CHAPTER **ONE** 1

Cells: The Fundamental Units of Life

What does it mean to be living? Petunias, people, and pond scum are all alive; stones, sand, and summer breezes are not. But what are the fundamental properties that characterize living things and distinguish them from nonliving matter?

The answer begins with a basic fact that is taken for granted now, but marked a revolution in thinking when first established 175 years ago. All living things (or *organisms*) are built from **cells**: small, membrane-enclosed units filled with a concentrated aqueous solution of chemicals and endowed with the extraordinary ability to create copies of themselves by growing and then dividing in two. The simplest forms of life are solitary cells. Higher organisms, including ourselves, are communities of cells derived by growth and division from a single founder cell. Every animal or plant is a vast colony of individual cells, each of which performs a specialized function that is regulated by intricate systems of cell-to-cell communication.

Cells, therefore, are the fundamental units of life. Thus it is to *cell biology*—the study of cells and their structure, function, and behavior—that we must look for an answer to the question of what life is and how it works. With a deeper understanding of cells, we can begin to tackle the grand historical problems of life on Earth: its mysterious origins, its stunning diversity produced by billions of years of evolution, and its invasion of every conceivable habitat. At the same time, cell biology can provide us with answers to the questions we have about ourselves: Where did we come from? How do we develop from a single fertilized egg cell? How is each of us similar to—yet different from—everyone else on Earth? Why do we get sick, grow old, and die?

In this chapter, we begin by looking at the great variety of forms that cells can show, and we take a preliminary glimpse at the chemical machinery that all cells have in common. We then consider how cells are made visible under the microscope and what we see when we peer inside them. Finally, we discuss how we can exploit the similarities of living things to achieve a coherent understanding of all forms of life on Earth—from the tiniest bacterium to the mightiest oak.

UNITY AND DIVERSITY OF CELLS

Cell biologists often speak of "the cell" without specifying any particular cell. But cells are not all alike; in fact, they can be wildly different. Biologists estimate that there may be up to 100 million distinct species of living things on our planet. Before delving deeper into cell biology, we must take stock: What does a bacterium have in common with a butterfly? What do the cells of a rose have in common with those of a dolphin? And in what ways do the plethora of cell types within an individual multicellular organism differ?

Cells Vary Enormously in Appearance and Function

Let us begin with size. A bacterial cell—say a *Lactobacillus* in a piece of cheese—is a few **micrometers**, or μm, in length. That's about 25 times smaller than the width of a human hair. A frog egg—which is also a single cell—has a diameter of about 1 millimeter. If we scaled them up to make the *Lactobacillus* the size of a person, the frog egg would be half a mile high.

Cells vary just as widely in their shape (**Figure 1–1**). A typical nerve cell in your brain, for example, is enormously extended; it sends out its electrical signals along a fine protrusion that is 10,000 times longer than it is thick, and it receives signals from other nerve cells through a mass of shorter processes that sprout from its body like the branches of a tree (see Figure 1–1A). A *Paramecium* in a drop of pond water is shaped like a submarine and is covered with thousands of *cilia*—hairlike extensions whose sinuous beating sweeps the cell forward, rotating as it goes (Figure 1–1B). A cell in the surface layer of a plant is squat and immobile, surrounded

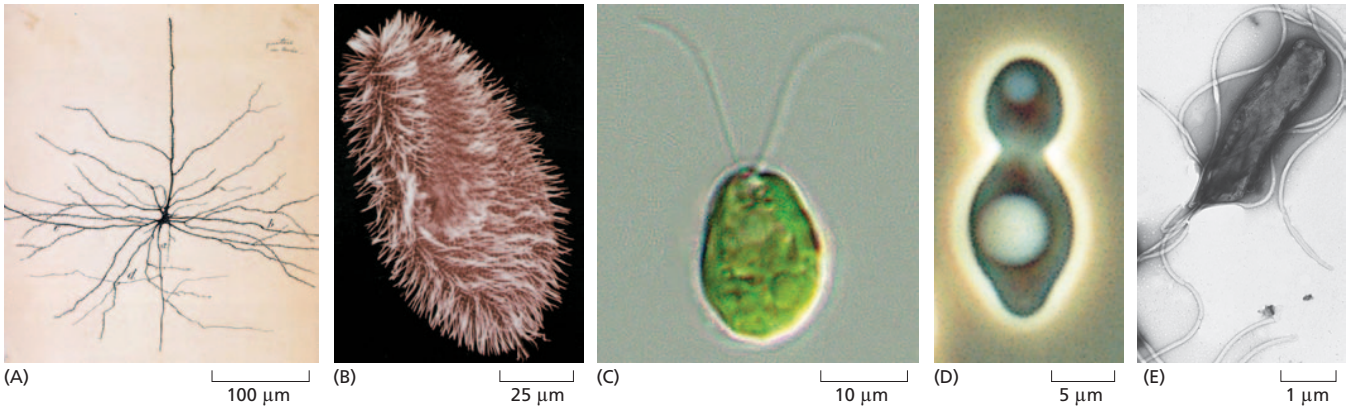


Figure 1–1 Cells come in a variety of shapes and sizes. Note the very different scales of these micrographs. (A) Drawing of a single nerve cell from a mammalian brain. This cell has a huge branching tree of processes, through which it receives signals from as many as 100,000 other nerve cells. (B) *Paramecium*. This protozoan—a single giant cell—swims by means of the beating cilia that cover its surface. (C) *Chlamydomonas*. This type of single-celled green algae is found all over the world—in soil, fresh water, oceans, and even in the snow at the top of mountains. The cell makes its food like plants do—via photosynthesis—and it pulls itself through the water using its paired flagella to do the breaststroke. (D) *Saccharomyces cerevisiae*. This yeast cell, used in baking bread, reproduces itself by a process called budding. (E) *Helicobacter pylori*. This bacterium—a causative agent of stomach ulcers—uses a handful of whiplike flagella to propel itself through the stomach lining. (A, copyright Herederos de Santiago Ramón y Cajal, 1899; B, courtesy of Anne Fleury, Michel Laurent, and André Adoutte; C, courtesy of Brian Piasecki; E, courtesy of Yutaka Tsutsumi.)

by a rigid box of cellulose with an outer waterproof coating of wax. A neutrophil or a macrophage in the body of an animal, by contrast, crawls through tissues, constantly pouring itself into new shapes, as it searches for and engulfs debris, foreign microorganisms, and dead or dying cells. And so on.

Cells are also enormously diverse in their chemical requirements. Some require oxygen to live; for others this gas is deadly. Some cells consume little more than air, sunlight, and water as their raw materials; others need a complex mixture of molecules produced by other cells.

These differences in size, shape, and chemical requirements often reflect differences in cell function. Some cells are specialized factories for the production of particular substances, such as hormones, starch, fat, latex, or pigments. Others are engines, like muscle cells that burn fuel to do mechanical work. Still others are electricity generators, like the modified muscle cells in the electric eel.

Some modifications specialize a cell so much that they spoil its chances of leaving any descendants. Such specialization would be senseless for a cell that lived a solitary life. In a multicellular organism, however, there is a division of labor among cells, allowing some cells to become specialized to an extreme degree for particular tasks and leaving them dependent on their fellow cells for many basic requirements. Even the most basic need of all, that of passing on the genetic instructions of the organism to the next generation, is delegated to specialists—the egg and the sperm.

QUESTION 1–1

"Life" is easy to recognize but difficult to define. According to one popular biology text, living things:
1. Are highly organized compared to natural inanimate objects.
2. Display homeostasis, maintaining a relatively constant internal environment.
3. Reproduce themselves.
4. Grow and develop from simple beginnings.
5. Take energy and matter from the environment and transform it.
6. Respond to stimuli.
7. Show adaptation to their environment.

Score a person, a vacuum cleaner, and a potato with respect to these characteristics.

Living Cells All Have a Similar Basic Chemistry

Despite the extraordinary diversity of plants and animals, people have recognized from time immemorial that these organisms have something in common, something that entitles them all to be called living things. But while it seemed easy enough to recognize life, it was remarkably difficult to say in what sense all living things were alike. Textbooks had to settle for defining life in abstract general terms related to growth, reproduction, and an ability to respond to the environment.

The discoveries of biochemists and molecular biologists have provided an elegant solution to this awkward situation. Although the cells of all living things are infinitely varied when viewed from the outside, they are fundamentally similar inside. We now know that cells resemble one another to an astonishing degree in the details of their chemistry. They are composed of the same sorts of molecules, which participate in the same types of chemical reactions (discussed in Chapter 2). In all organisms, genetic information—in the form of *genes*—is carried in DNA molecules. This information is written in the same chemical code, constructed out of the same chemical building blocks, interpreted by essentially the same chemical machinery, and replicated in the same way when an organism reproduces. Thus, in every cell, the long **DNA** polymer chains are made from the same set of four monomers, called *nucleotides*, strung together in different sequences like the letters of an alphabet to convey information. In every cell, the information encoded in the DNA is read out, or *transcribed*, into a chemically related set of polymers called **RNA**. A subset of these RNA molecules is in turn *translated* into yet another type of polymer called a **protein**. This flow of information—from DNA to RNA to protein—is so fundamental to life that it is referred to as the *central dogma* (**Figure 1–2**).

The appearance and behavior of a cell are dictated largely by its protein molecules, which serve as structural supports, chemical catalysts,

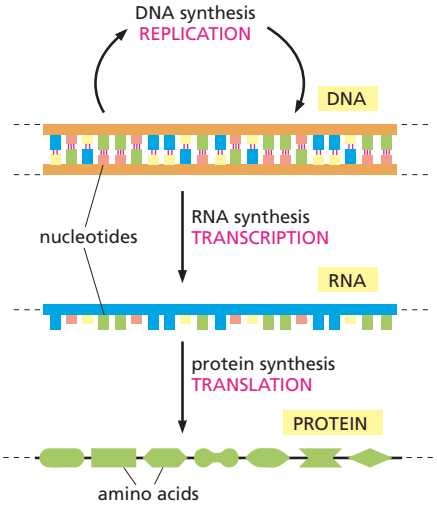


Figure 1–2 In all living cells, genetic information flows from DNA to RNA (transcription) and from RNA to protein (translation)—a sequence known as the central dogma. The sequence of nucleotides in a particular segment of DNA (a gene) is transcribed into an RNA molecule, which can then be translated into the linear sequence of amino acids of a protein. Only a small part of the gene, RNA, and protein are shown.

(A) (B) (C) (D)

Figure 1–3 All living organisms are constructed from cells. A colony of bacteria, a butterfly, a rose, and a dolphin are all made of cells that have a fundamentally similar chemistry and operate according to the same basic principles. (A, courtesy of Janice Carr; C, courtesy of the John Innes Foundation; D, courtesy of Jonathan Gordon, IFAW.)

molecular motors, and so on. Proteins are built from *amino acids*, and all organisms use the same set of 20 amino acids to make their proteins. But the amino acids are linked in different sequences, giving each type of protein molecule a different three-dimensional shape, or *conformation*, just as different sequences of letters spell different words. In this way, the same basic biochemical machinery has served to generate the whole gamut of life on Earth (**Figure 1–3**). A more detailed discussion of the structure and function of proteins, RNA, and DNA is presented in Chapters 4 through 8.

If cells are the fundamental unit of living matter, then nothing less than a cell can truly be called living. Viruses, for example, are compact packages of genetic information—in the form of DNA or RNA—encased in protein but they have no ability to reproduce themselves by their own efforts. Instead, they get themselves copied by parasitizing the reproductive machinery of the cells that they invade. Thus, viruses are chemical zombies: they are inert and inactive outside their host cells, but they can exert a malign control over a cell once they gain entry.

All Present-Day Cells Have Apparently Evolved from the Same Ancestral Cell

A cell reproduces by replicating its DNA and then dividing in two, passing a copy of the genetic instructions encoded in its DNA to each of its daughter cells. That is why daughter cells resemble the parent cell. However, the copying is not always perfect, and the instructions are occasionally corrupted by *mutations* that change the DNA. For this reason, daughter cells do not always match the parent cell exactly.

Mutations can create offspring that are changed for the worse (in that they are less able to survive and reproduce), changed for the better (in that they are better able to survive and reproduce), or changed in a neutral way (in that they are genetically different but equally viable). The struggle for survival eliminates the first, favors the second, and tolerates the third. The genes of the next generation will be the genes of the survivors.

On occasion, the pattern of descent may be complicated by sexual reproduction, in which two cells of the same species fuse, pooling their DNA. The genetic cards are then shuffled, re-dealt, and distributed in new combinations to the next generation, to be tested again for their ability to promote survival and reproduction.

These simple principles of genetic change and selection, applied repeatedly over billions of cell generations, are the basis of **evolution**—the process by which living species become gradually modified and adapted to their environment in more and more sophisticated ways. Evolution offers a startling but compelling explanation of why present-day cells are so similar in their fundamentals: they have all inherited their genetic instructions from the same common ancestor. It is estimated that this ancestral cell existed between 3.5 and 3.8 billion years ago, and we must

QUESTION 1–2

Mutations are mistakes in the DNA that change the genetic plan from the previous generation. Imagine a shoe factory. Would you expect mistakes (i.e., unintentional changes) in copying the shoe design to lead to improvements in the shoes produced? Explain your answer.

suppose that it contained a prototype of the universal machinery of all life on Earth today. Through a very long process of mutation and natural selection, the descendants of this ancestral cell have gradually diverged to fill every habitat on Earth with organisms that exploit the potential of the machinery in an endless variety of ways.

Genes Provide the Instructions for Cell Form, Function, and Complex Behavior

A cell's **genome**—that is, the entire sequence of nucleotides in an organism's DNA—provides a genetic program that instructs the cell how to behave. For the cells of plant and animal embryos, the genome directs the growth and development of an adult organism with hundreds of different cell types. Within an individual plant or animal, these cells can be extraordinarily varied, as we discuss in Chapter 20. Fat cells, skin cells, bone cells, and nerve cells seem as dissimilar as any cells could be. Yet all these *differentiated cell types* are generated during embryonic development from a single fertilized egg cell, and all contain identical copies of the DNA of the species. Their varied characters stem from the way that individual cells use their genetic instructions. Different cells *express* different genes: that is, they use their genes to produce some proteins and not others, depending on their internal state and on cues that they and their ancestor cells have received from their surroundings—mainly signals from other cells in the organism.

The DNA, therefore, is not just a shopping list specifying the molecules that every cell must make, and a cell is not just an assembly of all the items on the list. Each cell is capable of carrying out a variety of biological tasks, depending on its environment and its history, and it selectively uses the information encoded in its DNA to guide its activities. Later in this book, we will see in detail how DNA defines both the parts list of the cell and the rules that decide when and where these parts are to be made.

CELLS UNDER THE MICROSCOPE

Today, we have the technology to decipher the underlying principles that govern the structure and activity of the cell. But cell biology started without these tools. The earliest cell biologists began by simply looking at tissues and cells, and later breaking them open or slicing them up, attempting to view their contents. What they saw was to them profoundly baffling—a collection of tiny and scarcely visible objects whose relationship to the properties of living matter seemed an impenetrable mystery. Nevertheless, this type of visual investigation was the first step toward understanding cells, and it remains essential in the study of cell biology.

Cells were not made visible until the seventeenth century, when the **microscope** was invented. For hundreds of years afterward, all that was known about cells was discovered using this instrument. *Light microscopes* use visible light to illuminate specimens, and they allowed biologists to see for the first time the intricate structure that underpins all living things.

Although these instruments now incorporate many sophisticated improvements, the properties of light itself set a limit to the fineness of detail they reveal. *Electron microscopes*, invented in the 1930s, go beyond this limit by using beams of electrons instead of beams of light as the source of illumination, greatly extending our ability to see the fine details of cells and even making some of the larger molecules visible individually. These and other forms of microscopy remain vital tools in the modern cell biology laboratory, where they continue to reveal new and sometimes surprising details about the way cells are built and how they operate.

The Invention of the Light Microscope Led to the Discovery of Cells

The development of the light microscope depended on advances in the production of glass lenses. By the seventeenth century, lenses were powerful enough to make out details invisible to the naked eye. Using an instrument equipped with such a lens, Robert Hooke examined a piece of cork and in 1665 reported to the Royal Society of London that the cork was composed of a mass of minute chambers. He called these chambers "cells," based on their resemblance to the simple rooms occupied by monks in a monastery. The name stuck, even though the structures Hooke described were actually the cell walls that remained after the living plant cells inside them had died. Later, Hooke and his Dutch contemporary Antoni van Leeuwenhoek were able to observe living cells, seeing for the first time a world teeming with motile microscopic organisms.

For almost 200 years, such instruments—the first light microscopes—remained exotic devices, available only to a few wealthy individuals. It was not until the nineteenth century that microscopes began to be widely used to look at cells. The emergence of cell biology as a distinct science was a gradual process to which many individuals contributed, but its official birth is generally said to have been signaled by two publications: one by the botanist Matthias Schleiden in 1838 and the other by the zoologist Theodor Schwann in 1839. In these papers, Schleiden and Schwann documented the results of a systematic investigation of plant and animal tissues with the light microscope, showing that cells were the universal building blocks of all living tissues. Their work, and that of other nineteenth-century microscopists, slowly led to the realization that all living cells are formed by the growth and division of existing cells—a principle sometimes referred to as the *cell theory* (**Figure 1–4**). The implication that

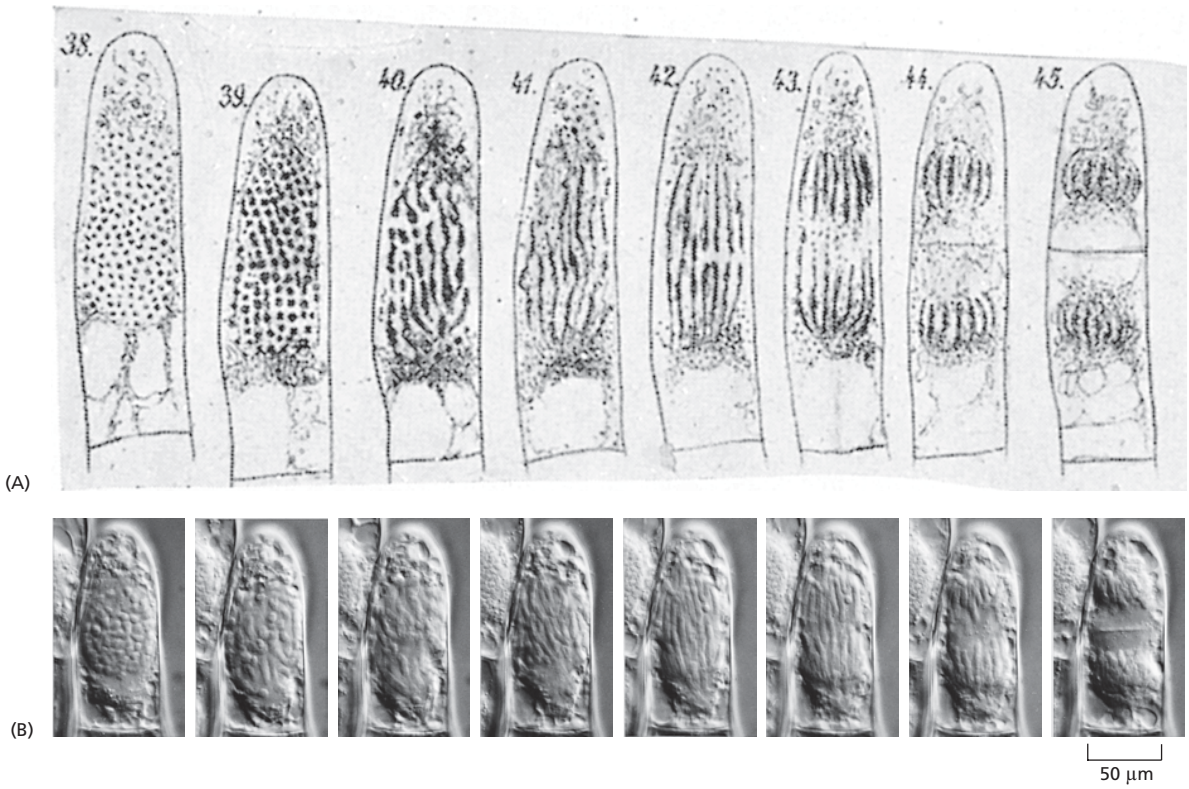


Figure 1–4 New cells form by growth and division of existing cells. (A) In 1880, Eduard Strasburger drew a living plant cell (a hair cell from a *Tradescantia* flower), which he observed dividing into two daughter cells over a period of 2.5 hours. (B) A comparable living plant cell photographed recently through a modern light microscope. (B, courtesy of Peter Hepler.)

living organisms do not arise spontaneously but can be generated only from existing organisms was hotly contested, but it was finally confirmed in the 1860s by an elegant set of experiments performed by Louis Pasteur.

