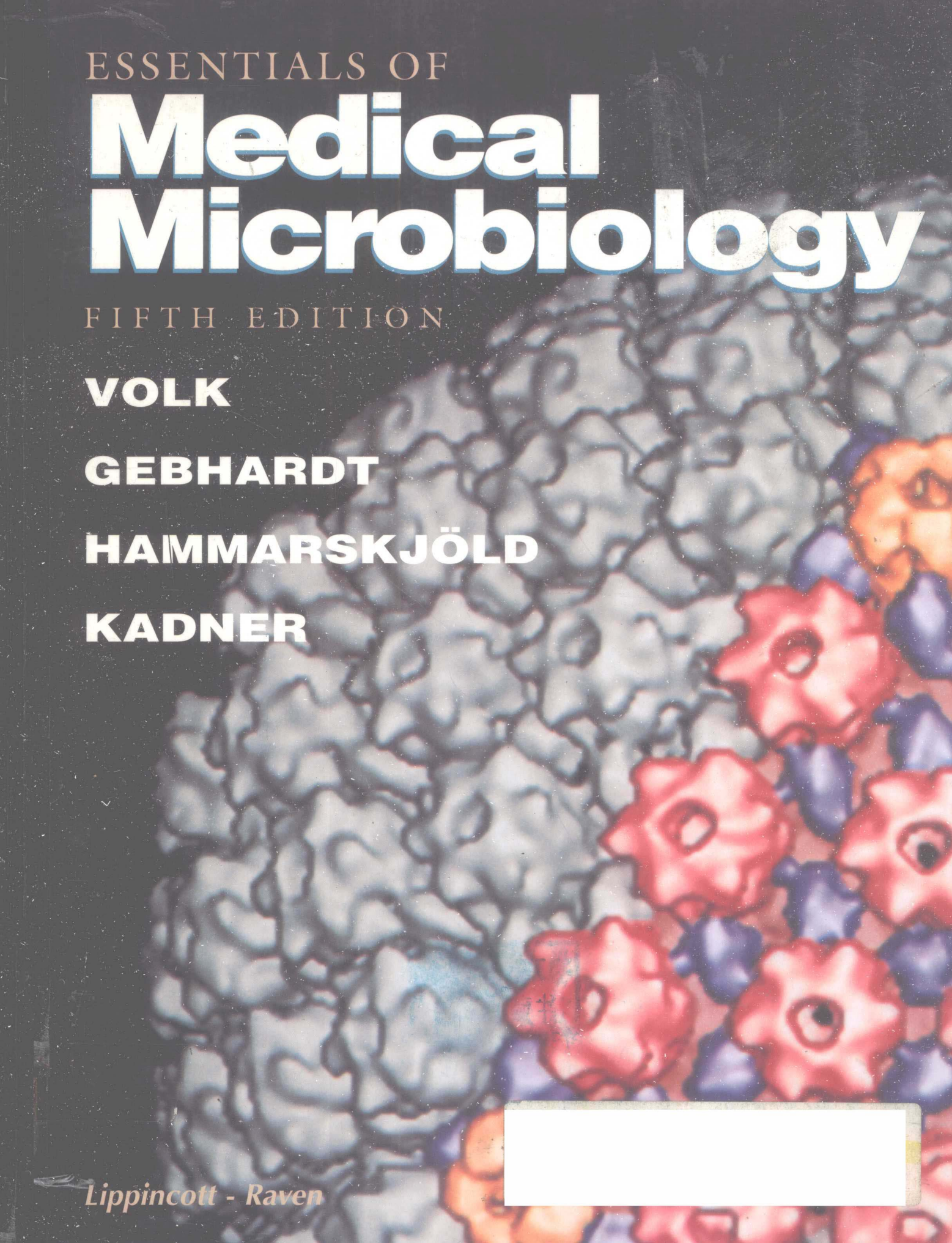
FIFTH EDITION

VOLK

GEBHARDT

HAMMARSKJÖLD

KADNER



Lippincott - Raven

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Lippincott - Raven
PUBLISHERS
Philadelphia • New York

Acquisitions Editor: Rich Winters
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Senior Design Coordinator: Kathy Kelley-Luedtke
Indexer: Maria Coughlin
Compositor: Bi-Comp, Incorporated
Printer/Binder: Courier Book Company/Kendallville

Fifth Edition

Library of Congress Cataloging-in-Publication Data

Essentials of medical microbiology / Wesley A. Volk ... [et al.]. — 5th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-397-51308-9 (alk. paper)
1. Medical microbiology. I. Volk, Wesley A.
[DNLM: 1. Microbiology. QW 4 E78 1995]
QR46.V64 1995
616′.01—dc20
DNLM/DLC
for Library of Congress 95-16385
CIP

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PREFACE

The overall objectives of this edition remain unchanged from those of the first, namely, to provide a single text that encompasses the fundamentals of basic and medical microbiology as well as a comprehensive coverage of immunology, all of which can be read in a one-semester course.

We would like to stress that this text is neither an outline nor a review, nor is it a collection of isolated examples, leaving important areas of the field untouched. Rather, it is, within the confines of space, a small reference book that should be valuable long after the formal course is completed.

This text does not require a previous knowledge of microbiology, and should be readily understood by any reader who has completed an introduction to biochemistry. It is modeled after the course in microbiology taught to medical students at the University of Virginia, but would also serve as a text for any course whose objectives are to provide a solid understanding of medical microbiology and immunology.

The overall organization of the fifth edition is similar to the previous edition. Users of the previous edition will note, however, that two of the four authors are new to this edition. Bryan M. Gebhardt has revised the unit on immunology and Marie-Louise Hammarskjöld has updated the unit covering virology. All units have undergone extensive revisions including many new or revised illustrations.

The organization of this edition is designed to provide a brief introduction to basic molecular biology before the beginning of the more specialized sections of the text. However, those students who are familiar with microscopy and cell structure, as well as gene structure and function, may choose to omit the first two chapters and begin with the immunology unit in Chapter 3.

Previous users of this text will also note that there has been an extensive rearrangement of Unit 3 and considerable revision of Unit 1. This includes a rearrangement of the order and emphasis of presentation to reflect current advances in basic microbiology. A few of the more notable upgrades include an expanded coverage of the mechanism of antibiotic action and of the prevalence, sources, and transmission of antibiotic resistance. Other revisions include recent advances in the understanding of the molecular mechanisms of bacterial virulence factors, the control of their expression, and some examples of their genetic variability. There is also an expanded discussion of the interplay between bacteria and the immune system.

All of the chapters in Units 4 and 5 have been extensively updated to reflect epidemiology, virulence factors, and mechanisms of immunity for both bacterial and viral diseases. A new section on hantavirus is included as well as an expanded discussion on hepatitis viruses and human retroviruses.

Many thanks are due to David Benjamin for his comments on parts of the revised immunology unit and for his work on earlier editions which provided the basic outline for this unit. We are indebted to J. Thomas Parsons for the earlier virology unit which provided much of the outline used in the present text. We are indebted also to Richard Guerrant and Erik Hewlett for their comments on various chapters in unit 4. And, last, but not least, we wish to extend our warmest appreciation to all of our colleagues who provided help and useful information during the revision of this text.

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FIFTH EDITION

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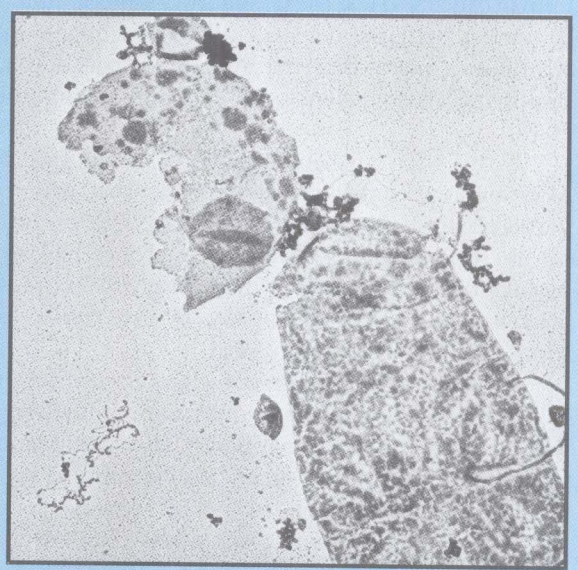
UNIT ONE

Introduction to Medical Microbiology



MANY human and animal diseases are caused by microorganisms, and we are learning some molecular details of the mechanisms by which bacteria, viruses, fungi, and protozoa cause diseases and how these diseases can be prevented or treated. Furthermore, we can see the biochemical unity in the living world that allows us to extrapolate our knowledge of bacterial genetics toward a better understanding of the regulation and control of human physiology.

The growth of knowledge in biology during the past half-century is analogous to the advances in physics that have taken us from horsepower to rocket power. This knowledge allows us to question the role of viruses in human cancer, to test the feasibility of genetic engineering to correct heritable defects, and to anticipate an understanding of many hitherto mysterious maladies such as multiple sclerosis, juvenile diabetes, and autoimmune diseases.

Is this what microbiology is all about? In part, yes. Microbiology is that part of biology that primarily involves organisms too small for the naked eye to see. Medical microbiology is the subdivision concerned with the biology of microorganisms that can grow on or in a host organism and produce disease. It also studies the responses of the host to infection.

In this book, we present clues or answers to the following basic questions of medical microbiology: How does the immune system operate to recognize and respond to the presence of an almost infinite variety of infectious agents or foreign objects? How do the various branches of the immune system inactivate or eliminate the different types of infectious agents? How does the overzealous action of the immune system, in its response to the presence of an infectious agent or after its inappropriate targeting of the host's own structures, lead to many of the symptoms of disease? How do successful pathogens evade or subvert the immune system? How do antimicrobial and antiviral agents act, and how is the resistance to these therapeutic agents established and spread? And finally, how are the infectious agents identified, how are they spread, and how do they cause their particular type of disease?

Before we can begin to address these questions, we must first learn what bacteria are, how they grow, and how they can be controlled. Unit One is comprised of two chapters, which briefly compare the structures of eucaryotic and procaryotic cells and introduce the reader to the structure of genes and the expression of genetic information. Knowledge of these subjects is a prerequisite to an understanding of the molecular biology of the immune response, which is discussed in Unit Two, and of the properties of the bacteria, fungi, viruses, and parasites that cause human disease.

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Essentials of Medical Microbiology, Fifth Edition, edited by Wesley A. Volk, Bryan M. Gebhardt, Marie-Louise Hammarskjöld, and Robert J. Kadner. Lippincott-Raven Publishers, Philadelphia © 1996.

Chapter 1

Microbial Cells and Their Function: A Review of Cell Biology

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Medical microbiology involves the study of the activities and interactions of many different types of cells. The bacterial, fungal, and protozoan parasitic cells have structures and products that allow them to cause disease. Viruses infect specific host cells to kill them or alter their growth behavior. The various cells that constitute the immune system respond to the presence of infectious agents to neutralize and eliminate them. In addition, human disorders can result from either excessive or deficient action of any of the cell types of the immune system. Because medical microbiology is concerned with this multiplicity of different cell types and their interactions, a general description of cellular structure and function is presented in this chapter to review the properties of the various types of microorganisms and to emphasize the differences between eucaryotic and procaryotic or bacterial cells.