The principle that cells are generated only from preexisting cells and inherit their characteristics from them underlies all of biology and gives the subject a unique flavor: in biology, questions about the present are inescapably linked to questions about the past. To understand why present-day cells and organisms behave as they do, we need to understand their history, all the way back to the misty origins of the first cells on Earth. Charles Darwin provided the key insight that makes this history comprehensible. His theory of evolution, published in 1859, explains how random variation and natural selection gave rise to diversity among organisms that share a common ancestry. When combined with the cell theory, the theory of evolution leads us to view all life, from its beginnings to the present day, as one vast family tree of individual cells. Although this book is primarily about how cells work today, we will encounter the theme of evolution again and again.

Light Microscopes Allow Examination of Cells and Some of Their Components

If you cut a very thin slice from a suitable plant or animal tissue and view it using a light microscope, you will see that the tissue is divided into thousands of small cells. These may be either closely packed or separated from one another by an *extracellular matrix*, a dense material often made of protein fibers embedded in a polysaccharide gel (**Figure 1–5**). Each cell is typically about 5–20 μm in diameter. If you have taken care of your specimen so that its cells remain alive, you will be able to see particles moving around inside individual cells. And if you watch patiently, you may even see a cell slowly change shape and divide into two (see Figure 1–4 and a speeded-up video of cell division in a frog embryo in **Movie 1.1**).

To see the internal structure of a cell is difficult, not only because the parts are small, but also because they are transparent and mostly colorless. One way around the problem is to stain cells with dyes that color particular components differently (see Figure 1–5). Alternatively, one can exploit the fact that cell components differ slightly from one another in

QUESTION 1–3

You have embarked on an ambitious research project: to create life in a test tube. You boil up a rich mixture of yeast extract and amino acids in a flask along with a sprinkling of the inorganic salts known to be essential for life. You seal the flask and allow it to cool. After several months, the liquid is as clear as ever, and there are no signs of life. A friend suggests that excluding the air was a mistake, since most life as we know it requires oxygen. You repeat the experiment, but this time you leave the flask open to the atmosphere. To your great delight, the liquid becomes cloudy after a few days and under the microscope you see beautiful small cells that are clearly growing and dividing. Does this experiment prove that you managed to generate a novel life-form? How might you redesign your experiment to allow air into the flask, yet eliminate the possibility that contamination is the explanation for the results? (For a ready-made answer, look up the classic experiments of Louis Pasteur.)

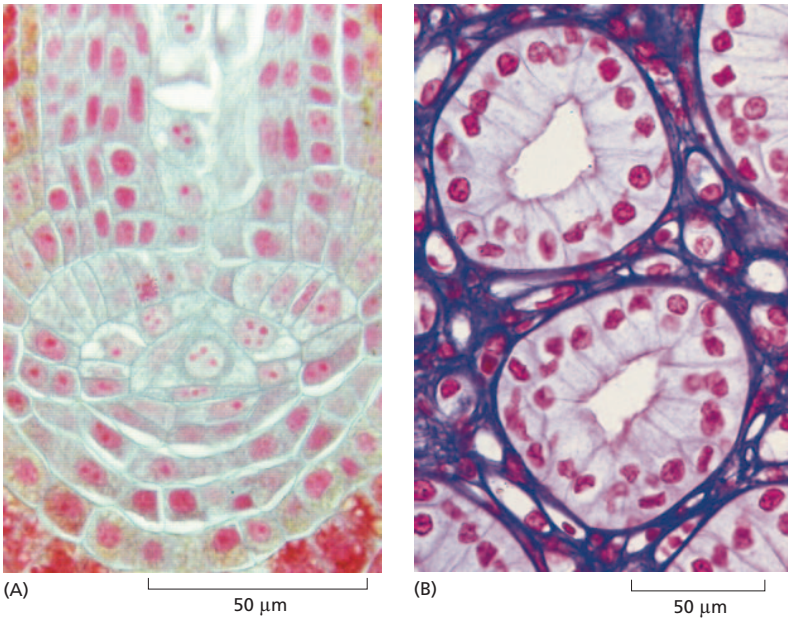


Figure 1–5 Cells form tissues in plants and animals. (A) Cells in the root tip of a fern. The nuclei are stained *red*, and each cell is surrounded by a thin cell wall (*light blue*). (B) Cells in the urine-collecting ducts of the kidney. Each duct appears in this cross section as a ring of closely packed cells (with nuclei stained *red*). The ring is surrounded by extracellular matrix, stained *purple*. (A, courtesy of James Mauseth; B, from P.R. Wheater et al., Functional Histology, 2nd ed. Edinburgh: Churchill Livingstone, 1987. With permission from Elsevier.)

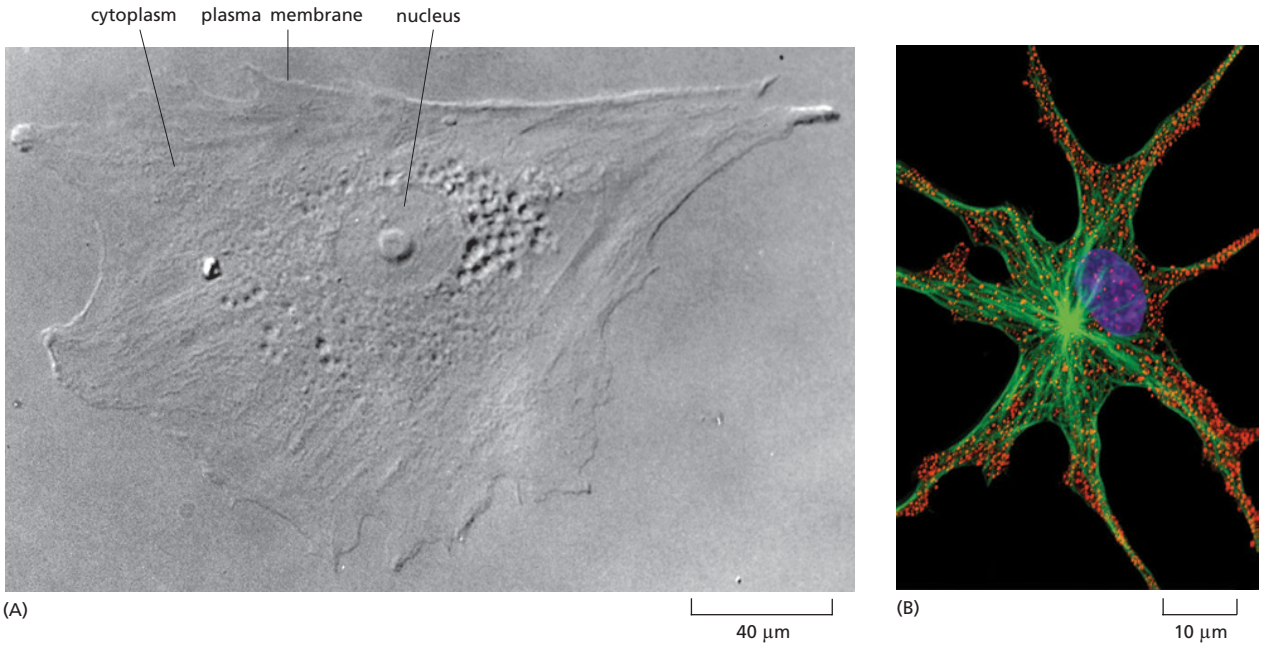


Figure 1–6 Some of the internal structures of a living cell can be seen with a light microscope. (A) A cell taken from human skin and grown in culture was photographed through a light microscope using interference-contrast optics (see Panel 1–1, pp. 10–11). The nucleus is especially prominent. (B) A pigment cell from a frog, stained with fluorescent dyes and viewed with a confocal fluorescence microscope (see Panel 1–1). The nucleus is shown in *purple*, the pigment granules in *red*, and the microtubules—a class of filaments built from protein molecules in the cytoplasm—in *green*. (A, courtesy of Casey Cunningham; B, courtesy of Stephen Rogers and the Imaging Technology Group of the Beckman Institute, University of Illinois, Urbana.)

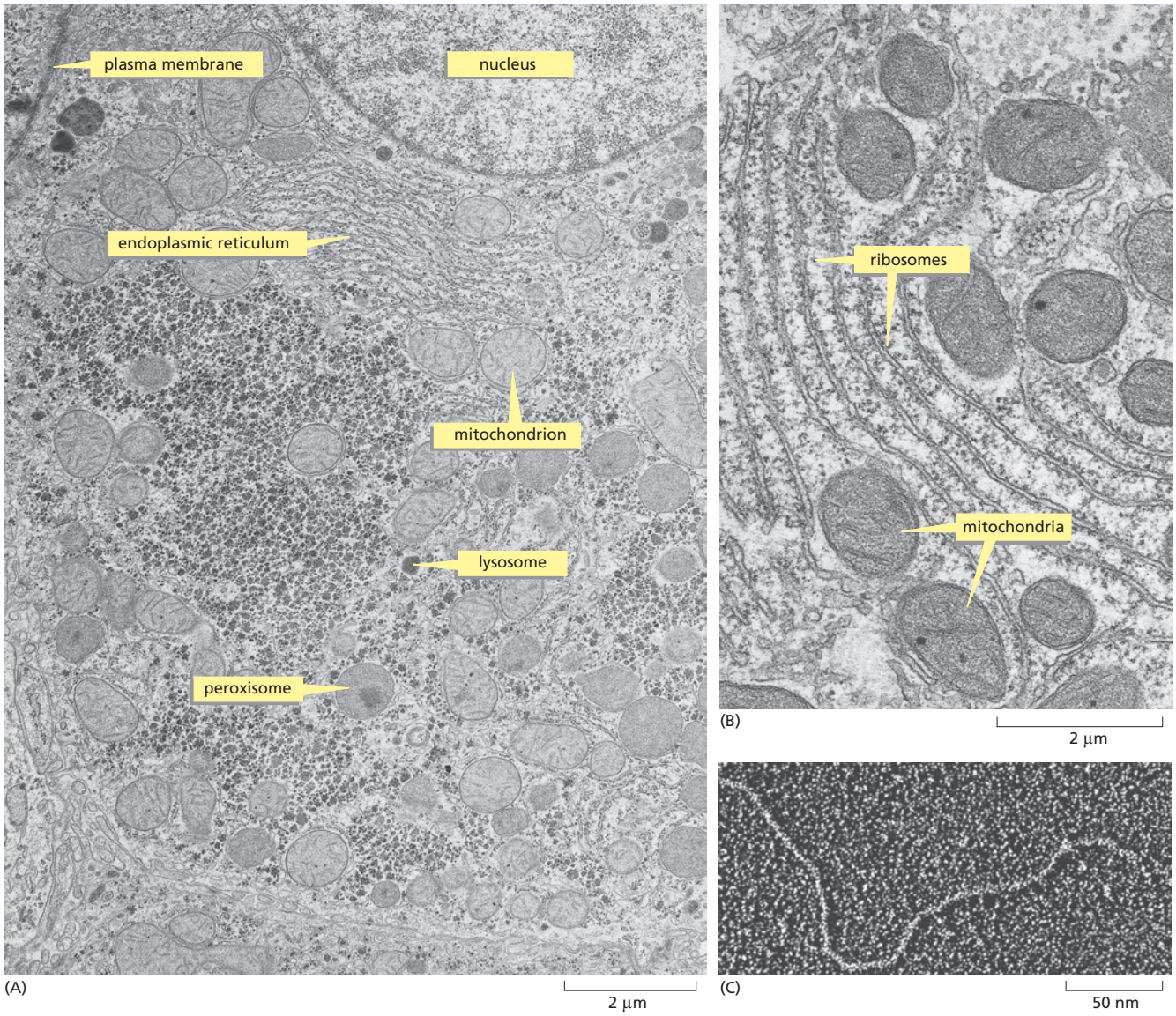
refractive index, just as glass differs in refractive index from water, causing light rays to be deflected as they pass from the one medium into the other. The small differences in refractive index can be made visible by specialized optical techniques, and the resulting images can be enhanced further by electronic processing.

The cell thus revealed has a distinct anatomy (**Figure 1–6A**). It has a sharply defined boundary, indicating the presence of an enclosing membrane. A large, round structure, the *nucleus*, is prominent in the middle of the cell. Around the nucleus and filling the cell's interior is the **cytoplasm**, a transparent substance crammed with what seems at first to be a jumble of miscellaneous objects. With a good light microscope, one can begin to distinguish and classify some of the specific components in the cytoplasm, but structures smaller than about 0.2 μm—about half the wavelength of visible light—cannot normally be resolved; points closer than this are not distinguishable and appear as a single blur.

In recent years, however, new types of **fluorescence microscopes** have been developed that use sophisticated methods of illumination and electronic image processing to see fluorescently labeled cell components in much finer detail (**Figure 1–6B**). The most recent super-resolution fluorescence microscopes, for example, can push the limits of resolution down even further, to about 20 nanometers (nm). That is the size of a single **ribosome**, a large macromolecular complex composed of 80–90 individual proteins and RNA molecules.

The Fine Structure of a Cell Is Revealed by Electron Microscopy

For the highest magnification and best resolution, one must turn to an **electron microscope**, which can reveal details down to a few nanometers. Cell samples for the electron microscope require painstaking preparation. Even for light microscopy, a tissue often has to be *fixed* (that is, preserved by pickling in a reactive chemical solution), supported by *embedding* in a solid wax or resin, cut or *sectioned* into thin slices, and *stained* before it is viewed. For electron microscopy, similar procedures are required, but the sections have to be much thinner and there is no possibility of looking at living, wet cells.



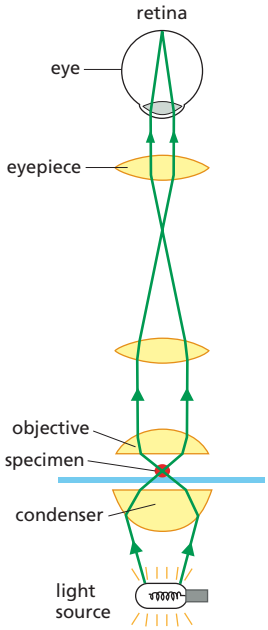
When thin sections are cut, stained, and placed in the electron microscope, much of the jumble of cell components becomes sharply resolved into distinct **organelles**—separate, recognizable substructures with specialized functions that are often only hazily defined with a light microscope. A delicate membrane, only about 5 nm thick, is visible enclosing the cell, and similar membranes form the boundary of many of the organelles inside (**Figure 1–7A, B**). The membrane that separates the interior of the cell from its external environment is called the **plasma membrane**, while the membranes surrounding organelles are called *internal membranes*. All of these membranes are only two molecules thick (as discussed in Chapter 11). With an electron microscope, even individual large molecules can be seen (**Figure 1–7C**).

The type of electron microscope used to look at thin sections of tissue is known as a *transmission electron microscope*. This is, in principle, similar to a light microscope, except that it transmits a beam of electrons rather than a beam of light through the sample. Another type of electron microscope—the *scanning electron microscope*—scatters electrons off the surface of the sample and so is used to look at the surface detail of cells and other structures. A survey of the principal types of microscopy used to examine cells is given in **Panel 1–1** (pp. 10–11).

Figure 1–7 The fine structure of a cell can be seen in a transmission electron microscope. (A) Thin section of a liver cell showing the enormous amount of detail that is visible. Some of the components to be discussed later in the chapter are labeled; they are identifiable by their size and shape. (B) A small region of the cytoplasm at higher magnification. The smallest structures that are clearly visible are the ribosomes, each of which is made of 80–90 or so individual large molecules. (C) Portion of a long, threadlike DNA molecule isolated from a cell and viewed by electron microscopy. (A and B, courtesy of Daniel S. Friend; C, courtesy of Mei Lie Wong.)

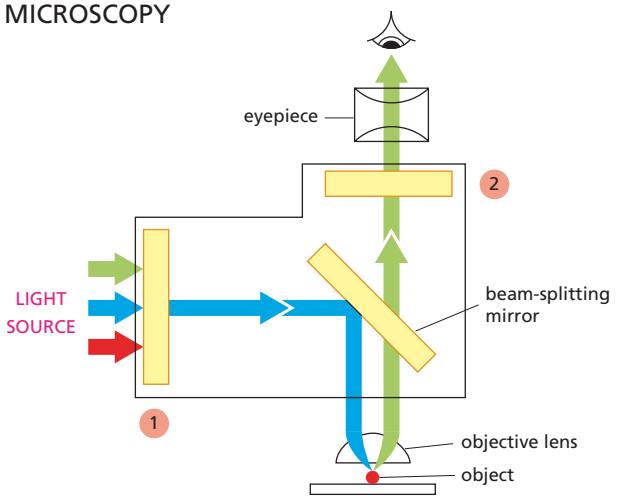
THE LIGHT MICROSCOPE

The light microscope allows us to magnify cells up to 1000 times and to resolve details as small as 0.2 μm (a limitation imposed by the wavelike nature of light, not by the quality of the lenses). Three things are required for viewing cells in a light microscope. First, a bright light must be focused onto the specimen by lenses in the condenser. Second, the specimen must be carefully prepared to allow light to pass through it. Third, an appropriate set of lenses (objective and eyepiece) must be arranged to focus an image of the specimen in the eye.