The Microbial World

In the last century, biologists realized that the simple organisms that constitute the microbial world did not fit into the plant or animal kingdoms. For example, some algae have a plant's characteristic photosynthetic capabilities combined with an animal's motility. Conversely, fungi are immotile but lack other plant-like traits. Thus, in 1886 Haeckel proposed a third kingdom, the Protista, to include the algae, protozoa, fungi, and bacteria. Subsequent advances in microscopy revealed that bacteria possess a very different cellular architecture from that found in the other members of the Protista. The latter have a complex cell structure that is similar to that of plant and animal cells. The algae, fungi, and protozoa, as well as plant and animal cells, are termed *eucaryotic cells.* The bacteria have a much simpler internal organization and are termed *procaryotic cells* to reflect their lack of a true nucleus.

EUCARYOTIC PROTISTS

The eucaryotic protists are comprised of algae, protozoa, fungi (yeasts and molds), and slime molds. Distinctions between these groups are often blurred by the existence of transitional forms. Here we are concerned only with those groups whose members cause disease.

Fungi

The fungi are immotile, nonphotosynthetic protists that usually grow as a mat of branched filaments (hyphae) known as a *mycelium*. The hyphal filaments sometimes are not divided into individual cells by septa, allowing exchange of nuclei and cytoplasm along a considerable length of the growing tip of the hyphae. Mycelial forms, commonly called *molds,* frequently produce both sexual and asexual spores, and the structure, arrangement, and location of the spores are a major taxonomic key to their identification. Most fungi are saprophytic, that is, they degrade organic materials in soil or on vegetation, and they form the mildew that grows on clothes, food, and leather goods in humid conditions. Among the pathogenic fungi, some infect only keratinized layers of skin, whereas others cause serious systemic infections. These are described in Chapter 34.

Some fungi, known as *yeasts,* do not form a mycelium but remain as single cells that generally reproduce by budding. Many yeasts have evolved to grow in high-sugar environments, and those that convert sugar to ethanol and carbon dioxide are widely used for the production of alcoholic beverages (beer, wine, and spirits) or in the baking process because of their ability to produce copious amounts of carbon dioxide in bread dough. Unlike the saprophytic yeasts, many of the systemic fungal pathogens grow as single yeast cells at 37°C but develop a mycelium at 25°C, a condition known as dimorphic growth.

Protozoa

Protozoa are unicellular eucaryotes that have various mechanisms for movement, including ameboid crawling on surfaces and swimming with flagella or cilia. They exhibit a wide variety of shapes and sizes: some are oval or spherical, others are elongated, and some can change shape as they move along a surface. Some species are as small as 5 or 10 μm in diameter, whereas others reach diameters of 1 to 2 mm and are visible to the unaided eye.

Most protozoa reproduce asexually or sexually and, although they do not form spores as do the fungi, many secrete a thick coating around themselves for protection against adverse environments. These organisms are described in Unit Six.

PROCARYOTES

Bacteria are called procaryotic cells because of their much simpler cellular organization than eucaryotic cells and their lack of nuclei and other membrane-bound organelles. Procaryotic cells are divided into two major taxonomic groups, the *eubacteria* and the *archaebacteria* or *archaea;* members of each group are as different from each other as they are from eucaryotic cells. All bacteria of medical importance are in the eubacterial kingdom. Many of the archaebacteria inhabit unusual environmental niches, including extreme thermophiles that thrive in thermal springs and mid-oceanic vents, and extreme halophiles that live in the highly concentrated brine in evaporating salt flats. Other archaebacteria are major inhabitants of rumen flora, marshes, or sewage treatment plants. One major branch of the archaebacteria carry out the unique metabolic reactions of methanogenesis, or the production of methane. One species of methanogenic archaebacteria, *Methanobrevibacter smithii,* is part of the normal human intestinal flora. Some characteristic features of archaebacteria are the presence of isoprenoid ether lipids in place of the fatty acid esters present in eubacteria and eucaryotes, and unique types of cell walls. They carry out several unusual types of metabolic reactions, such as methane synthesis, using enzyme cofactors that are related to, but distinctly different from, the familiar cofactors found in eubacteria or eucaryotes.

Even among the eubacterial procaryotes, there is considerable diversity of cell shape and metabolic capability. The *Cyanobacteria* (formerly called the *blue-green algae*) carry out plant-like photosynthesis with the formation of oxygen. Many other procaryotes are also capable of using light as an energy source, but these bacteria have a simpler photosynthetic system than the photosynthetic eucaryotes or Cyanobacteria and are unable to generate oxygen.

Bacteria inhabit almost every environmental niche on Earth, and some have adapted to survival under extremely harsh conditions, ranging from lakes in Antarctica to boiling hot springs. Most bacteria are unable to grow or even survive in animals or humans and, thus, are only of peripheral interest in medical microbiology. The major groups of bacteria of medical concern are described in Chapter 15 and Unit 4.

VIRUSES

Viruses are infectious particles that can reproduce only when inside a living cell. These obligate intracellular parasites differ from cells in their size, physical and genetic complexity, and pattern of replication. There are viruses specific for almost every organism, but the range of species they can infect usually is restricted. A virus particle consists of a single type of nucleic acid (either RNA or DNA, never both) enclosed in a protein coat, or *capsid,* and, in some cases, surrounded by a membrane. The capsid protects the nucleic acid from attack by enzymes or physical agents and also is responsible for entry of the viral nucleic acid into the cell. Once inside the cell, the viral nucleic acid subverts the host's replication machinery to

favor the synthesis of viral nucleic acids and proteins. These new viral subunits are then assembled into progeny virions and released from the cell.

The fate of the virus-infected cell varies for different viruses and ranges from rapid lysis to continued growth of the cell with prolonged release of new virus particles. Some viruses can integrate their nucleic acid into the cell's genome, and thereby remain quiescent within growing cells for long periods before being triggered to reinitiate viral replication and cause lysis of the host cell.

Microscopy

The study of microbes began in 1683 when Antony van Leeuwenhoek (1632 to 1723) described his observations of some of the myriad members of the microbial flora from various environmental sources. His hobby of lens grinding led to the construction of simple but effective microscopes, which allowed him to view the delightful world of "animalcules" of all sizes and shapes. Microscopy still provides a crucial tool for identifying microorganisms and studying their structures and interactions. In this section, some of the types of microscopic techniques used to visualize bacteria and eucaryotic cells are described.

LIGHT MICROSCOPE

van Leeuwenhoek made simple microscopes that contained a single lens capable of 200- to 300-fold magnification (Fig. 1-1). The compound microscopes now in use contain two sets of lenses, the objective lens next to the sample and the ocular lenses next to the observer's eyes. In this arrangement, the magnifications achieved by each set of lenses are multiplied to give the final magnification.

Modern microscopes contain multiple objective lenses mounted on a revolving turret. The low-power (10×) and high-power (44×) objectives are useful for the study of large eucaryotic cells, whereas the oil immersion (97×) objective generally is best for the study of bacteria. Use of the oil immersion lens requires that the sample be covered with a drop of oil, so that the light illuminating the sample passes through the glass slide, the sample, and the oil before entering the objective lens. This greatly reduces the diffraction or bending of light rays that occurs on crossing an interface between media of different refractive indices, such as that between glass and air.

The resolving power of any microscope, namely its ability to discriminate between two adjacent objects, is limited to roughly half the wavelength of the light used. The wavelength of visible light ranges from 400 to 800 nm, so the smallest object that can be observed in a light microscope must be at least 200 nm (0.2 μm). Because the diameters of most bacteria range from 0.3 to 1.0 μm, light microscopes cannot provide information on the internal structure of bacterial cells; therefore, they are used mainly to visualize the general shape of the cell and the reaction to specific staining procedures.

Ultraviolet Microscope

The shorter wavelengths of ultraviolet light (200 to 300 nm) can extend the limit of microscopic resolution to about 0.1 μm. However, ultraviolet light is invisible to the human eye (harmful, in fact), so the image must be

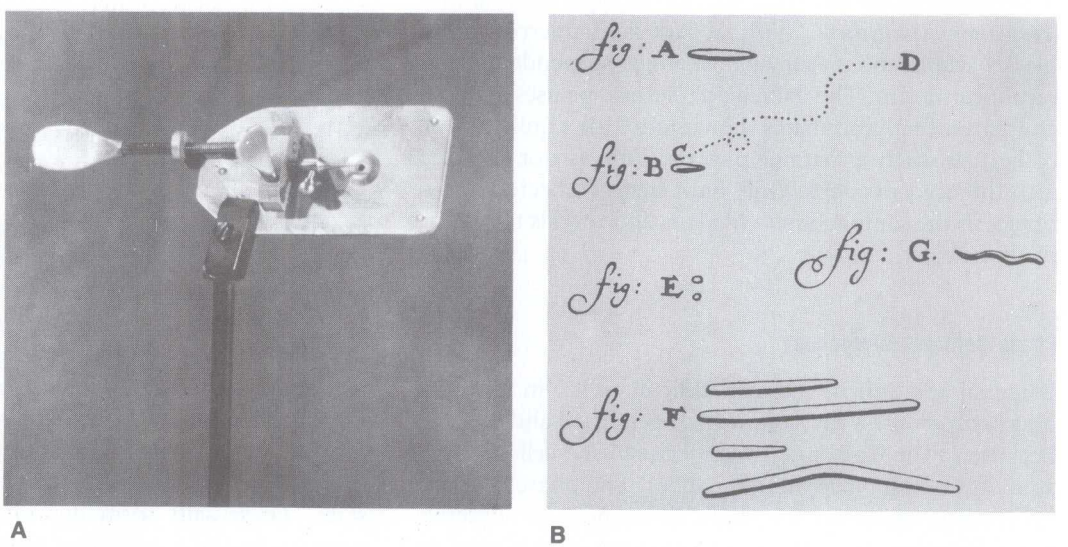


FIGURE 1-1 **A.** Leeuwenhoek used a microscope with a single biconvex lens to view bacteria suspended in a drop of liquid placed on a moveable pin. **B.** Although his microscope was capable of only 200- to 300-fold magnification, Leeuwenhoek was able to achieve these remarkable drawings of different bacterial types, which he submitted to the Royal Society of London.

recorded on a photographic plate or fluorescent screen. Because this light is absorbed by glass, all lenses must be made of quartz; such microscopes are too intricate and expensive for routine use.

Fluorescence Microscope

In fluorescence microscopy, a sample is labeled with a fluorescent dye and illuminated with ultraviolet light. The location of the dye in the specimen is revealed by its fluorescence, or emission of visible light of a longer wavelength. If the dye is selectively taken up by certain cells in a specimen, the presence of those cells can be readily detected. For example, the tubercle bacillus, *Mycobacterium tuberculosis,* will selectively take up the fluorescent dye auramine and appear bright against a dark background, even when small numbers are present in a large population of other types of cells.

Fluorescence microscopy is frequently used to detect microorganisms by coupling a fluorescent dye to a specific antibody that binds only to the target bacterium. The specificity of antigen–antibody reactions is thereby combined with a sensitive and dramatic assay to reveal the presence of a specific organism by its cell-bound fluorescence. This powerful technique can also be used to reveal the presence and cellular location of any antigen. Different antigens within a single preparation can be detected by using specific antibodies labeled with dyes that emit light of different colors.