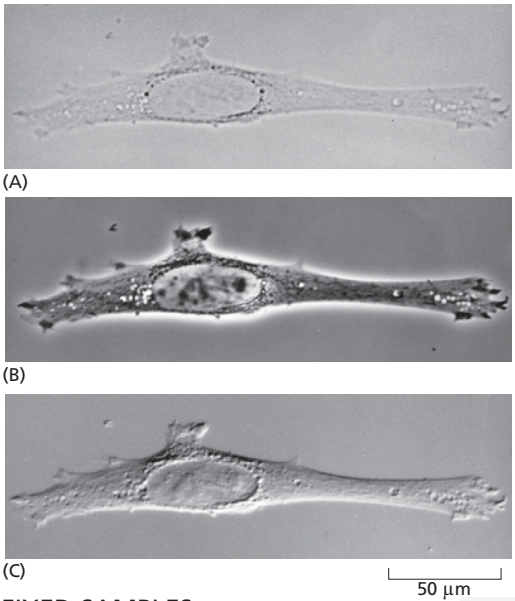


the light path in a light microscope

FLUORESCENCE MICROSCOPY



Fluorescent dyes used for staining cells are detected with the aid of a *fluorescence microscope*. This is similar to an ordinary light microscope except that the illuminating light is passed through two sets of filters. The first (1) filters the light before it reaches the specimen, passing only those wavelengths that excite the particular fluorescent dye. The second (2) blocks out this light and passes only those wavelengths emitted when the dye fluoresces. Dyed objects show up in bright color on a dark background.

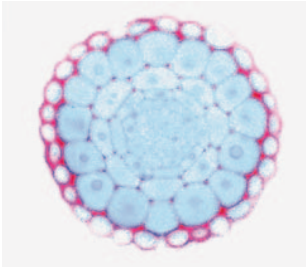


LOOKING AT LIVING CELLS

The same unstained, living animal cell (fibroblast) in culture viewed with (A) straightforward (bright-field) optics; (B) phase-contrast optics; (C) interference-contrast optics. The two latter systems exploit differences in the way light travels through regions of the cell with differing refractive indexes. All three images can be obtained on the same microscope simply by interchanging optical components.

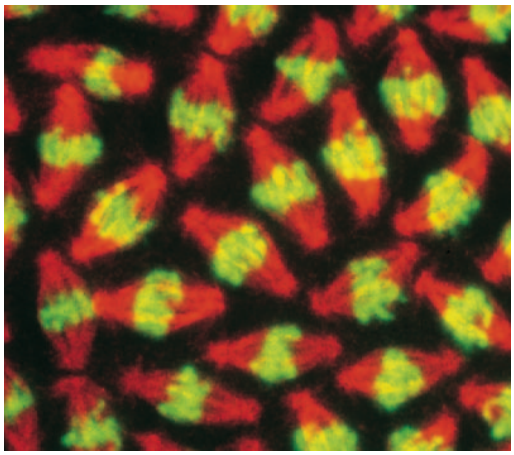
FIXED SAMPLES

Most tissues are neither small enough nor transparent enough to examine directly in the microscope. Typically, therefore, they are chemically fixed and cut into very thin slices, or *sections*, that can be mounted on a glass microscope slide and subsequently stained to reveal different components of the cells. A stained section of a plant root tip is shown here (D). (Courtesy of Catherine Kidner.)



FLUORESCENT PROBES

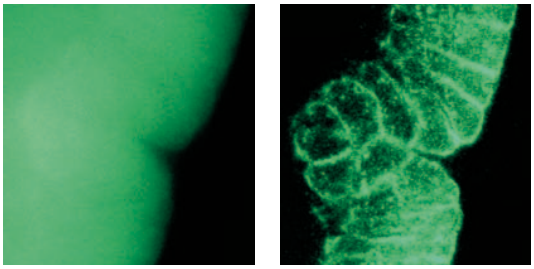
Dividing nuclei in a fly embryo seen with a fluorescence microscope after staining with specific fluorescent dyes.



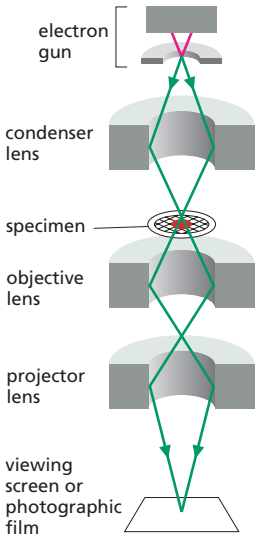
Fluorescent dyes absorb light at one wavelength and emit it at another, longer wavelength. Some such dyes bind specifically to particular molecules in cells and can reveal their location when examined with a fluorescence microscope. An example is the stain for DNA shown here (*green*). Other dyes can be coupled to antibody molecules, which then serve as highly specific and versatile staining reagents that bind selectively to particular large molecules, allowing us to see their distribution in the cell. In the example shown, a microtubule protein in the mitotic spindle is stained *red* with a fluorescent antibody. (Courtesy of William Sullivan.)

CONFOCAL MICROSCOPY

A confocal microscope is a specialized type of fluorescence microscope that builds up an image by scanning the specimen with a laser beam. The beam is focused onto a single point at a specific depth in the specimen, and a pinhole aperture in the detector allows only fluorescence emitted from this same point to be included in the image. Scanning the beam across the specimen generates a sharp image of the plane of focus—an *optical* section. A series of optical sections at different depths allows a three-dimensional image to be constructed. An intact insect embryo is shown here stained with a fluorescent probe for actin filaments. (A) Conventional fluorescence microscopy gives a blurry image due to the presence of fluorescent structures above and below the plane of focus. (B) Confocal microscopy provides an optical section showing the individual cells clearly. (Courtesy of Richard Warn and Peter Shaw.)

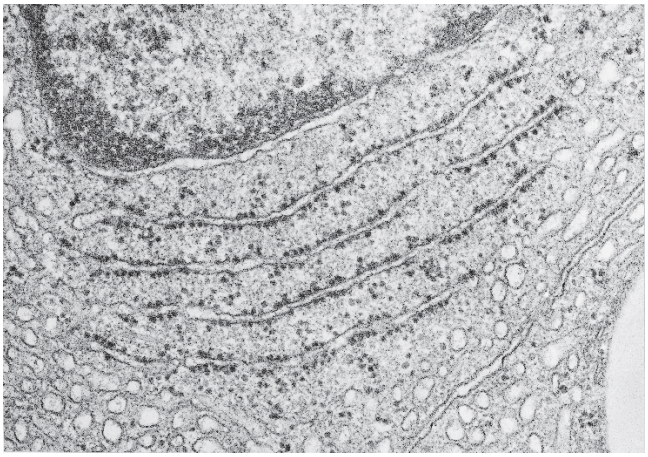


TRANSMISSION ELECTRON MICROSCOPY



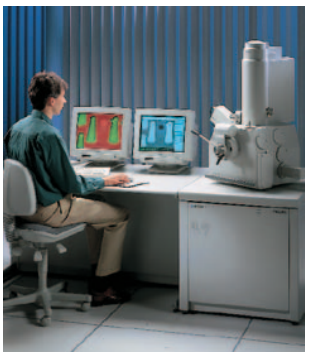
Courtesy of Philips Electron Optics, with permission from FEI Co.

The electron micrograph below shows a small region of a cell in a piece of testis. The tissue has been chemically fixed, embedded in plastic, and cut into very thin sections that have then been stained with salts of uranium and lead. (Courtesy of Daniel S. Friend.)



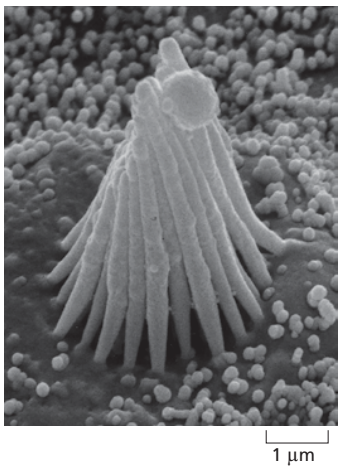
The transmission electron microscope (TEM) is in principle similar to a light microscope, but it uses a beam of electrons instead of a beam of light, and magnetic coils to focus the beam instead of glass lenses. The specimen, which is placed in a vacuum, must be very thin. Contrast is usually introduced by staining the specimen with electron-dense heavy metals that locally absorb or scatter electrons, removing them from the beam as it passes through the specimen. The TEM has a useful magnification of up to a million-fold and can resolve details as small as about 1 nm in biological specimens.

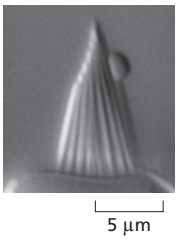
SCANNING ELECTRON MICROSCOPY



Courtesy of Philips Electron Optics, with permission from FEI Co.

In the scanning electron microscope (SEM), the specimen, which has been coated with a very thin film of a heavy metal, is scanned by a beam of electrons brought to a focus on the specimen by magnetic coils that act as lenses. The quantity of electrons scattered or emitted as the beam bombards each successive point on the surface of the specimen is measured by the detector, and is used to control the intensity of successive points in an image built up on a video screen. The microscope creates striking images of three-dimensional objects with great depth of focus and can resolve details down to somewhere between 3 nm and 20 nm, depending on the instrument.





Scanning electron micrograph of stereocilia projecting from a hair cell in the inner ear (*left*). For comparison, the same structure is shown by light microscopy, at the limit of its resolution (*above*). (Courtesy of Richard Jacobs and James Hudspeth.)

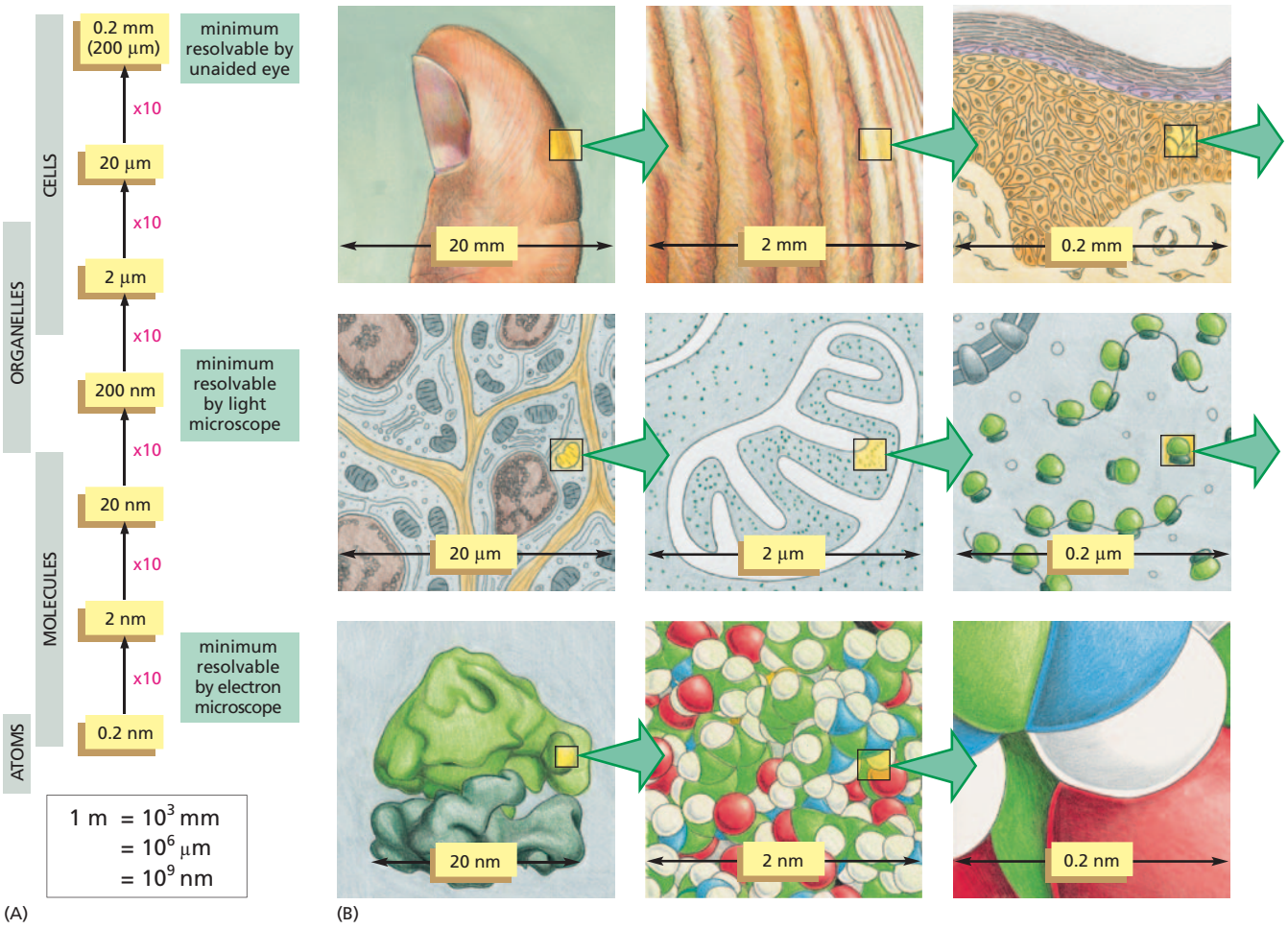


Figure 1–8 How big is a cell and its components? (A) The sizes of cells and of their component parts, plus the units in which they are measured. (B) Drawings to convey a sense of scale between living cells and atoms. Each panel shows an image that is magnified by a factor of 10 compared to its predecessor—producing an imaginary progression from a thumb, to skin, to skin cells, to a mitochondrion, to a ribosome, and ultimately to a cluster of atoms forming part of one of the many protein molecules in our bodies. Note that ribosomes are present inside mitochondria (as shown here), as well as in the cytoplasm. Details of molecular structure, as shown in the last two panels, are beyond the power of the electron microscope.

Even the most powerful electron microscopes, however, cannot visualize the individual atoms that make up biological molecules (**Figure 1–8**). To study the cell's key components in atomic detail, biologists have developed even more sophisticated tools. A technique called X-ray crystallography, for example, is used to determine the precise three-dimensional structure of protein molecules (discussed in Chapter 4).

THE PROKARYOTIC CELL

Of all the types of cells revealed by the microscope, *bacteria* have the simplest structure and come closest to showing us life stripped down to its essentials. Indeed, a bacterium contains essentially no organelles—not even a nucleus to hold its DNA. This property—the presence or absence of a nucleus—is used as the basis for a simple but fundamental classification of all living things. Organisms whose cells have a nucleus are called **eukaryotes** (from the Greek words *eu*, meaning "well" or "truly," and *karyon*, a "kernel" or "nucleus"). Organisms whose cells do not have a nucleus are called **prokaryotes** (from *pro*, meaning "before"). The terms

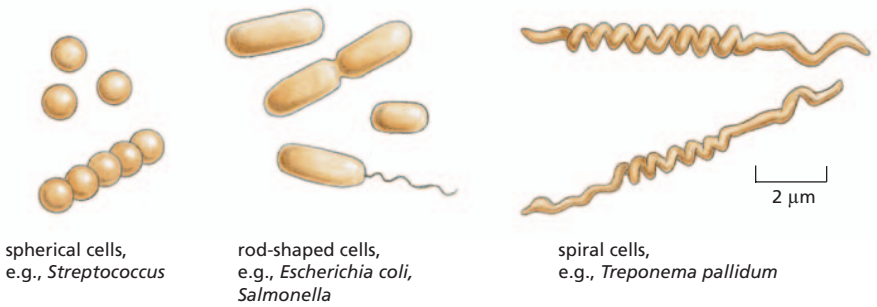


Figure 1–9 Bacteria come in different shapes and sizes. Typical spherical, rodlike, and spiral-shaped bacteria are drawn to scale. The spiral cells shown are the organisms that cause syphilis.

"bacterium" and "prokaryote" are often used interchangeably, although we will see that the category of prokaryotes also includes another class of cells, the *archaea* (singular archaeon), which are so remotely related to bacteria that they are given a separate name.

Prokaryotes are typically spherical, rodlike, or corkscrew-shaped (**Figure 1–9**). They are also small—generally just a few micrometers long, although there are some giant species as much as 100 times longer than this. Prokaryotes often have a tough protective coat, or cell wall, surrounding the plasma membrane, which encloses a single compartment containing the cytoplasm and the DNA. In the electron microscope, the cell interior typically appears as a matrix of varying texture, without any obvious organized internal structure (**Figure 1–10**). The cells reproduce quickly by dividing in two. Under optimum conditions, when food is plentiful, many prokaryotic cells can duplicate themselves in as little as 20 minutes. In 11 hours, by repeated divisions, a single prokaryote can give rise to more than 8 billion progeny (which exceeds the total number of humans presently on Earth). Thanks to their large numbers, rapid growth rates, and ability to exchange bits of genetic material by a process akin to sex, populations of prokaryotic cells can evolve fast, rapidly acquiring the ability to use a new food source or to resist being killed by a new antibiotic.

QUESTION 1–4

A bacterium weighs about 10^{-12} g and can divide every 20 minutes. If a single bacterial cell carried on dividing at this rate, how long would it take before the mass of bacteria would equal that of the Earth (6×10^{24} kg)? Contrast your result with the fact that bacteria originated at least 3.5 billion years ago and have been dividing ever since. Explain the apparent paradox. (The number of cells N in a culture at time t is described by the equation $N = N_0 \times 2^{t/G}$, where N_0 is the number of cells at zero time and G is the population doubling time.)

Prokaryotes Are the Most Diverse and Numerous Cells on Earth

Most prokaryotes live as single-celled organisms, although some join together to form chains, clusters, or other organized multicellular structures. In shape and structure, prokaryotes may seem simple and limited, but in terms of chemistry, they are the most diverse and inventive class of cells. Members of this class exploit an enormous range of habitats, from hot puddles of volcanic mud to the interiors of other living cells, and they vastly outnumber all eukaryotic organisms on Earth. Some are aerobic, using oxygen to oxidize food molecules; some are strictly anaerobic and are killed by the slightest exposure to oxygen. As we discuss later in this

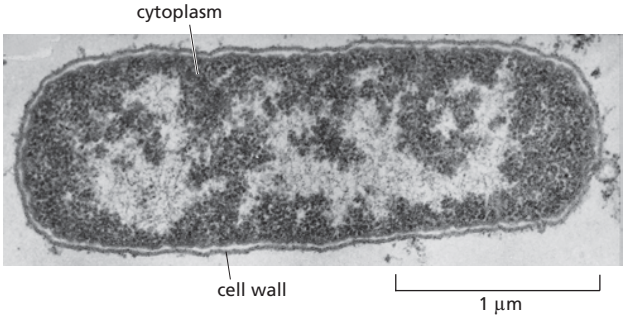


Figure 1–10 The bacterium *Escherichia coli* (*E. coli*) has served as an important model organism. An electron micrograph of a longitudinal section is shown here; the cell's DNA is concentrated in the lightly stained region. (Courtesy of E. Kellenberger.)