Dark-Field Microscopy

The dark-field microscope is useful for detecting unstained bacteria in fluids and is particularly valuable for observing thin spirochetes, such as the syphilis organism, *Treponema pallidum.* With a dark-field microscope, a black background is seen against which suspended bacteria appear bright. The dark-field microscope uses a special condenser that illuminates the sample with a hollow cone of light in such a manner that the light is not directed into the objective lens. Only light that is reflected off an object in the sample enters the lens and reveals the shape of that object.

Phase-Contrast Microscopy

Bacterial and animal cells are difficult to see in the light microscope unless the sample has been dried and stained, because of the lack of contrast between the cells and the aqueous medium surrounding them. The phase-contrast microscope enhances the slight differences in refractive index between the cell and the medium, and is used to visualize live bacteria in an unfixed state.

The optics of this instrument are complex; they convert a difference in refractive index at any site in the specimen into a difference in the phase of the light passing through that point. Because of the constructive or destructive interference that occurs with light waves differing in phase, regions of the sample that differ in refractive index are revealed as differences in light intensity. For example, endospores have a low water content and, thus, differ markedly in refractive index from the medium. These structures are much brighter than the surrounding medium or the vegetative cells when viewed in this microscope.

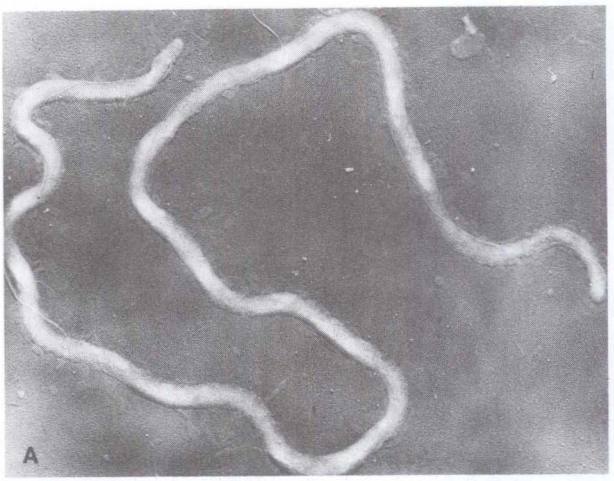
ELECTRON MICROSCOPE

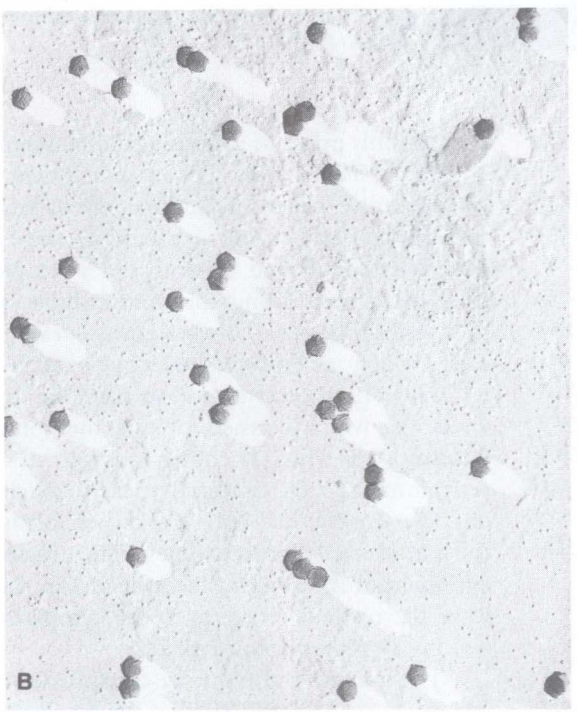
Almost all our understanding of microbial and subcellular ultrastructure comes from use of the electron microscope, a device that uses a beam of electrons rather than light to illuminate the sample. The shorter wavelength of electrons increases the resolving power to about 0.001 μm (1 nm). The image generated by the transmission of electrons through, or their reflection from, the sample is visualized by projection onto a photographic plate or a fluorescent screen. Two types of electron microscopes are used.

Transmission Electron Microscope

The transmission electron microscope yields an image from the electrons that pass through the sample; thus, extremely thin slices (1 μm or less) of the specimen must be used because electrons are readily absorbed by biologic materials. Detection of fine details of cellular structure requires careful techniques for sample fixing, embedding, and sectioning. Freeze drying of samples reduces the distortions caused by conventional dehydration and drying procedures. Examination of serial thin sections permits a detailed reconstruction of organelles or even whole cells in three dimensions. The location of specific proteins within the sectioned samples can be determined by immunoelectron microscopy, in which antibodies that bind to the specific protein are labeled with an electron-dense marker, such as ferritin or colloidal gold. The electron-dense marker is readily detected in the electron micrograph. Alternatively, immunohistochemical methods allow detection of specific enzymes that yield electron-dense reaction products at the site of the enzyme.

Negative staining is a useful technique to complement the examination of sectioned samples. This procedure involves suspension of the sample in solutions of electron-dense heavy metal salts such as phosphotungstate. These salts form deposits on the surface of the particles in the sample and provide a detailed image of surface structures. Shadow casting is another technique used to reveal the surface architecture of an object, especially of viruses. In this case, an electron-dense material