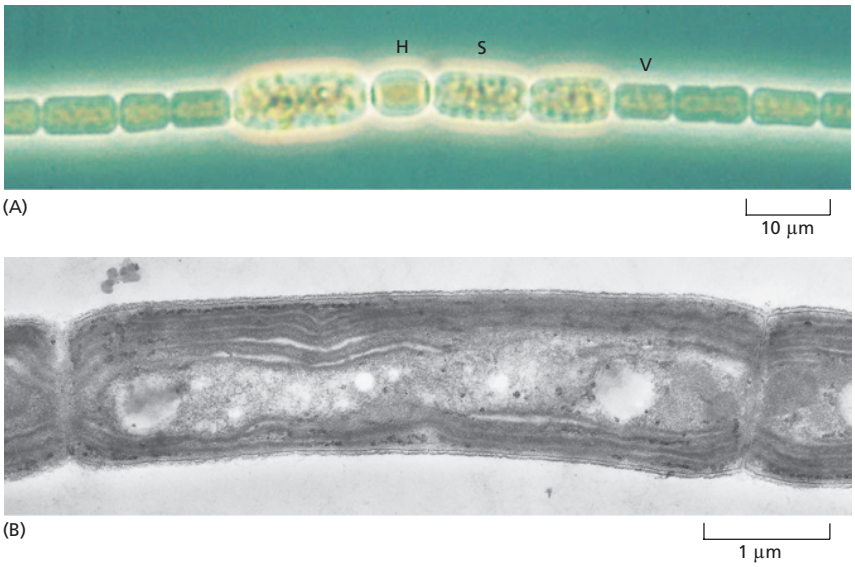


Figure 1–11 Some bacteria are photosynthetic. (A) *Anabaena cylindrica* forms long, multicellular filaments. This light micrograph shows specialized cells that either fix nitrogen (that is, capture N_2 from the atmosphere and incorporate it into organic compounds; labeled *H*), fix CO_2 through photosynthesis (labeled *V*), or become resistant spores (labeled *S*). (B) An electron micrograph of a related species, *Phormidium laminosum*, shows the intracellular membranes where photosynthesis occurs. These micrographs illustrate that even some prokaryotes can form simple multicellular organisms. (A, courtesy of David Adams; B, courtesy of D.P. Hill and C.J. Howe.)

chapter, *mitochondria*—the organelles that generate energy in eukaryotic cells—are thought to have evolved from aerobic bacteria that took to living inside the anaerobic ancestors of today's eukaryotic cells. Thus our own oxygen-based metabolism can be regarded as a product of the activities of bacterial cells.

Virtually any organic, carbon-containing material—from wood to petroleum—can be used as food by one sort of bacterium or another. Even more remarkably, some prokaryotes can live entirely on inorganic substances: they can get their carbon from CO_2 in the atmosphere, their nitrogen from atmospheric N_2, and their oxygen, hydrogen, sulfur, and phosphorus from air, water, and inorganic minerals. Some of these prokaryotic cells, like plant cells, perform *photosynthesis*, using energy from sunlight to produce organic molecules from CO_2 (**Figure 1–11**); others derive energy from the chemical reactivity of inorganic substances in the environment (**Figure 1–12**). In either case, such prokaryotes play a unique and fundamental part in the economy of life on Earth: other living things depend on the organic compounds that these cells generate from inorganic materials.

Plants, too, can capture energy from sunlight and carbon from atmospheric CO_2. But plants unaided by bacteria cannot capture N_2 from the atmosphere, and in a sense even plants depend on bacteria for photosynthesis. It is almost certain that the organelles in the plant cell that

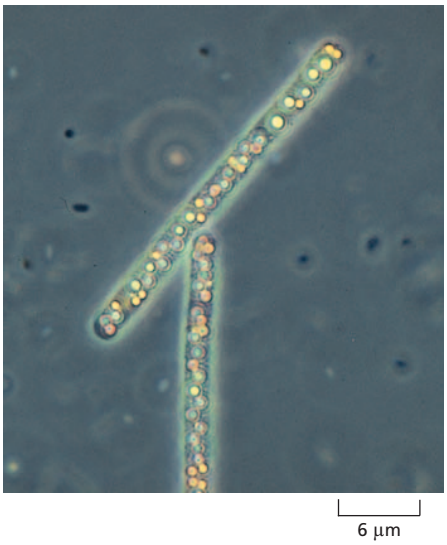


Figure 1–12 A sulfur bacterium gets its energy from H_2S. *Beggiatoa*, a prokaryote that lives in sulfurous environments, oxidizes H_2S to produce sulfur and can fix carbon even in the dark. In this light micrograph, yellow deposits of sulfur can be seen inside both of the cells. (Courtesy of Ralph W. Wolfe.)

perform photosynthesis—the *chloroplasts*—have evolved from photosynthetic bacteria that long ago found a home inside the cytoplasm of a plant cell ancestor.

The World of Prokaryotes Is Divided into Two Domains: Bacteria and Archaea

Traditionally, all prokaryotes have been classified together in one large group. But molecular studies reveal that there is a gulf within the class of prokaryotes, dividing it into two distinct *domains* called the **bacteria** and the **archaea**. Remarkably, at a molecular level, the members of these two domains differ as much from one another as either does from the eukaryotes. Most of the prokaryotes familiar from everyday life—the species that live in the soil or make us ill—are bacteria. Archaea are found not only in these habitats, but also in environments that are too hostile for most other cells: concentrated brine, the hot acid of volcanic springs, the airless depths of marine sediments, the sludge of sewage treatment plants, pools beneath the frozen surface of Antarctica, and in the acidic, oxygen-free environment of a cow's stomach where they break down cellulose and generate methane gas. Many of these extreme environments resemble the harsh conditions that must have existed on the primitive Earth, where living things first evolved before the atmosphere became rich in oxygen.

THE EUKARYOTIC CELL

Eukaryotic cells, in general, are bigger and more elaborate than bacteria and archaea. Some live independent lives as single-celled organisms, such as amoebae and yeasts (**Figure 1–13**); others live in multicellular assemblies. All of the more complex multicellular organisms—including plants, animals, and fungi—are formed from eukaryotic cells.

By definition, all eukaryotic cells have a nucleus. But possession of a nucleus goes hand-in-hand with possession of a variety of other organelles, most of which are membrane-enclosed and common to all eukaryotic organisms. In this section, we take a look at the main organelles found in eukaryotic cells from the point of view of their functions, and we consider how they came to serve the roles they have in the life of the eukaryotic cell.

The Nucleus Is the Information Store of the Cell

The **nucleus** is usually the most prominent organelle in a eukaryotic cell (**Figure 1–14**). It is enclosed within two concentric membranes that form the *nuclear envelope*, and it contains molecules of DNA—extremely long polymers that encode the genetic information of the organism. In the light microscope, these giant DNA molecules become visible as individual **chromosomes** when they become more compact before a cell divides into two daughter cells (**Figure 1–15**). DNA also carries the genetic information in prokaryotic cells; these cells lack a distinct nucleus not because they lack DNA, but because they do not keep their DNA inside a nuclear envelope, segregated from the rest of the cell contents.

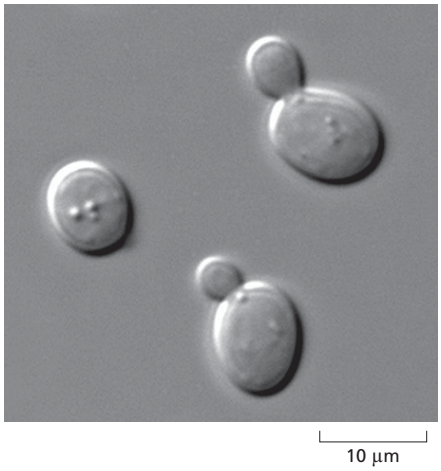


Figure 1–13 Yeasts are simple free-living eukaryotes. The cells shown in this micrograph belong to the species of yeast, *Saccharomyces cerevisiae*, used to make dough rise and turn malted barley juice into beer. As can be seen in this image, the cells reproduce by growing a bud and then dividing asymmetrically into a large mother cell and a small daughter cell; for this reason, they are called budding yeast.

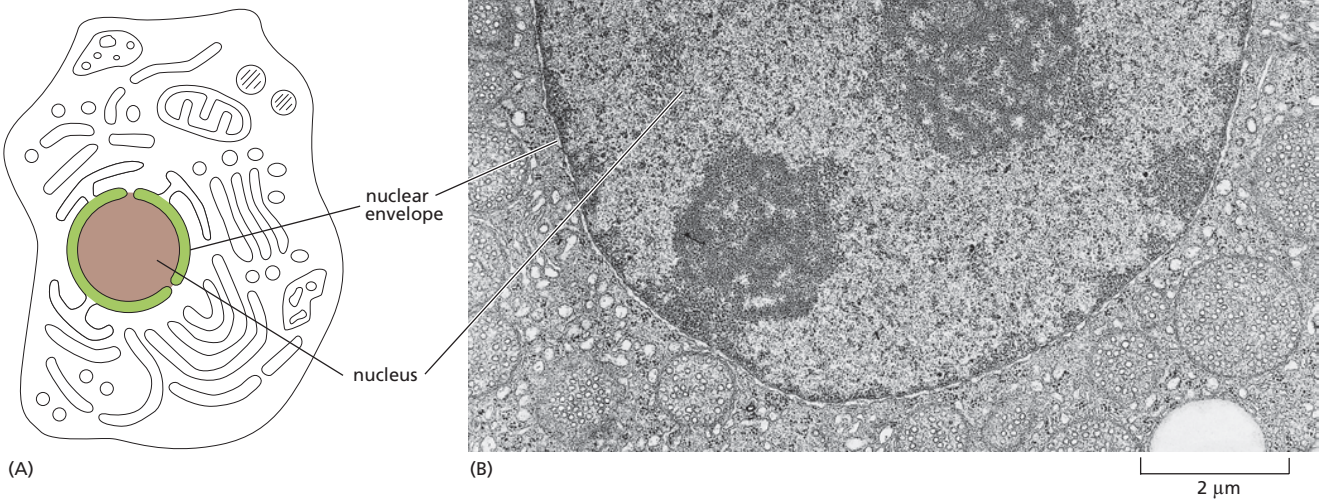


Figure 1–14 The nucleus contains most of the DNA in a eukaryotic cell. (A) This drawing of a typical animal cell shows its extensive system of membrane-enclosed organelles. The nucleus is colored *brown*, the nuclear envelope is *green*, and the cytoplasm (the interior of the cell outside the nucleus) is *white*. (B) An electron micrograph of the nucleus in a mammalian cell. Individual chromosomes are not visible because at this stage of the cell's growth its DNA molecules are dispersed as fine threads throughout the nucleus. (B, courtesy of Daniel S. Friend.)

Mitochondria Generate Usable Energy from Food to Power the Cell

Mitochondria are present in essentially all eukaryotic cells, and they are among the most conspicuous organelles in the cytoplasm (see Figure 1–7B). In a fluorescence microscope, they appear as worm-shaped structures that often form branching networks (**Figure 1–16**). When seen with an electron microscope, individual mitochondria are found to be enclosed in two separate membranes, with the inner membrane formed into folds that project into the interior of the organelle (**Figure 1–17**).

Microscopic examination by itself, however, gives little indication of what mitochondria do. Their function was discovered by breaking open cells and then spinning the soup of cell fragments in a centrifuge; this

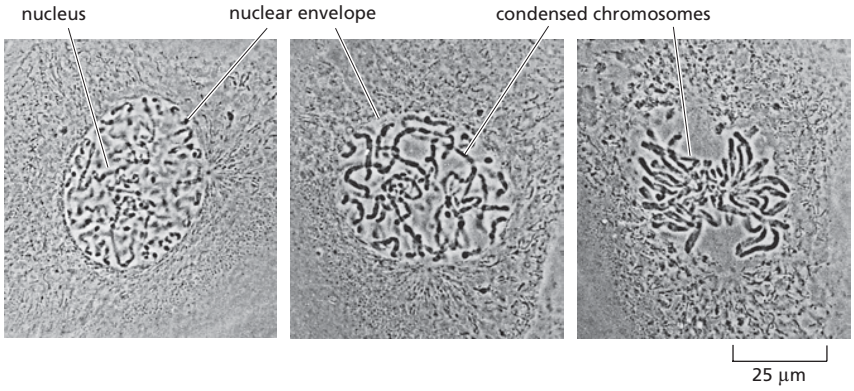


Figure 1–15 Chromosomes become visible when a cell is about to divide. As a eukaryotic cell prepares to divide, its DNA molecules become progressively more compacted (condensed), forming wormlike chromosomes that can be distinguished in the light microscope. The photographs show three successive steps in this process in a cultured cell from a newt's lung; note that in the last micrograph on the right, the nuclear envelope has broken down. (Courtesy of Conly L. Rieder.)

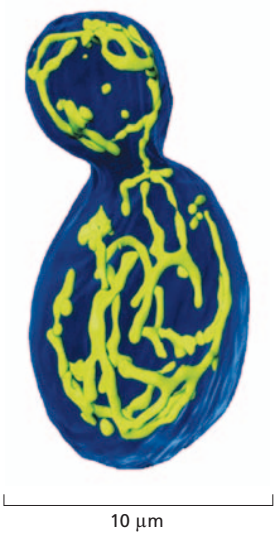


Figure 1–16 Mitochondria can be variable in shape and size. This budding yeast cell, which contains a green fluorescent protein in its mitochondria, was viewed in a super-resolution confocal fluorescence microscope. In this three-dimensional image, the mitochondria are seen to form complex branched networks. (From A. Egner et al., *Proc. Natl Acad. Sci. USA* 99:3370–3375, 2002. With permission from the National Academy of Sciences.)

separates the organelles according to their size and density. Purified mitochondria were then tested to see what chemical processes they could perform. This revealed that mitochondria are generators of chemical energy for the cell. They harness the energy from the oxidation of food molecules, such as sugars, to produce *adenosine triphosphate*, or *ATP*—the basic chemical fuel that powers most of the cell's activities. Because the mitochondrion consumes oxygen and releases carbon dioxide in the course of this activity, the entire process is called *cellular respiration*—essentially, breathing on a cellular level. Without mitochondria, animals, fungi, and plants would be unable to use oxygen to extract the energy they need from the food molecules that nourish them. The process of cellular respiration is considered in detail in Chapter 14.

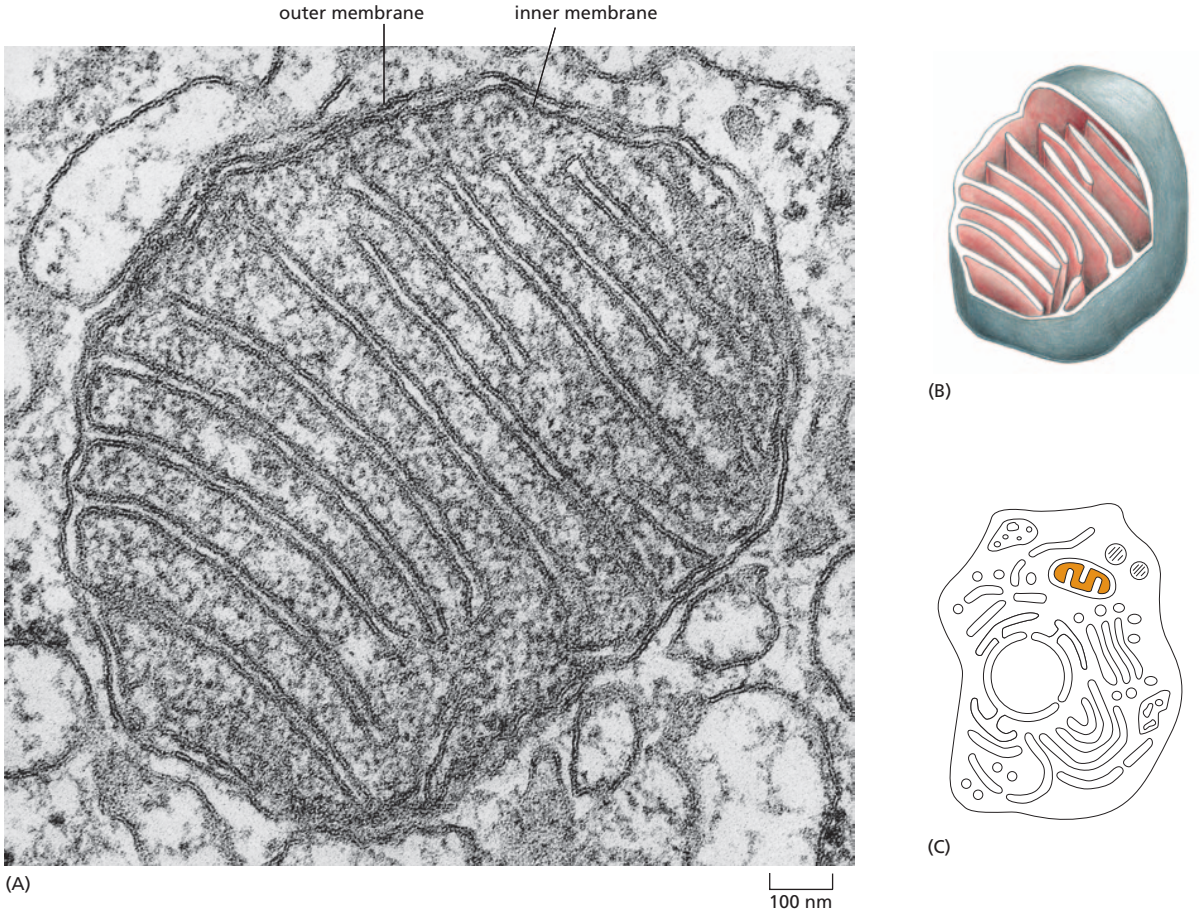


Figure 1–17 Mitochondria have a distinctive structure. (A) An electron micrograph of a cross section of a mitochondrion reveals the extensive infolding of the inner membrane. (B) This three-dimensional representation of the arrangement of the mitochondrial membranes shows the smooth outer membrane (*gray*) and the highly convoluted inner membrane (*red*). The inner membrane contains most of the proteins responsible for cellular respiration—one of the mitochondrion's main functions—and it is highly folded to provide a large surface area for this activity. (C) In this schematic cell, the interior space of the mitochondrion is colored *orange*. (A, courtesy of Daniel S. Friend.)

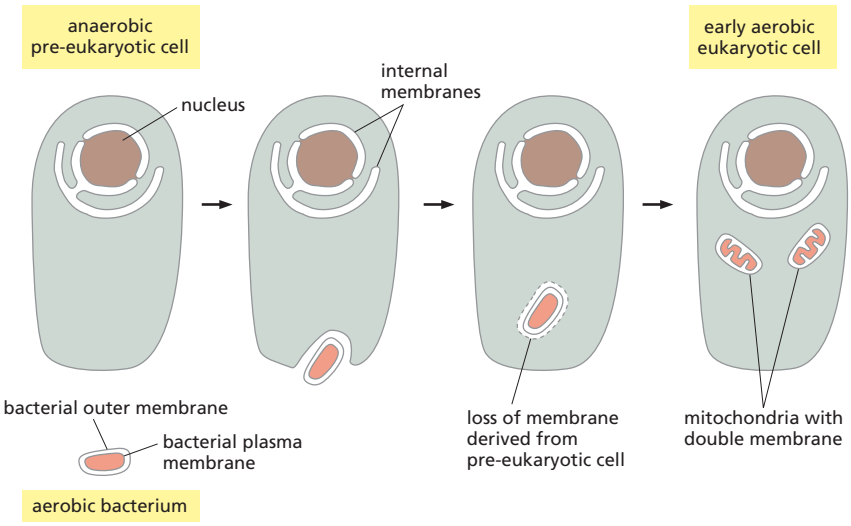


Figure 1–18 Mitochondria most likely evolved from engulfed bacteria. It is virtually certain that mitochondria originate from bacteria that were engulfed by an ancestral pre-eukaryotic cell and survived inside it, living in symbiosis with their host. Note that the double membrane of present-day mitochondria is thought to have been derived from the plasma membrane and outer membrane of the engulfed bacterium.

Mitochondria contain their own DNA and reproduce by dividing in two. Because they resemble bacteria in so many ways, they are thought to have been derived from bacteria that were engulfed by some ancestor of present-day eukaryotic cells (**Figure 1–18**). This evidently created a *symbiotic* relationship in which the host eukaryote and the engulfed bacterium helped one another to survive and reproduce.

Chloroplasts Capture Energy from Sunlight

Chloroplasts are large, green organelles that are found only in the cells of plants and algae, not in the cells of animals or fungi. These organelles have an even more complex structure than mitochondria: in addition to their two surrounding membranes, they possess internal stacks of membranes containing the green pigment *chlorophyll* (**Figure 1–19**).

Chloroplasts carry out **photosynthesis**—trapping the energy of sunlight in their chlorophyll molecules and using this energy to drive the manufacture of energy-rich sugar molecules. In the process, they release

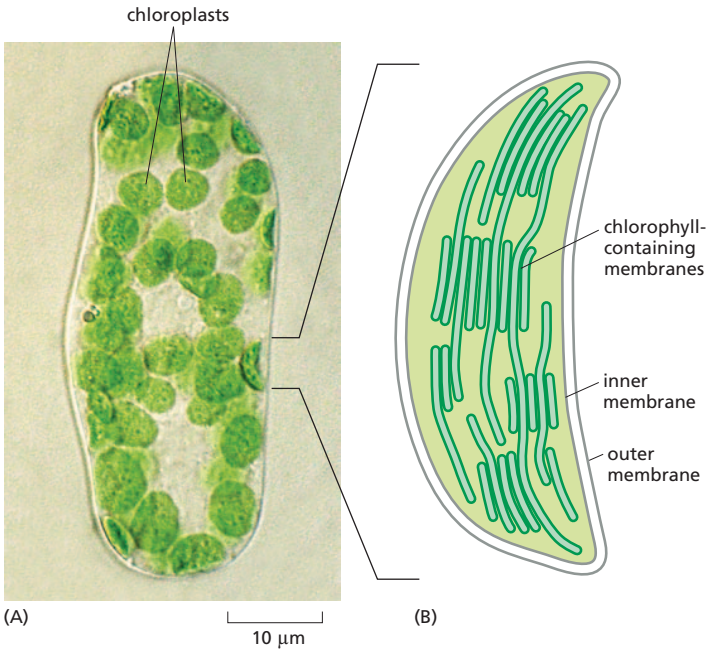


Figure 1–19 Chloroplasts in plant cells capture the energy of sunlight. (A) A single cell isolated from a leaf of a flowering plant, seen in the light microscope, showing many green chloroplasts. (B) A drawing of one of the chloroplasts, showing the inner and outer membranes, as well as the highly folded system of internal membranes containing the green chlorophyll molecules that absorb light energy. (A, courtesy of Preeti Dahiya.)

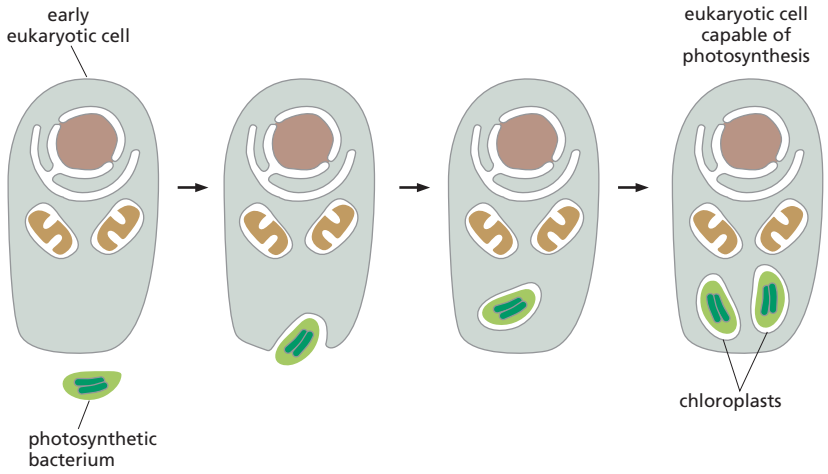


Figure 1–20 Chloroplasts almost certainly evolved from engulfed photosynthetic bacteria. The bacteria are thought to have been taken up by early eukaryotic cells that already contained mitochondria.

oxygen as a molecular by-product. Plant cells can then extract this stored chemical energy when they need it, by oxidizing these sugars in their mitochondria, just as animal cells do. Chloroplasts thus enable plants to get their energy directly from sunlight. And they allow plants to produce the food molecules—and the oxygen—that mitochondria use to generate chemical energy in the form of ATP. How these organelles work together is discussed in Chapter 14.

Like mitochondria, chloroplasts contain their own DNA, reproduce by dividing in two, and are thought to have evolved from bacteria—in this case, from photosynthetic bacteria that were engulfed by an early eukaryotic cell (**Figure 1–20**).

Internal Membranes Create Intracellular Compartments with Different Functions

Nuclei, mitochondria, and chloroplasts are not the only membrane-enclosed organelles inside eukaryotic cells. The cytoplasm contains a profusion of other organelles that are surrounded by single membranes (see Figure 1–7A). Most of these structures are involved with the cell's ability to import raw materials and to export both the useful substances and waste products that are produced by the cell.

The *endoplasmic reticulum* (*ER*) is an irregular maze of interconnected spaces enclosed by a membrane (**Figure 1–21**). It is the site where most cell-membrane components, as well as materials destined for export from the cell, are made. This organelle is enormously enlarged in cells that are specialized for the secretion of proteins. Stacks of flattened, membrane-enclosed sacs constitute the *Golgi apparatus* (**Figure 1–22**), which modifies and packages molecules made in the ER that are destined to be either secreted from the cell or transported to another cell compartment. *Lysosomes* are small, irregularly shaped organelles in which intracellular digestion occurs, releasing nutrients from ingested food particles and breaking down unwanted molecules for either recycling within the cell or excretion from the cell. Indeed, many of the large and small molecules within the cell are constantly being broken down and remade. *Peroxisomes* are small, membrane-enclosed vesicles that provide a safe environment for a variety of reactions in which hydrogen peroxide is used to inactivate toxic molecules. Membranes also form many different types of small *transport vesicles* that ferry materials between one membrane-enclosed organelle and another. All of these membrane-enclosed organelles are sketched in **Figure 1–23A**.

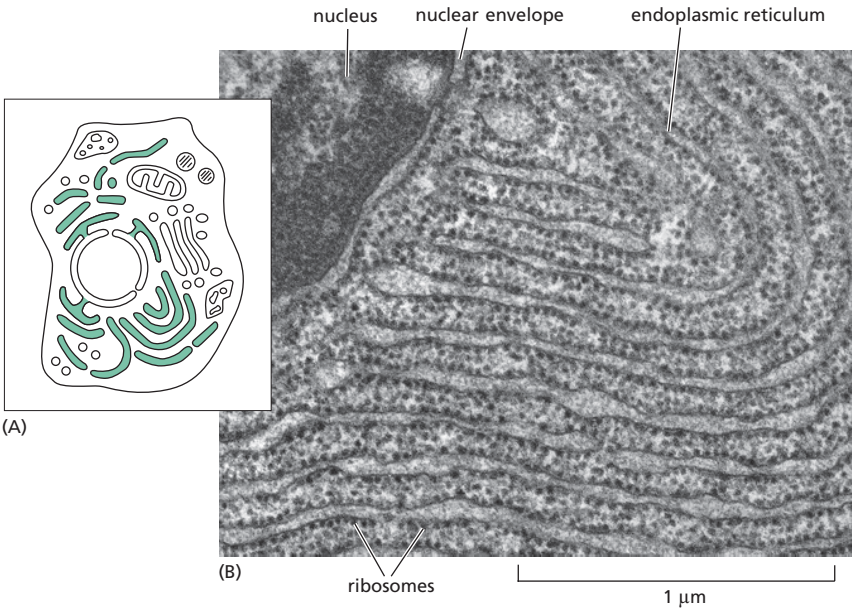


Figure 1–21 The endoplasmic reticulum produces many of the components of a eukaryotic cell. (A) Schematic diagram of an animal cell shows the endoplasmic reticulum (ER) in *green*. (B) Electron micrograph of a thin section of a mammalian pancreatic cell shows a small part of the ER, of which there are vast amounts in this cell type, which is specialized for protein secretion. Note that the ER is continuous with the membranes of the nuclear envelope. The black particles studding the particular region of the ER shown here are ribosomes, structures that translate RNAs into proteins. Because of its appearance, ribosome-coated ER is often called "rough ER" to distinguish it from the "smooth ER," which does not have ribosomes bound to it. (B, courtesy of Lelio Orci.)

A continual exchange of materials takes place between the endoplasmic reticulum, the Golgi apparatus, the lysosomes, and the outside of the cell. The exchange is mediated by transport vesicles that pinch off from the membrane of one organelle and fuse with another, like tiny soap bubbles budding from and rejoining larger bubbles. At the surface of the cell, for example, portions of the plasma membrane tuck inward and pinch off to form vesicles that carry material captured from the external medium into the cell—a process called *endocytosis* (**Figure 1–24**). Animal cells can

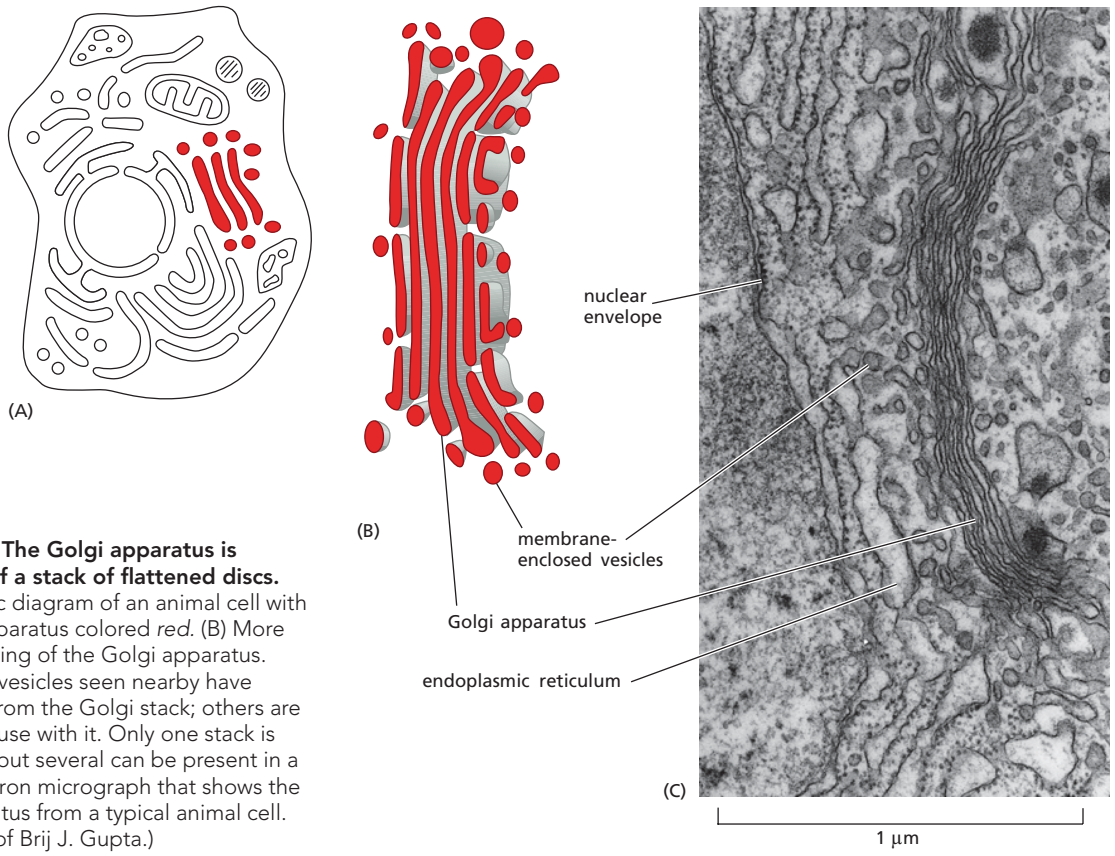


Figure 1–22 The Golgi apparatus is composed of a stack of flattened discs. (A) Schematic diagram of an animal cell with the Golgi apparatus colored *red*. (B) More realistic drawing of the Golgi apparatus. Some of the vesicles seen nearby have pinched off from the Golgi stack; others are destined to fuse with it. Only one stack is shown here, but several can be present in a cell. (C) Electron micrograph that shows the Golgi apparatus from a typical animal cell. (C, courtesy of Brij J. Gupta.)

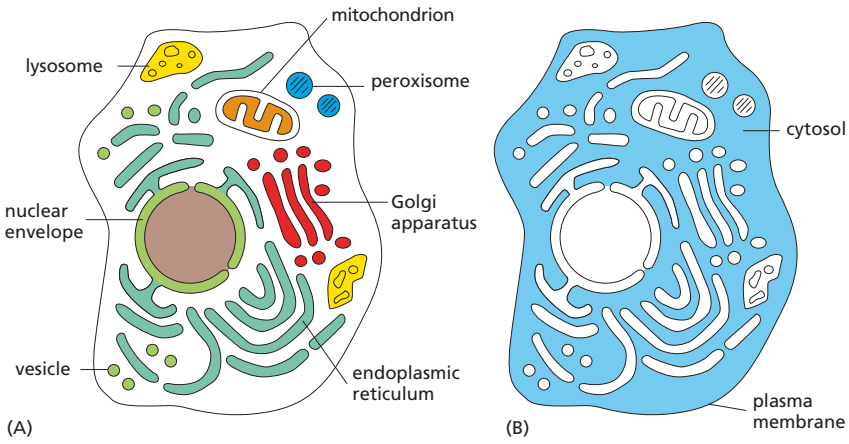


Figure 1–23 Membrane-enclosed organelles are distributed throughout the eukaryotic cell cytoplasm. (A) The membrane-enclosed organelles, shown in different colors, are each specialized to perform a different function. (B) The cytoplasm that fills the space outside of these organelles is called the cytosol (colored *blue*).

engulf very large particles, or even entire foreign cells, by endocytosis. In the reverse process, called *exocytosis*, vesicles from inside the cell fuse with the plasma membrane and release their contents into the external medium (see Figure 1–24); most of the hormones and signal molecules that allow cells to communicate with one another are secreted from cells by exocytosis. How membrane-enclosed organelles move proteins and other molecules from place to place inside the cell is discussed in detail in Chapter 15.

The Cytosol Is a Concentrated Aqueous Gel of Large and Small Molecules

If we were to strip the plasma membrane from a eukaryotic cell and then remove all of its membrane-enclosed organelles, including the nucleus, endoplasmic reticulum, Golgi apparatus, mitochondria, chloroplasts, and so on, we would be left with the **cytosol** (see Figure 1–23B). In other words, the cytosol is the part of the cytoplasm that is not contained within intracellular membranes. In most cells, the cytosol is the largest single compartment. It contains a host of large and small molecules, crowded together so closely that it behaves more like a water-based gel than a liquid solution (**Figure 1–25**). The cytosol is the site of many chemical reactions that are fundamental to the cell's existence. The early steps in the breakdown of nutrient molecules take place in the cytosol, for example, and it is here that most proteins are made by ribosomes.

The Cytoskeleton Is Responsible for Directed Cell Movements

The cytoplasm is not just a structureless soup of chemicals and organelles. Using an electron microscope, one can see that in eukaryotic cells the cytosol is criss-crossed by long, fine filaments. Frequently, the filaments are seen to be anchored at one end to the plasma membrane or to radiate out from a central site adjacent to the nucleus. This system of protein filaments, called the **cytoskeleton**, is composed of three major filament types (**Figure 1–26**). The thinnest of these filaments are the *actin filaments*; they are abundant in all eukaryotic cells but occur in especially large numbers inside muscle cells, where they serve as a central part of the machinery responsible for muscle contraction. The thickest filaments in the cytosol are called *microtubules*, because they have the form of minute hollow tubes. In dividing cells, they become reorganized into a spectacular array that helps pull the duplicated chromosomes in opposite

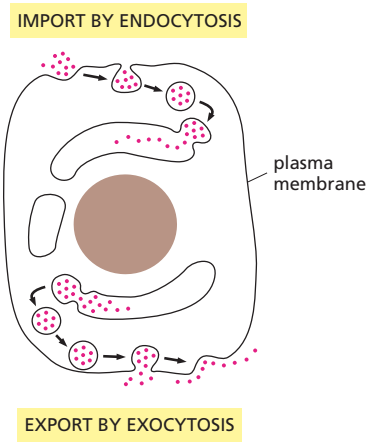


Figure 1–24 Eukaryotic cells engage in continual endocytosis and exocytosis. They import extracellular materials by endocytosis and secrete intracellular materials by exocytosis.

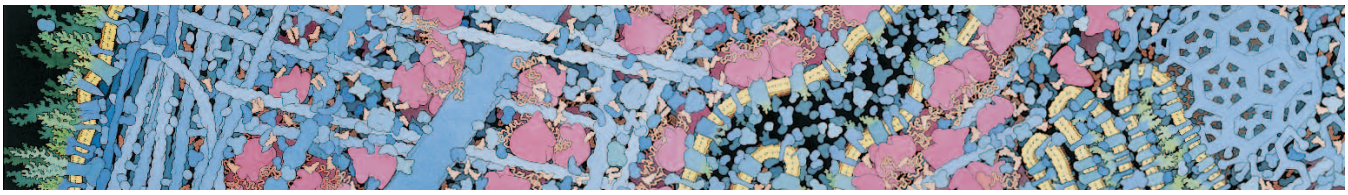


Figure 1–25 The cytoplasm is stuffed with organelles and a host of large and small molecules. This schematic drawing, which extends across two pages and is based on the known sizes and concentrations of molecules in the cytosol, shows how crowded the cytoplasm is. Proteins are *blue*, membrane lipids are *yellow*, and ribosomes and DNA are *pink*. The panorama begins on the far left at the plasma membrane, moves through the endoplasmic reticulum, Golgi apparatus, and a mitochondrion, and ends on the far right in the nucleus. (Courtesy of D. Goodsell.)

directions and distribute them equally to the two daughter cells (**Figure 1–27**). Intermediate in thickness between actin filaments and microtubules are the *intermediate filaments*, which serve to strengthen the cell. These three types of filaments, together with other proteins that attach to them, form a system of girders, ropes, and motors that gives the cell its mechanical strength, controls its shape, and drives and guides its movements (**Movie 1.2** and **Movie 1.3**).