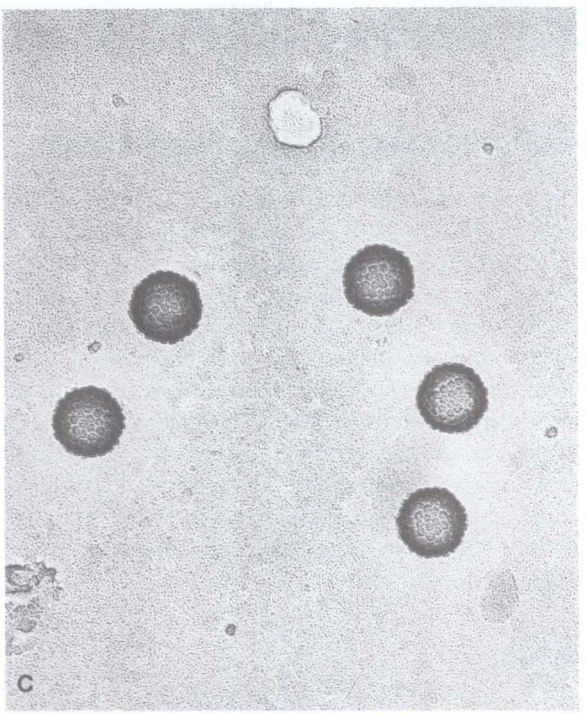


FIGURE 1-2 **A.** Electron micrograph of the spirochete *Spirochaeta stenostrepta* shadowed with platinum. (Original magnification ×12,000.) **B.** Electron micrograph of adenovirus with oblique shadowing. **C.** Electron micrograph of herpesvirus with rotary shadowing.

such as platinum or chromium is deposited at an angle on the sample by placing it in an oblique beam of the metal ions. In this way, an object casts a shadow on the side opposite the direction of the ion beam, resulting in a three-dimensional effect (Fig. 1-2).

Freeze etching is a technique in which the unfixed sample is frozen at very low temperature and then fractured by a sharp blow from a knife. The newly exposed surfaces are replicated by deposition of carbon metal. The fracture planes often extend along cell surfaces, yielding detailed views of surface structures and especially the intramembranous distribution of proteins. Ion bombardment is a technique in which the outer layers of viruses or cells are eroded in an ion beam, to reveal the otherwise inaccessible internal structures.

Scanning Electron Microscope

The scanning electron microscope uses a fine beam or spot of electrons that is focused rapidly back and forth over the specimen. As the electrons strike the surface of particles in the sample, secondary electrons are emitted, which are collected by a detector to provide an image of the specimen's surface. This instrument does not require that the sample be sectioned and provides some spectacular three-dimensional images, as shown in Figure 1-3. In addition, because the energy of the secondary emitted electron is determined by the identity of the scattering atom, the energy spectrum of these electrons provides information about the location and content of the different elements.

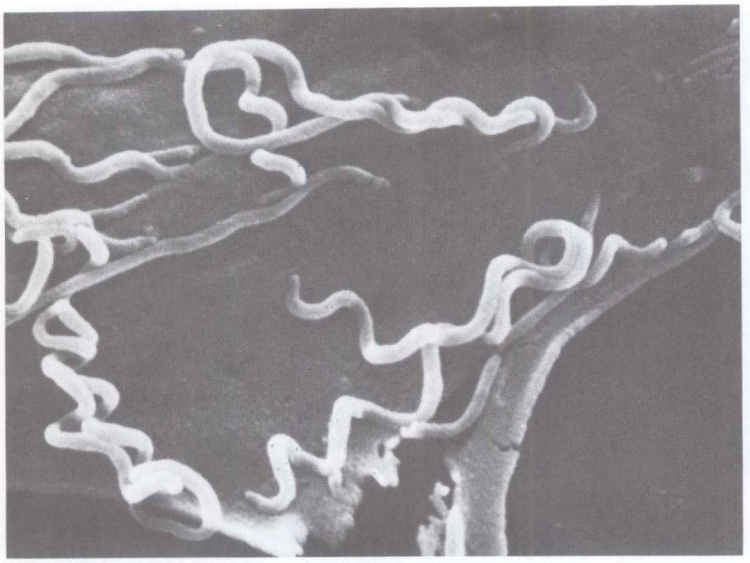


FIGURE 1-3 The three-dimensional qualities of scanning electron microscopy clearly reveal the corkscrew shape of cells of the syphilis-causing spirochete *Treponema pallidum*, attached here to rabbit testicular cells grown in culture. (Original magnification ×8000.)

Eucaryotic Cells: Structure and Function

The following sections briefly summarize the general features of the structure and composition of eucaryotic and procaryotic cells, with emphasis on the differences between these two fundamentally distinct cell types. Eucaryotic cells are larger and more complex than procaryotic cells, and possess intracellular membrane-enclosed organelles, which are invariably absent from procaryotic cells. The following sections describe briefly some of the characteristic structures found in higher eucaryotic cells and their contribution to the life of the cell. The "Closer Look" at the end of the chapter follows the steps involved in the production of an antibody molecule by an antibody-producing cell.

NUCLEUS

The possession of a membrane-enclosed nucleus is the hallmark of any eucaryotic cell. The nucleus contains almost all the cell's deoxyribonucleic acid (DNA), which is carried on chromosomes and represents the cell's genetic information. Diploid organisms contain two versions of each chromosome. In each chromosome, the linear double-stranded DNA is organized into higher order structures and is bound to numerous proteins, the most prevalent of which are the basic and universally conserved histones. The nucleus is the site of DNA replication, in which each chromosome is copied during the synthesis (S) phase of each cell cycle. The mechanism of DNA replication is described in Chapter 2. Chromosomes generally are not visible in the light microscope until they condense into compact units (metaphase chromosomes) long after completion of the S phase and just before cell division, during the mitosis (M) phase of the cell cycle. At that time, the mitotic spindle apparatus forms to pull the two copies of each chromosome into the two progeny cells. In this process, a cytoskeletal filament, called a microtubule, forms between an attachment site on each chromosome (called the centromere or kinetosome) and the spindle body at one or the other end of the nucleus. The newly replicated chromosomes are pulled apart by their movement along the microtubular strand toward the opposite poles. This system accurately ensures that each progeny cell receives one copy of each chromosome.