Because the cytoskeleton governs the internal organization of the cell as well as its external features, it is as necessary to a plant cell—boxed in by a tough wall of extracellular matrix—as it is to an animal cell that freely bends, stretches, swims, or crawls. In a plant cell, for example, organelles such as mitochondria are driven in a constant stream around the cell interior along cytoskeletal tracks (**Movie 1.4**). And animal cells and plant cells alike depend on the cytoskeleton to separate their internal components into two daughter cells during cell division (see Figure 1–27).

The cytoskeleton's role in cell division may be its most ancient function. Even bacteria contain proteins that are distantly related to those of eukaryotic actin filaments and microtubules, forming filaments that play a part in prokaryotic cell division. We examine the cytoskeleton in detail in Chapter 17, discuss its role in cell division in Chapter 18, and review how it responds to signals from outside the cell in Chapter 16.

QUESTION 1–5

Suggest a reason why it would be advantageous for eukaryotic cells to evolve elaborate internal membrane systems that allow them to import substances from the outside, as shown in Figure 1–24.

The Cytoplasm Is Far from Static

The cell interior is in constant motion. The cytoskeleton is a dynamic jungle of protein ropes that are continually being strung together and taken apart; its filaments can assemble and then disappear in a matter of minutes. *Motor proteins* use the energy stored in molecules of ATP to trundle along these tracks and cables, carrying organelles and proteins throughout the cytoplasm, and racing across the width of the cell in seconds. In addition, the large and small molecules that fill every free space in the cell are swept to and fro by random thermal motion, constantly colliding with one another and with other structures in the cell's crowded cytoplasm (**Movie 1–5**).

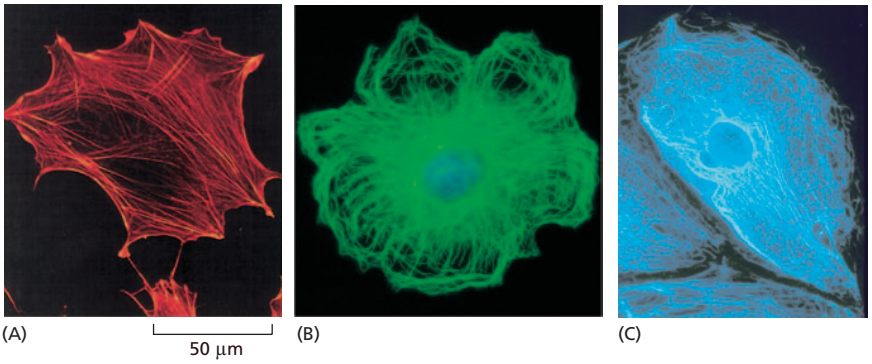
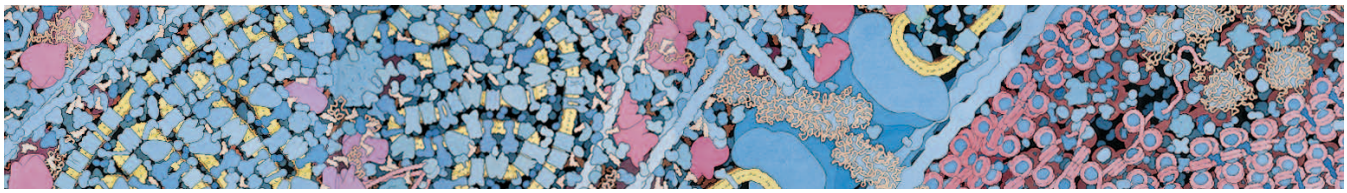


Figure 1–26 The cytoskeleton is a network of protein filaments that criss-crosses the cytoplasm of eukaryotic cells. The three major types of filaments can be detected using different fluorescent stains. Shown here are (A) actin filaments, (B) microtubules, and (C) intermediate filaments. (A, courtesy of Simon Barry and Chris D'Lacey; B, courtesy of Nancy Kedersha; C, courtesy of Clive Lloyd.)



Of course, neither the bustling nature of the cell's interior nor the details of cell structure were appreciated when scientists first peered at cells in a microscope; our knowledge of cell structure accumulated slowly. A few of the key discoveries are listed in **Table 1–1**. In addition, **Panel 1–2** summarizes the differences between animal, plant, and bacterial cells.

Eukaryotic Cells May Have Originated as Predators

Eukaryotic cells are typically 10 times the length and 1000 times the volume of prokaryotic cells, although there is huge size variation within each category. They also possess a whole collection of features—a cytoskeleton, mitochondria, and other organelles—that set them apart from bacteria and archaea.

When and how eukaryotes evolved these systems remains something of a mystery. Although eukaryotes, bacteria, and archaea must have diverged from one another very early in the history of life on Earth (discussed in Chapter 14), the eukaryotes did not acquire all of their distinctive features at the same time (**Figure 1–28**). According to one theory, the ancestral eukaryotic cell was a predator that fed by capturing other cells. Such a way of life requires a large size, a flexible membrane, and a cytoskeleton to help the cell move and eat. The nuclear compartment may have evolved to keep the DNA segregated from this physical and chemical hurly-burly, so as to allow more delicate and complex control of the way the cell reads out its genetic information.

Such a primitive cell, witha nucleus and cytoskeleton, was most likely the sort of cell that engulfed the free-living, oxygen-consuming bacteria that were the likely ancestors of the mitochondria (see Figure 1–18). This partnership is thought to have been established 1.5 billion years ago, when the Earth's atmosphere first became rich in oxygen. A subset of

QUESTION 1–6

Discuss the relative advantages and disadvantages of light and electron microscopy. How could you best visualize (a) a living skin cell, (b) a yeast mitochondrion, (c) a bacterium, and (d) a microtubule?

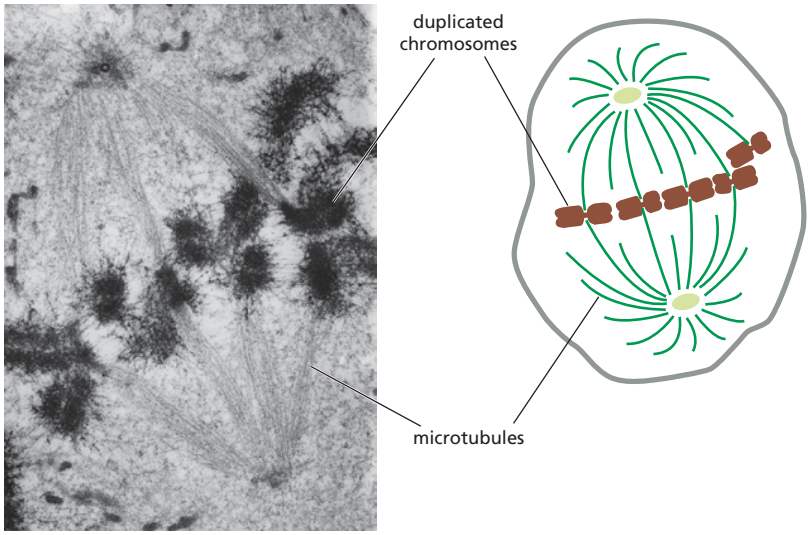


Figure 1–27 Microtubules help distribute the chromosomes in a dividing cell. When a cell divides, its nuclear envelope breaks down and its DNA condenses into visible chromosomes, each of which has duplicated to form a pair of conjoined chromosomes that will ultimately be pulled apart into separate cells by microtubules. In the transmission electron micrograph (*left*), the microtubules are seen to radiate from foci at opposite ends of the dividing cell. (Photomicrograph courtesy of Conly L. Rieder.)

TABLE 1–1 HISTORICAL LANDMARKS IN DETERMINING CELL STRUCTURE

1665	Hooke uses a primitive microscope to describe small chambers in sections of cork that he calls "cells."
1674	Leeuwenhoek reports his discovery of protozoa. Nine years later, he sees bacteria for the first time.
1833	Brown publishes his microscopic observations of orchids, clearly describing the cell nucleus.
1839	Schleiden and Schwann propose the cell theory, stating that the nucleated cell is the universal building block of plant and animal tissues.
1857	Kölliker describes mitochondria in muscle cells.
1879	Flemming describes with great clarity chromosome behavior during mitosis in animal cells.
1881	Cajal and other histologists develop staining methods that reveal the structure of nerve cells and the organization of neural tissue.
1898	Golgi first sees and describes the Golgi apparatus by staining cells with silver nitrate.
1902	Boveri links chromosomes and heredity by observing chromosome behavior during sexual reproduction.
1952	Palade, Porter, and Sjöstrand develop methods of electron microscopy that enable many intracellular structures to be seen for the first time. In one of the first applications of these techniques, Huxley shows that muscle contains arrays of protein filaments—the first evidence of a cytoskeleton.
1957	Robertson describes the bilayer structure of the cell membrane, seen for the first time in the electron microscope.
1960	Kendrew describes the first detailed protein structure (sperm whale myoglobin) to a resolution of 0.2 nm using X-ray crystallography. Perutz proposes a lower-resolution structure for hemoglobin.
1965	Christian de Duve and his colleagues use a cell-fractionation technique to separate peroxisomes, mitochondria, and lysosomes from a preparation of rat liver.
1968	Petran and collaborators make the first confocal microscope.
1970	Frye and Edidin use fluorescent antibodies to show that plasma membrane molecules can diffuse in the plane of the membrane, indicating that cell membranes are fluid.
1974	Lazarides and Weber use fluorescent antibodies to stain the cytoskeleton.
1994	Chalfie and collaborators introduce green fluorescent protein (GFP) as a marker to follow the behavior of proteins in living cells.

these cells later acquired chloroplasts by engulfing photosynthetic bacteria (see Figure 1–20). The likely history of these endosymbiotic events is illustrated in Figure 1–28.

That single-celled eukaryotes can prey upon and swallow other cells is borne out by the behavior of many of the free-living, actively motile

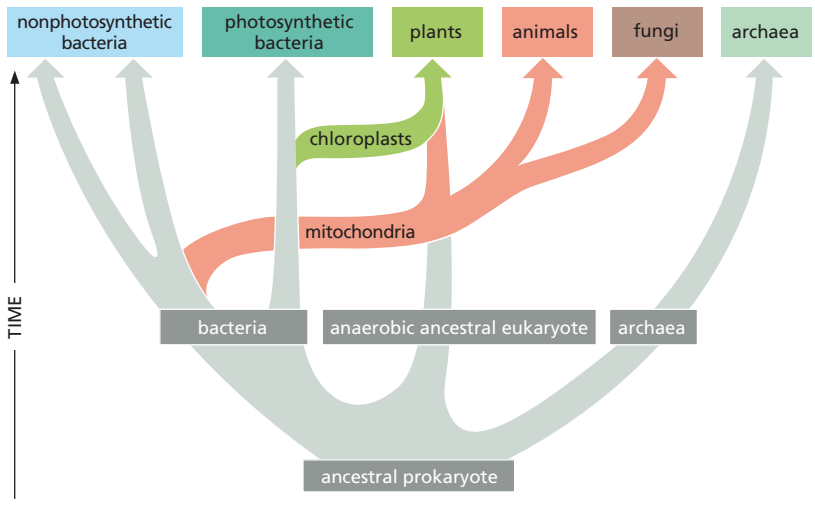
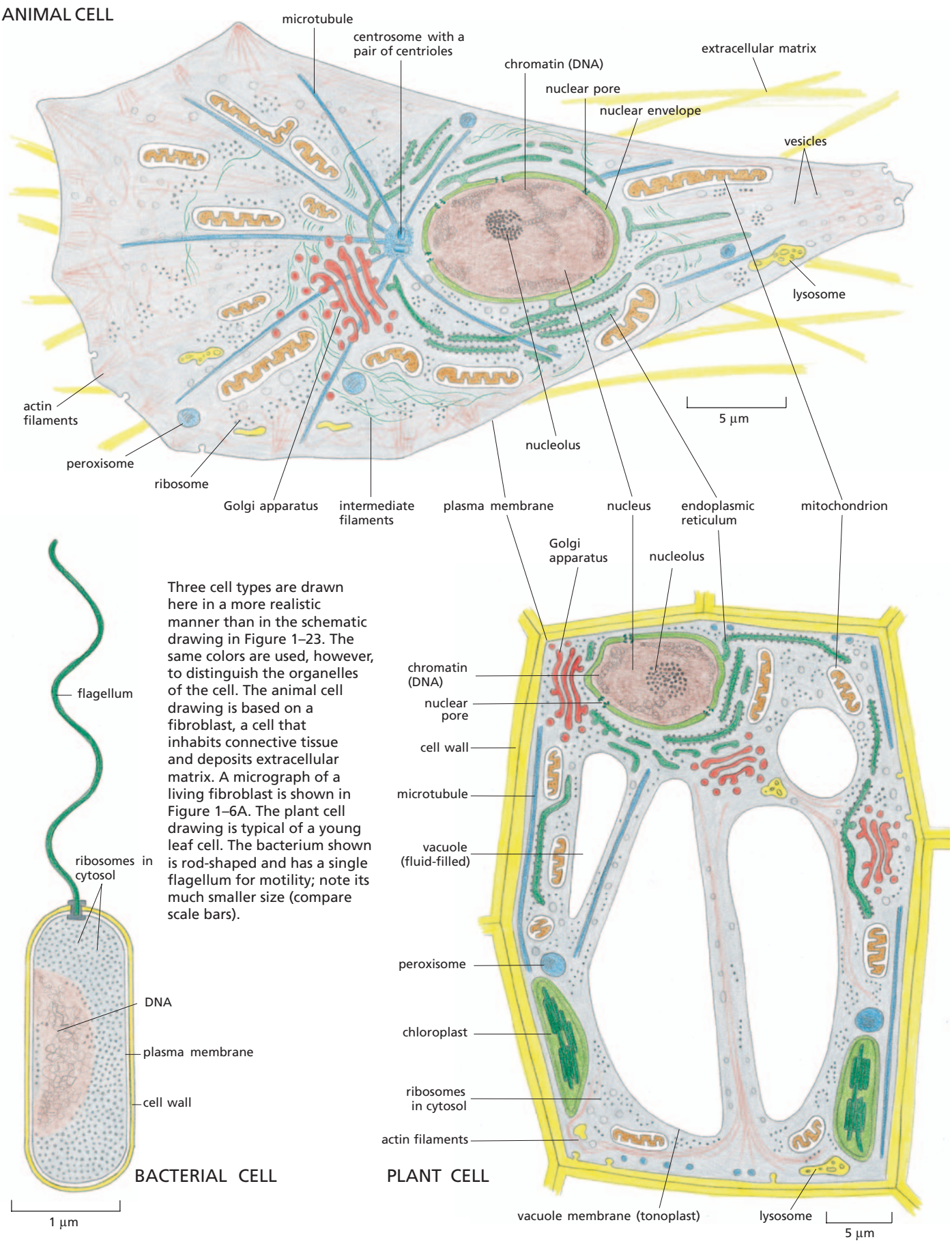


Figure 1–28 Where did eukaryotes come from? The eukaryotic, bacterial, and archaean lineages diverged from one another very early in the evolution of life on Earth. Some time later, eukaryotes are thought to have acquired mitochondria; later still, a subset of eukaryotes acquired chloroplasts. Mitochondria are essentially the same in plants, animals, and fungi, and therefore were presumably acquired before these lines diverged.



Three cell types are drawn here in a more realistic manner than in the schematic drawing in Figure 1–23. The same colors are used, however, to distinguish the organelles of the cell. The animal cell drawing is based on a fibroblast, a cell that inhabits connective tissue and deposits extracellular matrix. A micrograph of a living fibroblast is shown in Figure 1–6A. The plant cell drawing is typical of a young leaf cell. The bacterium shown is rod-shaped and has a single flagellum for motility; note its much smaller size (compare scale bars).

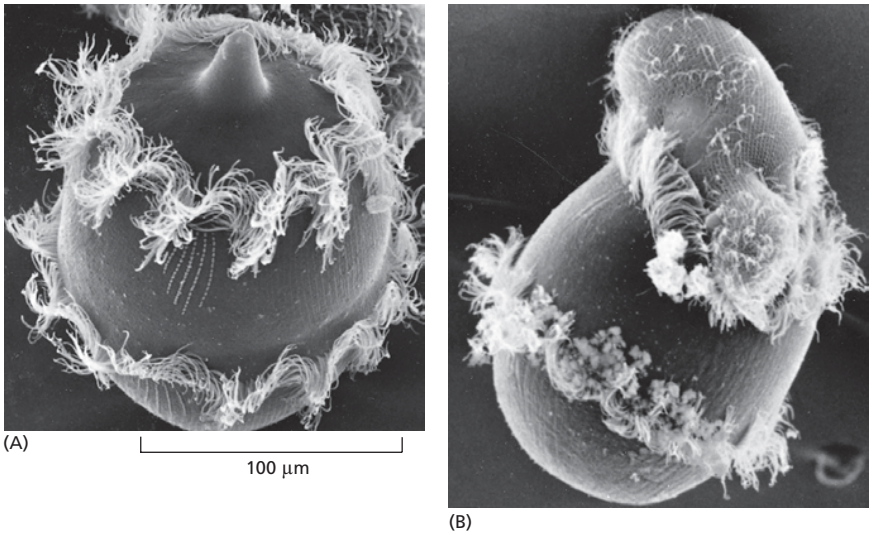


Figure 1–29 One protozoan eats another. (A) The scanning electron micrograph shows *Didinium* on its own, with its circumferential rings of beating cilia and its "snout" at the top. (B) *Didinium* is seen ingesting another ciliated protozoan, a *Paramecium*. (Courtesy of D. Barlow.)

microorganisms called **protozoans**. *Didinium*, for example, is a large, carnivorous protozoan with a diameter of about 150 μm—roughly 10 times that of the average human cell. It has a globular body encircled by two fringes of cilia, and its front end is flattened except for a single protrusion rather like a snout (**Figure 1–29A**). *Didinium* swims at high speed by means of its beating cilia. When it encounters a suitable prey, usually another type of protozoan, it releases numerous small, paralyzing darts from its snout region. *Didinium* then attaches to and devours the other cell, inverting like a hollow ball to engulf its victim, which can be almost as large as itself (**Figure 1–29B**).

Not all protozoans are predators. They can be photosynthetic or carnivorous, motile or sedentary. Their anatomy is often elaborate and includes such structures as sensory bristles, photoreceptors, beating cilia, stalklike appendages, mouthparts, stinging darts, and musclelike contractile bundles (**Figure 1–30**). Although they are single cells, protozoans can be as intricate and versatile as many multicellular organisms. Much remains to be learned about fundamental cell biology from studies of these fascinating life-forms.

MODEL ORGANISMS

All cells are thought to be descended from a common ancestor, whose fundamental properties have been conserved through evolution. Thus knowledge gained from the study of one organism contributes to our understanding of others, including ourselves. But certain organisms are easier than others to study in the laboratory. Some reproduce rapidly and are convenient for genetic manipulations; others are multicellular but transparent, so that one can directly watch the development of all their internal tissues and organs. For reasons such as these, large communities of biologists have become dedicated to studying different aspects of the biology of a few chosen species, pooling their knowledge to gain a deeper understanding than could be achieved if their efforts were spread over many different species. Although the roster of these representative organisms is continually expanding, a few stand out in terms of the breadth and depth of information that has been accumulated about them over the years—knowledge that contributes to our understanding of how all cells work. In this section, we examine some of these **model organisms** and review the benefits that each offers to the study of cell biology and, in many cases, to the promotion of human health.

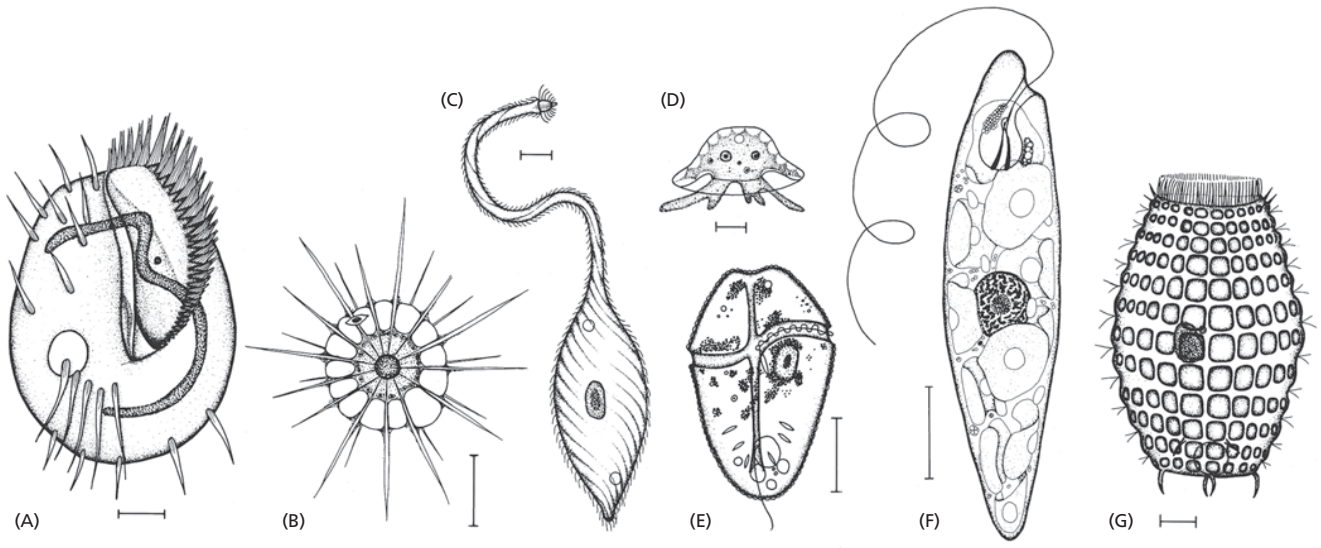


Figure 1–30 An assortment of protozoans illustrates the enormous variety within this class of single-celled microorganisms. These drawings are done to different scales, but in each case the scale bar represents 10 μm. The organisms in (A), (C), and (G) are ciliates; (B) is a heliozoan; (D) is an amoeba; (E) is a dinoflagellate; and (F) is a euglenoid. To see the latter in action, watch Movie 1.6. (From M.A. Sleigh, The Biology of Protozoa. London: Edward Arnold, 1973. With permission from Edward Arnold.)

Molecular Biologists Have Focused on *E. coli*

In molecular terms, we understand the workings of the bacterium *Escherichia coli—E. coli* for short—more thoroughly than those of any other living organism (see Figure 1–10). This small, rod-shaped cell normally lives in the gut of humans and other vertebrates, but it also grows happily and reproduces rapidly in a simple nutrient broth in a culture bottle.

Most of our knowledge of the fundamental mechanisms of life—including how cells replicate their DNA and how they decode these genetic instructions to make proteins—has come from studies of *E. coli*. Subsequent research has confirmed that these basic processes occur in essentially the same way in our own cells as they do in *E. coli*.

Brewer's Yeast Is a Simple Eukaryotic Cell

We tend to be preoccupied with eukaryotes because we are eukaryotes ourselves. But human cells are complicated and reproduce relatively slowly. To get a handle on the fundamental biology of eukaryotic cells, it is often advantageous to study a simpler cell that reproduces more rapidly. A popular choice has been the budding yeast *Saccharomyces cerevisiae* (**Figure 1–31**)—the same microorganism that is used for brewing beer and baking bread.

S. cerevisiae is a small, single-celled fungus that is at least as closely related to animals as it is to plants. Like other fungi, it has a rigid cell wall, is relatively immobile, and possesses mitochondria but not chloroplasts. When nutrients are plentiful, *S. cerevisiae* reproduces almost as rapidly as a bacterium. Yet it carries out all the basic tasks that every eukaryotic cell must perform. Genetic and biochemical studies in yeast have been crucial to understanding many basic mechanisms in eukaryotic cells, including the cell-division cycle—the chain of events by which the nucleus and all the other components of a cell are duplicated and parceled out to create two daughter cells. The machinery that governs cell division has been

QUESTION 1–7

Your next-door neighbor has donated $100 in support of cancer research and is horrified to learn that her money is being spent on studying brewer's yeast. How could you put her mind at ease?

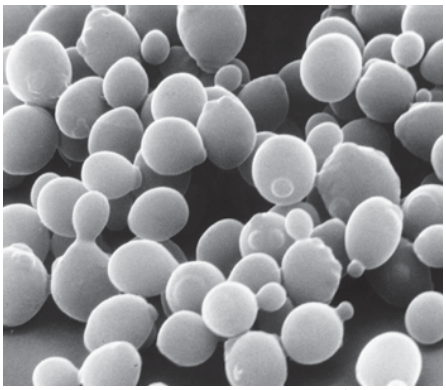


Figure 1–31 The yeast *Saccharomyces cerevisiae* is a model eukaryote. In this scanning electron micrograph, a few yeast cells are seen in the process of dividing, which they do by budding. Another micrograph of the same species is shown in Figure 1–13. (Courtesy of Ira Herskowitz and Eric Schabatach.)

so well conserved over the course of evolution that many of its components can function interchangeably in yeast and human cells (see **How We Know**, pp. 30–31). Darwin himself would no doubt have been stunned by this dramatic example of evolutionary conservation.

Arabidopsis Has Been Chosen as a Model Plant

The large multicellular organisms that we see around us—both plants and animals—seem fantastically varied, but they are much closer to one another in their evolutionary origins, and more similar in their basic cell biology, than the great host of microscopic single-celled organisms. Whereas bacteria, archaea, and eukaryotes separated from each other more than 3 billion years ago, plants, animals, and fungi diverged only about 1.5 billion years ago, and the different species of flowering plants less than 200 million years ago.

The close evolutionary relationship among all flowering plants means that we can gain insight into their cell and molecular biology by focusing on just a few convenient species for detailed analysis. Out of the several hundred thousand species of flowering plants on Earth today, molecular biologists have focused their efforts on a small weed, the common wall cress *Arabidopsis thaliana* (**Figure 1–32**), which can be grown indoors in large numbers: one plant can produce thousands of offspring within 8–10 weeks. Because genes found in *Arabidopsis* have counterparts in agricultural species, studying this simple weed provides insights into the development and physiology of the crop plants upon which our lives depend, as well as into the evolution of all the other plant species that dominate nearly every ecosystem on Earth.

Model Animals Include Flies, Fish, Worms, and Mice

Multicellular animals account for the majority of all named species of living organisms, and the majority of animal species are insects. It is fitting, therefore, that an insect, the small fruit fly *Drosophila melanogaster* (**Figure 1–33**), should occupy a central place in biological research. In fact, the foundations of classical genetics were built to a large extent on studies of this insect. More than 80 years ago, genetic analysis of the fruit fly provided definitive proof that genes—the units of heredity—are carried on chromosomes. In more recent times, *Drosophila*, more than any other organism, has shown us how the genetic instructions encoded in DNA molecules direct the development of a fertilized egg cell (or *zygote*) into an adult multicellular organism containing vast numbers of different cell types organized in a precise and predictable way. *Drosophila* mutants with body parts strangely misplaced or oddly patterned have provided the key to identifying and characterizing the genes that are needed to make a properly structured adult body, with gut, wings, legs, eyes, and all the other bits and pieces in their correct places. These genes—which are copied and passed on to every cell in the body—define how each cell will behave in its social interactions with its sisters and cousins, thus controlling the structures that the cells can create. Moreover, the genes

Figure 1–32 *Arabidopsis thaliana*, the common wall cress, is a model plant. This small weed has become the favorite organism of plant molecular and developmental biologists. (Courtesy of Toni Hayden and the John Innes Centre.)

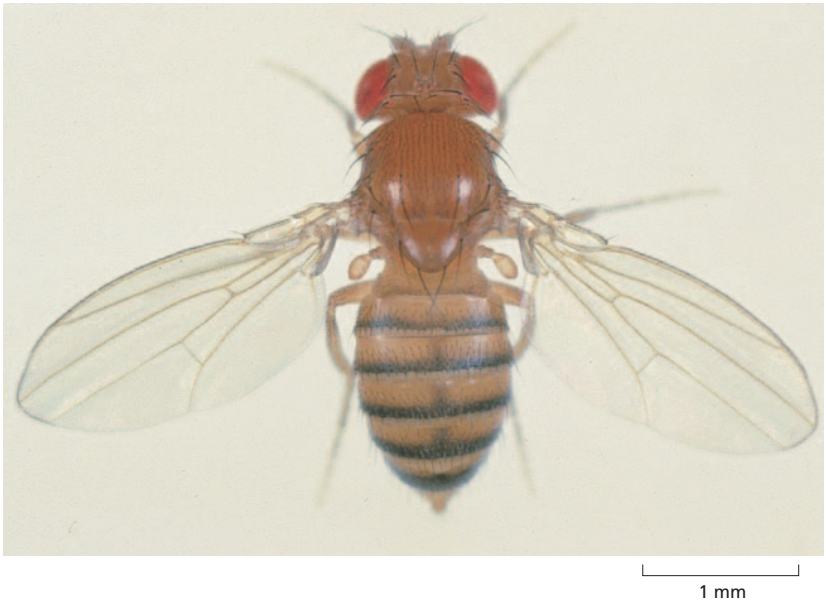


Figure 1–33 *Drosophila melanogaster* is a favorite among developmental biologists and geneticists. Molecular genetic studies on this small fly have provided a key to the understanding of how all animals develop. (Courtesy of E.B. Lewis.)

responsible for the development of *Drosophila* have turned out to be amazingly similar to those of humans—far more similar than one would suspect from outward appearances. Thus the fly serves as a valuable model for studying human development and disease.

Another widely studied organism is the nematode worm *Caenorhabditis elegans* (**Figure 1–34**), a harmless relative of the eelworms that attack the roots of crops. Smaller and simpler than *Drosophila*, this creature develops with clockwork precision from a fertilized egg cell into an adult that has exactly 959 body cells (plus a variable number of egg and sperm cells)—an unusual degree of regularity for an animal. We now have a minutely detailed description of the sequence of events by which this occurs—as the cells divide, move, and become specialized according to strict and predictable rules. And a wealth of mutants are available for testing how the worm's genes direct this developmental ballet. Some 70% of human genes have some counterpart in the worm, and *C. elegans*, like *Drosophila*, has proved to be a valuable model for many of the developmental processes that occur in our own bodies. Studies of nematode development, for example, have led to a detailed molecular understanding of *apoptosis*, a form of programmed cell death by which surplus cells are disposed of in all animals—a topic of great importance for cancer research (discussed in Chapters 18 and 20).

Another organism that is providing molecular insights into developmental processes, particularly in vertebrates, is the *zebrafish*. Because this

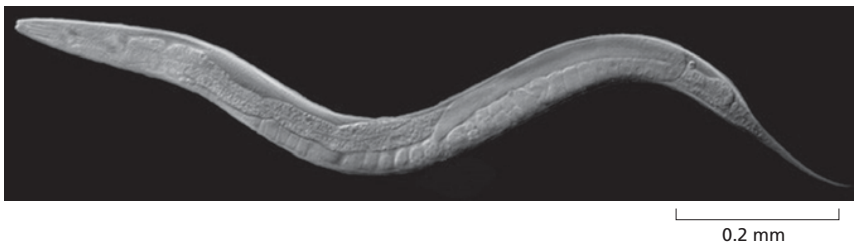


Figure 1–34 *Caenorhabditis elegans* is a small nematode worm that normally lives in the soil. Most individuals are hermaphrodites, producing both sperm and eggs (the latter of which can be seen along the underside of the animal). *C. elegans* was the first multicellular organism to have its complete genome sequenced. (Courtesy of Maria Gallegos.)

LIFE'S COMMON MECHANISMS

All living things are made of cells, and all cells—as we have discussed in this chapter—are fundamentally similar inside: they store their genetic instructions in DNA molecules, which direct the production of RNA molecules, which in turn direct the production of proteins. It is largely the proteins that carry out the cell's chemical reactions, give the cell its shape, and control its behavior. But how deep do these similarities between cells—and the organisms they comprise—really run? Are parts from one organism interchangeable with parts from another? Would an enzyme that breaks down glucose in a bacterium be able to digest the same sugar if it were placed inside a yeast cell or a cell from a lobster or a human? What about the molecular machines that copy and interpret genetic information? Are they functionally equivalent from one organism to another? Insights have come from many sources, but the most stunning and dramatic answer came from experiments performed on humble yeast cells. These studies, which shocked the biological community, focused on one of the most fundamental processes of life—cell division.

Division and discovery

All cells come from other cells, and the only way to make a new cell is through division of a preexisting one. To reproduce, a parent cell must execute an orderly sequence of reactions, through which it duplicates its contents and divides in two. This critical process of duplication and division—known as the *cell-division cycle*, or *cell cycle* for short—is complex and carefully controlled. Defects in any of the proteins involved can be devastating to the cell.

Fortunately for biologists, this acute reliance on crucial proteins makes them easy to identify and study. If a protein is essential for a given process, a mutation that results in an abnormal protein—or in no protein at all—can prevent the cell from carrying out the process. By isolating organisms that are defective in their cell-division cycle, scientists have worked backward to discover the proteins that control progress through the cycle.

The study of cell-cycle mutants has been particularly successful in yeasts. Yeasts are unicellular fungi and are popular organisms for such genetic studies. They are eukaryotes, like us, but they are small, simple, rapidly reproducing, and easy to manipulate genetically. Yeast mutants that are defective in their ability to complete cell division have led to the discovery of many genes that control the cell-division cycle—the so-called *Cdc* genes—and have provided a detailed understanding of how these genes, and the proteins they encode, actually work.

Paul Nurse and his colleagues used this approach to identify *Cdc* genes in the yeast *Schizosaccharomyces pombe*, which is named after the African beer from which it was first isolated. *S. pombe* is a rod-shaped cell, which grows by elongation at its ends and divides by fission into two, through the formation of a partition in the center of the rod. The researchers found that one of the *Cdc* genes they had identified, called *Cdc2*, was required to trigger several key events in the cell-division cycle. When that gene was inactivated by a mutation, the yeast cells would not divide. And when the cells were provided with a normal copy of the gene, their ability to reproduce was restored.

It's obvious that replacing a faulty *Cdc2* gene in *S. pombe* with a functioning *Cdc2* gene from the same yeast should repair the damage and enable the cell to divide normally. But what about using a similar cell-division gene from a different organism? That's the question the Nurse team tackled next.

Next of kin

Saccharomyces cerevisiae is another kind of yeast and is one of a handful of model organisms biologists have chosen to study to expand their understanding of how cells work. Also used to brew beer, *S. cerevisiae* divides by forming a small bud that grows steadily until it separates from the mother cell (see Figures 1–13 and 1–31). Although *S. cerevisiae* and *S. pombe* differ in their style of division, both rely on a complex network of interacting proteins to get the job done. But could the proteins from one type of yeast substitute for those of the other?

To find out, Nurse and his colleagues prepared DNA from healthy *S. cerevisiae*, and they introduced this DNA into *S. pombe* cells that contained a mutation in the *Cdc2* gene that kept the cells from dividing when the temperature was elevated. And they found that some of the mutant *S. pombe* cells regained the ability to proliferate when warm. If spread onto a culture plate containing a growth medium, the rescued cells could divide again and again to form visible colonies, each containing millions of individual yeast cells (**Figure 1–35**). Upon closer examination, the researchers discovered that these "rescued" yeast cells had received a fragment of DNA that contained the *S. cerevisiae* version of *Cdc2*—a gene that had been discovered in pioneering studies of the cell cycle by Lee Hartwell and colleagues.

The result was exciting, but perhaps not all that surprising. After all, how different can one yeast be from another? A more demanding test would be to use DNA from a more distant relative. So Nurse's team repeated the experiment, this time using human DNA. And the results were the same. The human equivalent of the

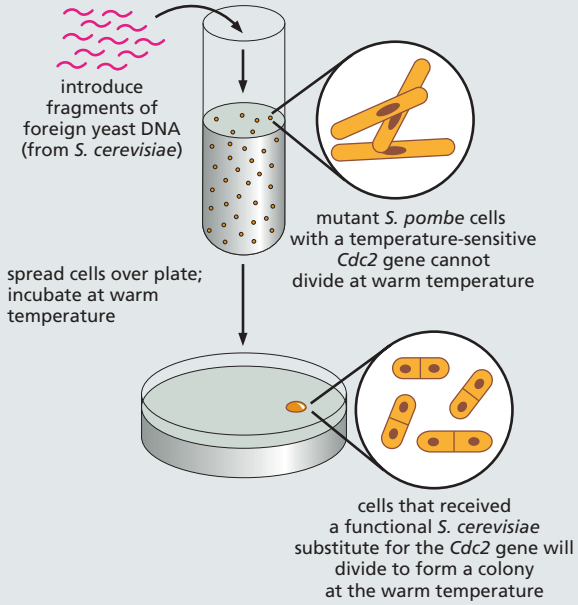


Figure 1–35 *S. pombe* mutants defective in a cell-cycle gene can be rescued by the equivalent gene from *S. cerevisiae*. DNA is collected from *S. cerevisiae* and broken into large fragments, which are introduced into a culture of mutant *S. pombe* cells dividing at room temperature. We discuss how DNA can be manipulated and transferred into different cell types in Chapter 10. These yeast cells are then spread onto a plate containing a suitable growth medium and are incubated at a warm temperature, at which the mutant Cdc2 protein is inactive. The rare cells that survive and proliferate on these plates have been rescued by incorporation of a foreign gene that allows them to divide normally at the higher temperature.