The chromosomes are surrounded by the nuclear envelope, which consists of two membrane layers, the outermost of which is contiguous with the endoplasmic reticulum (ER). In some cell types, the nuclear membrane dissolves during the M phase and then forms again around the partitioned chromosomes. The nuclear membrane contains pores through which the mature RNA molecules leave the nucleus en route to the cytoplasm, where they will be translated into protein.

The nucleus is also the site of expression of the genetic information. As described in Chapter 2, the sequence of bases in a particular region of the DNA is copied into an RNA molecule of the same sequence. In eucaryotic cells, the initial RNA copy, or transcript, is modified by the addition of extra nucleotides at both ends and, usually, by the removal of some stretches of sequences within the transcript. These modifications of the RNA transcript are important for its stability and efficient translation and export from the nucleus.

ENDOPLASMIC RETICULUM

The ER is a membranous network that extends throughout the cell. There are two types of ER, termed *rough ER* and *smooth ER*, which have multiple functions, mostly related to the synthesis and processing of proteins. The rough ER is studded with ribosomes that synthesize the proteins destined to become part of other organelles or to be exported from the cell. These proteins are made

with a short sequence of amino acids at their end that is removed during the process of export but targets the remainder of the protein for its translation on ribosomes bound to the ER. These ribosomes secrete the new polypeptides across the membrane and into the enclosed lumen of the ER. From there, these new proteins travel in membrane vesicles to the Golgi complex and other sites.

The Golgi complex consists of stacks of smooth ER membranes, and it carries out the further processing (primarily glycosylation) and sorting of proteins that are to be stored, transferred to other organelles, or secreted. Vesicles containing newly synthesized proteins can be observed moving from the rough ER to the Golgi complex and from there to the surface plasma membrane. Because of the complexity of these processes, the secretion of a protein by eucaryotic cells often takes more than an hour to complete.

The smooth ER is also involved in a variety of metabolic functions, including the biosynthesis of hormones and the conversion of some drugs to less toxic or more easily excreted forms.

MITOCHONDRIA

Mitochondria are distinctively shaped organelles that are the primary site of energy generation in the cell. Their membranes contain the respiratory electron transport system and the enzyme responsible for producing adenosine triphosphate (ATP), the primary form of metabolic energy in the cell. Mitochondria accomplish this by a three-step process: (1) Metabolites derived from various nutrients are converted ultimately to acetyl-CoA, which is oxidized to CO_2 by the enzymes of the tricarboxylic acid cycle. (2) The electrons released during this process of oxidation are passed along the proteins of the electron transport chain to oxygen. At several steps of the chain, electron passage results in the expulsion of protons from the interior of the mitochondrion, resulting in the generation of an electrical potential across the membrane. (3) The return of protons back into the mitochondrion through an enzyme complex called the *F_1F_0-proton-translocating adenosine triphosphatase* is coupled to the synthesis of ATP. All these events occur in the innermost of the mitochondrion's two membranes. Mitochondria, like chloroplasts in plant cells, originally were derived from a bacterium and are plastids, capable of self-replication and containing DNA and other machinery that permits the synthesis of a few of their constituent proteins and RNA molecules.

OTHER EUCARYOTIC STRUCTURES

Lysosomes are membrane-bound structures containing numerous hydrolytic enzymes and antimicrobial peptides that digest macromolecules and participate in the killing of ingested microorganisms. Lysosomes fuse with coated membrane vesicles (called *phagosomes*) that have budded in from the surface membrane and enclose portions of the exterior fluid and proteins or particles, including bacteria, that were bound on the cell surface.

Cell shape and numerous functions of the plasma membrane are dependent on the *cytoskeleton*, which is a filamentous scaffold-like structure extending throughout the cytoplasm. There are two basic types of cytoskeletal elements, termed *microtubules* and *microfilaments*. Microtubules are formed by the polymerization of a protein called *tubulin* and are the basic structure of the cytoskeleton. They contribute to chromosome separation during cell division. Microfilaments contain actin and myosin and are necessary for creeping (ameboid) motility. Many eucaryotic cells exhibit ameboid or creeping motion when moving along a surface, but some cell types are motile in liquid with cilia or flagella. These organelles are assembled from microtubules and consist of nine fibrils surrounding two fibers.

The cytoplasm is enclosed by the *plasma membrane*, which contains nutrient transport systems and receptors that are used in intracellular communications. Some nutrients are transported directly across the membrane. Other nutrients are taken up after they bind to receptors on the membrane surface while a segment of the membrane is pinched off and taken into the cell as a membrane vesicle that fuses with lysosomes. This membrane appears to be in constant motion and to be actively recycled from the surface into internal organelles and back. Figure 1-4 shows electron micrographs of two diverse eucaryotic cells, demonstrating many of the organelles found in these cells.

Procaryotic Cell Structure

Procaryotic cells are invariably smaller and simpler than eucaryotic cells. Most bacteria are similar in size to a mitochondrion. Because of their small size and cellular simplicity, many bacteria can divide in less than 30 minutes, in contrast to the 8 to 24 hours needed by many of the higher eucaryotic cells.

Procaryotic cells, examples of which appear in Figure 1-5, possess no separate internal membrane-bound organelles. Any internal membranous structures that do occur are extensions of the cytoplasmic membrane, which is the site of most of the functions carried out by the eucaryotic organelles. There is no nuclear membrane or mitotic apparatus. Instead, a nuclear region is seen, composed of DNA fibrils in direct contact with the cytoplasm. Some bacteria, such as *Escherichia coli*, possess only a single chromosome that, if extended, would be almost a thousand times the length of the cell. Other bacteria contain two chromosomes that have different genetic content. The chromosomes are circular in some bacteria and linear in others. The nucleoid does not condense into a more compact structure during cell division and there is no formation of an obvious mitotic apparatus to pull

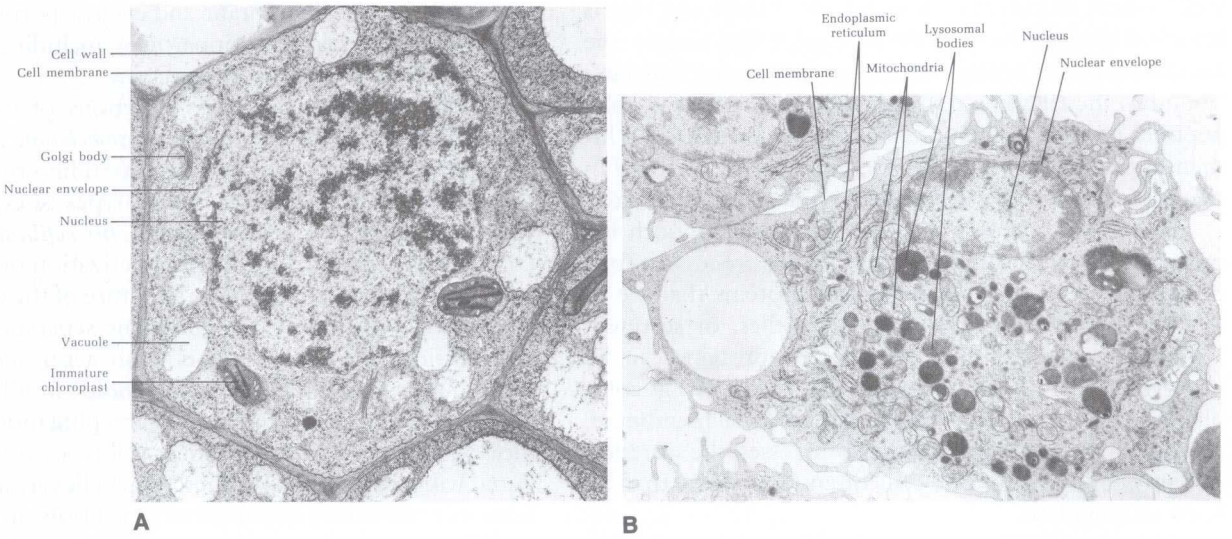


FIGURE 1-4 **A.** Section of a cell from the stem of a young pea plant, *Pisum sativum.* (Original magnification ×9945.) **B.** Section of an animal cell—in this case, a macrophage from a mouse. (Original magnification ×6240.)

the chromosomes apart into the dividing cells, as occurs in eucaryotic cells. Instead, partitioning the chromosomes into the daughter cells appears to be accomplished by attachment of a portion of the DNA to the cytoplasmic membrane or to a cytoskeletal element. Growth of the membrane or movement of the cytoskeleton between the chromosomal attachment sites brings about the segregation of the replicating chromosomes. In bacteria, the cell cycle is not divided into separate S and M phases, and bacterial cell division can occur even while the chromosome is still in the process of replication.

As in mitochondria, energy generation by oxidative phosphorylation in bacteria occurs by formation of a gradient of protons across the cytoplasmic membrane and its utilization for ATP synthesis by the F_1F_0-adenosine triphosphatase. The chlorophyll and other pigments in photosynthetic bacteria are organized into lamellar or tubular extensions of the cytoplasmic membrane, instead of the independent membrane-enclosed chloroplasts.

Bacterial flagella, described in Chapter 17, are much simpler in structure and composition than their eucaryotic counterparts and bring about motility in a fundamentally different manner than do eucaryotic flagella.

Bacteria produce storage granules, but these are never

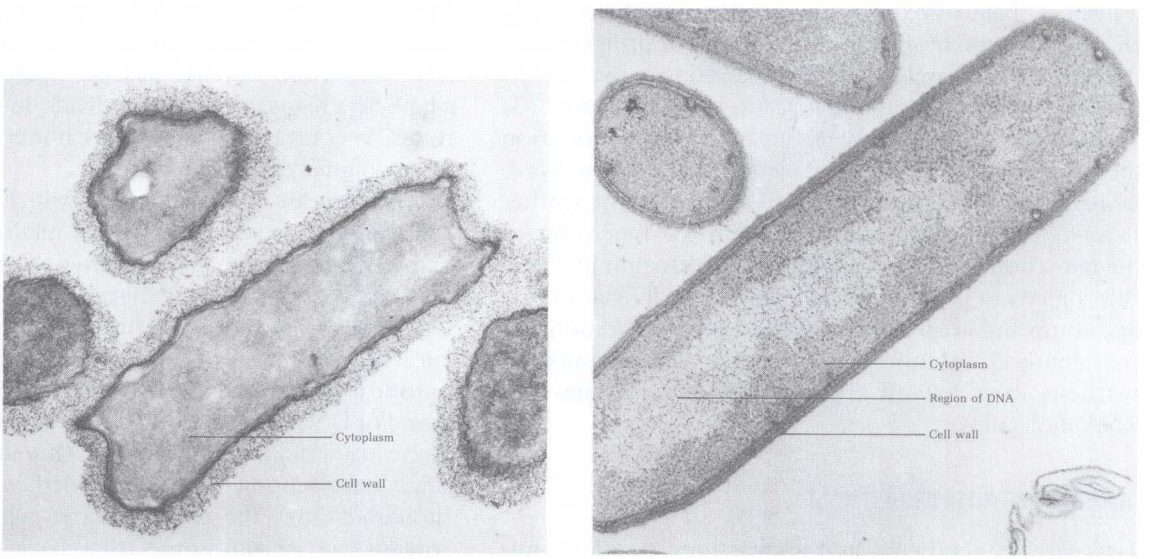


FIGURE 1-5 **A.** Section of bacterium-*Klebsiella aerogenes.* (Original magnification × 20,730.) **B.** Bacterium *Bacillus mucroides* (Original magnification ×26,000.)