S. pombe Cdc2 gene could rescue the mutant yeast cells, allowing them to divide normally.

Gene reading

This result was much more surprising—even to Nurse. The ancestors of yeast and humans diverged some 1.5 billion years ago. So it was hard to believe that these two organisms would orchestrate cell division in such a similar way. But the results clearly showed that the human and yeast proteins are functionally equivalent. Indeed, Nurse and colleagues demonstrated that the proteins are almost exactly the same size and consist of amino acids strung together in a very similar order; the human Cdc2 protein is identical to the *S. pombe* Cdc2 protein in 63% of its amino acids and is identical to the equivalent protein from *S. cerevisiae* in 58% of its amino acids (**Figure 1–36**). Together with Tim Hunt, who discovered a different cell-cycle protein called cyclin, Nurse and Hartwell shared a 2001 Nobel Prize for their studies of key regulators of the cell cycle.

The Nurse experiments showed that proteins from very different eukaryotes can be functionally interchangeable and suggested that the cell cycle is controlled in a similar fashion in every eukaryotic organism alive today. Apparently, the proteins that orchestrate the cycle in eukaryotes are so fundamentally important that they have been conserved almost unchanged over more than a billion years of eukaryotic evolution.

The same experiment also highlights another, even more basic, point. The mutant yeast cells were rescued, not by direct injection of the human protein, but by introduction of a piece of human DNA. Thus the yeast cells could read and use this information correctly, indicating that, in eukaryotes, the molecular machinery for reading the information encoded in DNA is also similar from cell to cell and from organism to organism. A yeast cell has all the equipment it needs to interpret the instructions encoded in a human gene and to use that information to direct the production of a fully functional human protein.

The story of Cdc2 is just one of thousands of examples of how research in yeast cells has provided critical insights into human biology. Although it may sound paradoxical, the shortest, most efficient path to improving human health will often begin with detailed studies of the biology of simple organisms such as brewer's or baker's yeast.

```
human          ···FGLARAFGIPIRVYTHEVVTLWYRSPEVLLGSARYSTPVDIWSIGTIFAELATKLPLFHGDSEIDQLFRIPRALGTPNNEVWPEVESLQDYKNTFP···
S. pombe       ···FGLARSFGVPLRNYTHEIVTLWYRAPEVLLGSRHYSTGVDIWSVGCIFAENIRRSPLFPGDSEIDEIFKIPQVLGTPNEEVWPGVTLLQDYKSTFP···
S. cerevisiae  ···FGLARAFGVPLRAYTHEIVTLWYRAPEVLLGGKQYSTGVDTWSIGCIFAEHCNRLPIFSGDSEIDQIFKIPRVLGTPNEAIWPDIVYLPDFKPSFP···
```

Figure 1–36 The cell-division-cycle proteins from yeasts and human are very similar in their amino acid sequences. Identities between the amino acid sequences of a region of the human Cdc2 protein and a similar region of the equivalent proteins in *S. pombe* and *S. cerevisiae* are indicated by *green* shading. Each amino acid is represented by a single letter.

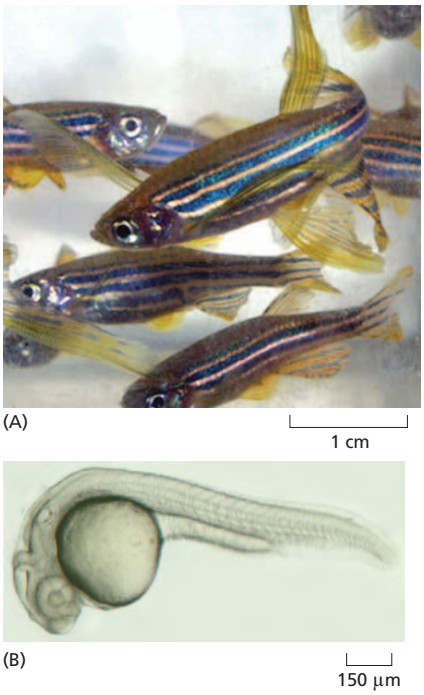


Figure 1–37 Zebrafish are popular models for studies of vertebrate development. (A) These small, hardy, tropical fish are a staple in many home aquaria. But they are also ideal for developmental studies, as their transparent embryos (B) make it easy to observe cells moving and changing their characters in the living organism as it develops. (A, courtesy of Steve Baskauf; B, from M. Rhinn et al., *Neural Dev.* 4:12, 2009. With permission from BioMed Central Ltd.)

creature is transparent for the first 2 weeks of its life, it provides an ideal system in which to observe how cells behave during development in a living animal (**Figure 1–37**).

Mammals are among the most complex of animals, and the mouse has long been used as the model organism in which to study mammalian genetics, development, immunology, and cell biology. Thanks to modern molecular biological techniques, it is now possible to breed mice with deliberately engineered mutations in any specific gene, or with artificially constructed genes introduced into them. In this way, one can test what a given gene is required for and how it functions. Almost every human gene has a counterpart in the mouse, with a similar DNA sequence and function. Thus, this animal has proven an excellent model for studying genes that are important in both human health and disease.

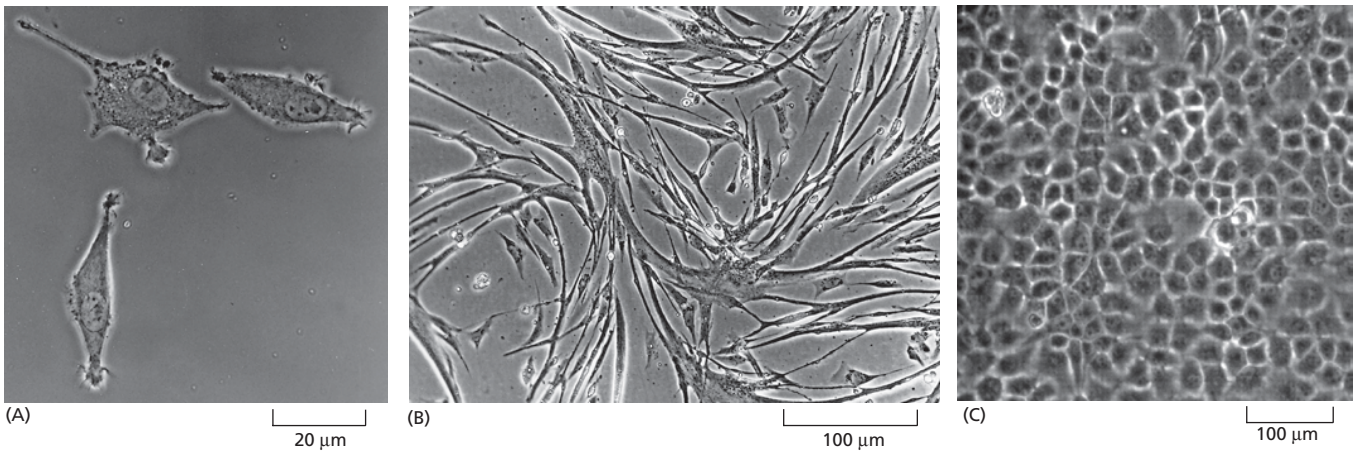
Biologists Also Directly Study Human Beings and Their Cells

Humans are not mice—or fish or flies or worms or yeast—and so we also study human beings themselves. Like bacteria or yeast, our individual cells can be harvested and grown in culture, where we can study their biology and more closely examine the genes that govern their functions. Given the appropriate surroundings, most human cells—indeed, most cells from animals or plants—will survive, proliferate, and even express specialized properties in a culture dish. Experiments using such cultured cells are sometimes said to be carried out *in vitro* (literally, "in glass") to contrast them with experiments on intact organisms, which are said to be carried out *in vivo* (literally, "in the living").

Although not true for all types of cells, many types of cells grown in culture display the differentiated properties appropriate to their origin: fibroblasts, a major cell type in connective tissue, continue to secrete collagen; cells derived from embryonic skeletal muscle fuse to form muscle fibers, which contract spontaneously in the culture dish; nerve cells extend axons that are electrically excitable and make synapses with other nerve cells; and epithelial cells form extensive sheets, with many of the properties of an intact epithelium (**Figure 1–38**). Because cultured cells are maintained in a controlled environment, they are accessible to study in ways that are often not possible *in vivo*. For example, cultured cells can be exposed to hormones or growth factors, and the effects that these signal molecules have on the shape or behavior of the cells can be easily explored.

In addition to studying human cells in culture, humans are also examined directly in clinics. Much of the research on human biology has been driven by medical interests, and the medical database on the human species is enormous. Although naturally occurring mutations in any given human gene are rare, the consequences of many mutations are well documented. This is because humans are unique among animals in that they report and record their own genetic defects: in no other species are billions of individuals so intensively examined, described, and investigated.

Nevertheless, the extent of our ignorance is still daunting. The mammalian body is enormously complex, being formed from thousands of



billions of cells, and one might despair of ever understanding how the DNA in a fertilized mouse egg cell makes it generate a mouse rather than a fish, or how the DNA in a human egg cell directs the development of a human rather than a mouse. Yet the revelations of molecular biology have made the task seem eminently approachable. As much as anything, this new optimism has come from the realization that the genes of one type of animal have close counterparts in most other types of animals, apparently serving similar functions (**Figure 1–39**). We all have a common evolutionary origin, and under the surface it seems that we share the same molecular mechanisms. Flies, worms, fish, mice, and humans thus provide a key to understanding how animals in general are made and how their cells work.

Figure 1–38 Cells in culture often display properties that reflect their origin. (A) Phase-contrast micrograph of fibroblasts in culture. (B) Micrograph of cultured myoblasts, some of which have fused to form multinucleate muscle cells that spontaneously contract in culture. (C) Cultured epithelial cells forming a cell sheet. **Movie 1.7** shows a single heart muscle cell beating in culture. (A, courtesy of Daniel Zicha; B, courtesy of Rosalind Zalin; C, from K.B. Chua et al., *Proc. Natl Acad. Sci. USA* 104:11424–11429, 2007, with permission from the National Academy of Sciences.)

Comparing Genome Sequences Reveals Life's Common Heritage

At a molecular level, evolutionary change has been remarkably slow. We can see in present-day organisms many features that have been preserved through more than 3 billion years of life on Earth—about one-fifth of the age of the universe. This evolutionary conservatism provides the foundation on which the study of molecular biology is built. To set the scene for the chapters that follow, therefore, we end this chapter by considering a little more closely the family relationships and basic similarities among all living things. This topic has been dramatically clarified in the past few years by technological advances that have allowed us to determine the complete genome sequences of thousands of organisms, including our own species (as discussed in more detail in Chapter 9).

The first thing we note when we look at an organism's genome is its overall size and how many genes it packs into that length of DNA. Prokaryotes carry very little superfluous genetic baggage and, nucleotide-

Figure 1–39 Different species share similar genes. The human baby and the mouse shown here have similar white patches on their foreheads because they both have defects in the same gene (called *Kit*), which is required for the development and maintenance of some pigment cells. (Courtesy of R.A. Fleischman, from *Proc. Natl Acad. Sci. USA* 88:10885–10889, 1991. With permission from the National Academy of Sciences.)

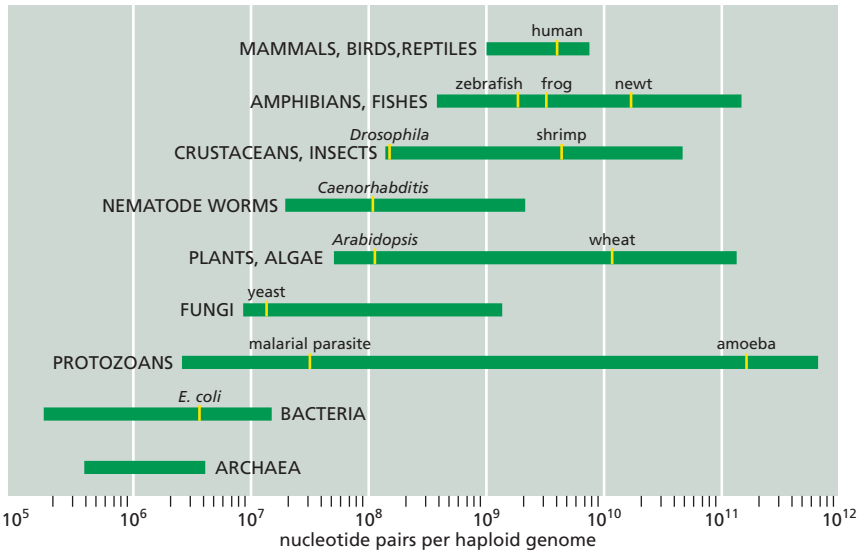


Figure 1–40 Organisms vary enormously in the size of their genomes. Genome size is measured in nucleotide pairs of DNA per haploid genome, that is, per single copy of the genome. (The body cells of sexually reproducing organisms such as ourselves are generally diploid: they contain two copies of the genome, one inherited from the mother, the other from the father.) Closely related organisms can vary widely in the quantity of DNA in their genomes (as indicated by the length of the *green* bars), even though they contain similar numbers of functionally distinct genes. (Adapted from T.R. Gregory, 2008, Animal Genome Size Database: www.genomesize.com)

for-nucleotide, they squeeze a lot of information into their relatively small genomes. *E. coli*, for example, carries its genetic instructions in a single, circular, double-stranded molecule of DNA that contains 4.6 million nucleotide pairs and 4300 genes. The simplest known bacterium contains only about 500 genes, but most prokaryotes have genomes that contain at least 1 million nucleotide pairs and 1000–8000 genes. With these few thousand genes, prokaryotes are able to thrive in even the most hostile environments on Earth.

The compact genomes of typical bacteria are dwarfed by the genomes of typical eukaryotes. The human genome, for example, contains about 700 times more DNA than the *E. coli* genome, and the genome of an amoeba contains about 100 times more than ours (**Figure 1–40**). The rest of the model organisms we have described have genomes that fall somewhere in between *E. coli* and human in terms of size. *S. cerevisiae* contains about 2.5 times as much DNA as *E. coli*; *Drosophila* has about 10 times more DNA per cell than yeast; and mice have about 20 times more DNA per cell than the fruit fly (**Table 1–2**).

TABLE 1–2 SOME MODEL ORGANISMS AND THEIR GENOMES

Organism	Genome size* (nucleotide pairs)	Approximate number of genes
Homo sapiens (human)	3200×10^6	30,000
Mus musculus (mouse)	2800×10^6	30,000
Drosophila melanogaster (fruit fly)	200×10^6	15,000
Arabidopsis thaliana (plant)	220×10^6	29,000
Caenorhabditis elegans (roundworm)	130×10^6	21,000
Saccharomyces cerevisiae (yeast)	13×10^6	6600
Escherichia coli (bacteria)	4.6×10^6	4300

*Genome size includes an estimate for the amount of highly repeated DNA sequence not in genome databases.

In terms of gene numbers, however, the differences are not so great. We have only about six times as many genes as *E. coli*. Moreover, many of our genes—and the proteins they encode—fall into closely related family groups, such as the family of hemoglobins, which has nine closely related members in humans. Thus the number of fundamentally different proteins in a human is not very many times more than in a bacterium, and the number of human genes that have identifiable counterparts in the bacterium is a significant fraction of the total.

This high degree of "family resemblance" is striking when we compare the genome sequences of different organisms. When genes from different organisms have very similar nucleotide sequences, it is highly probable that both descended from a common ancestral gene. Such genes (and their protein products) are said to be **homologous**. Now that we have the complete genome sequences of many different organisms from all three domains of life—archaea, bacteria, and eukaryotes—we can search systematically for homologies that span this enormous evolutionary divide. By taking stock of the common inheritance of all living things, scientists are attempting to trace life's origins back to the earliest ancestral cells.

Genomes Contain More Than Just Genes

Although our view of genome sequences tends to be "gene-centric," our genomes contain much more than just genes. The vast bulk of our DNA does not code for proteins or for functional RNA molecules. Instead, it includes a mixture of sequences that help regulate gene activity, plus sequences that seem to be dispensable. The large quantity of regulatory DNA contained in the genomes of eukaryotic multicellular organisms allows for enormous complexity and sophistication in the way different genes are brought into action at different times and places. Yet, in the end, the basic list of parts—the set of proteins that the cells can make, as specified by the DNA—is not much longer than the parts list of an automobile, and many of those parts are common not only to all animals, but also to the entire living world.

That DNA can program the growth, development, and reproduction of living cells and complex organisms is truly amazing. In the rest of this book, we will try to explain what is known about how cells work—by examining their component parts, how these parts work together, and how the genome of each cell directs the manufacture of the parts the cell needs to function and to reproduce.

ESSENTIAL CONCEPTS

- **Cells are the fundamental units of life. All present-day cells are believed to have evolved from an ancestral cell that existed more than 3 billion years ago.**
- **All cells are enclosed by a plasma membrane, which separates the inside of the cell from its environment.**
- **All cells contain DNA as a store of genetic information and use it to guide the synthesis of RNA molecules and proteins.**
- **Cells in a multicellular organism, though they all contain the same DNA, can be very different. They turn on different sets of genes according to their developmental history and to signals they receive from their environment.**
- **Animal and plant cells are typically 5–20 μm in diameter and can be seen with a light microscope, which also reveals some of their internal components, including the larger organelles.**

- The electron microscope reveals even the smallest organelles, but specimens require elaborate preparation and cannot be viewed while alive.
- Specific large molecules can be located in fixed or living cells with a fluorescence microscope.
- The simplest of present-day living cells are prokaryotes: although they contain DNA, they lack a nucleus and other organelles and probably resemble most closely the ancestral cell.
- Different species of prokaryotes are diverse in their chemical capabilities and inhabit an amazingly wide range of habitats. Two fundamental evolutionary subdivisions are recognized: bacteria and archaea.
- Eukaryotic cells possess a nucleus and other organelles not found in prokaryotes. They probably evolved in a series of stages, including the acquisition of mitochondria by engulfment of aerobic bacteria and (for plant cells) the acquisition of chloroplasts by engulfment of photosynthetic bacteria.
- The nucleus contains the genetic information of the eukaryotic organism, stored in DNA molecules.
- The cytoplasm includes all of the cell's contents outside the nucleus and contains a variety of membrane-enclosed organelles with specialized functions: mitochondria carry out the final oxidation of food molecules; in plant cells, chloroplasts perform photosynthesis; the endoplasmic reticulum and the Golgi apparatus synthesize complex molecules for export from the cell and for insertion in cell membranes; lysosomes digest large molecules.
- Outside the membrane-enclosed organelles in the cytoplasm is the cytosol, a very concentrated mixture of large and small molecules that carry out many essential biochemical processes.
- The cytoskeleton is composed of protein filaments that extend throughout the cytoplasm and are responsible for cell shape and movement and for the transport of organelles and other large molecular complexes from one location to another.
- Free-living, single-celled eukaryotic microorganisms are complex cells that can swim, mate, hunt, and devour other microorganisms.
- Animals, plants, and some fungi consist of diverse eukaryotic cell types, all derived from a single fertilized egg cell; the number of such cells cooperating to form a large multicellular organism such as a human runs into thousands of billions.
- Biologists have chosen a small number of model organisms to study closely, including the bacterium *E. coli*, brewer's yeast, a nematode worm, a fly, a small plant, a fish, a mouse, and humans themselves.
- The simplest known cell is a bacterium with about 500 genes, but most cells contain significantly more. The human genome has about 25,000 genes, which is only about twice as many as a fly and six times as many as *E. coli*.