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

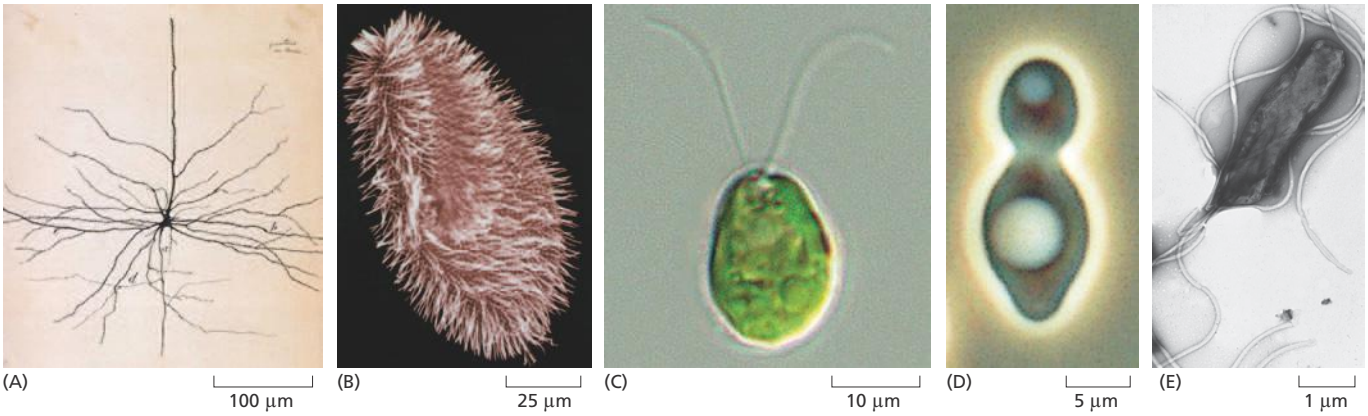


Figure 1–1 Cells come in a variety of shapes and sizes. Note the very different scales of these micrographs. (A) Drawing of a single nerve cell from a mammalian brain. This cell has a huge branching tree of processes, through which it receives signals from as many as 100,000 other nerve cells. (B) *Paramecium*. 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,

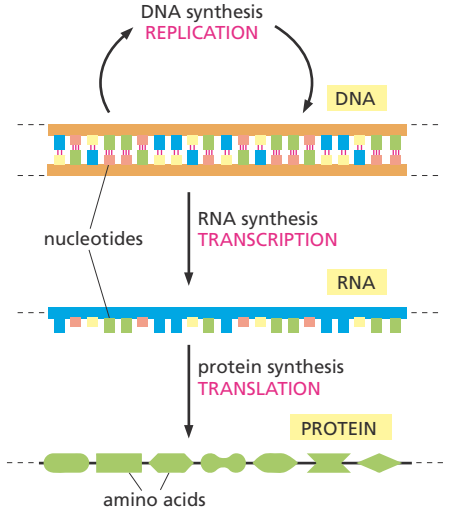


Figure 1–2 In all living cells, genetic information flows from DNA to RNA (transcription) and from RNA to protein (translation)—a sequence known as the central dogma. The sequence of nucleotides in a particular segment of DNA (a gene) is transcribed into an RNA molecule, which can then be translated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

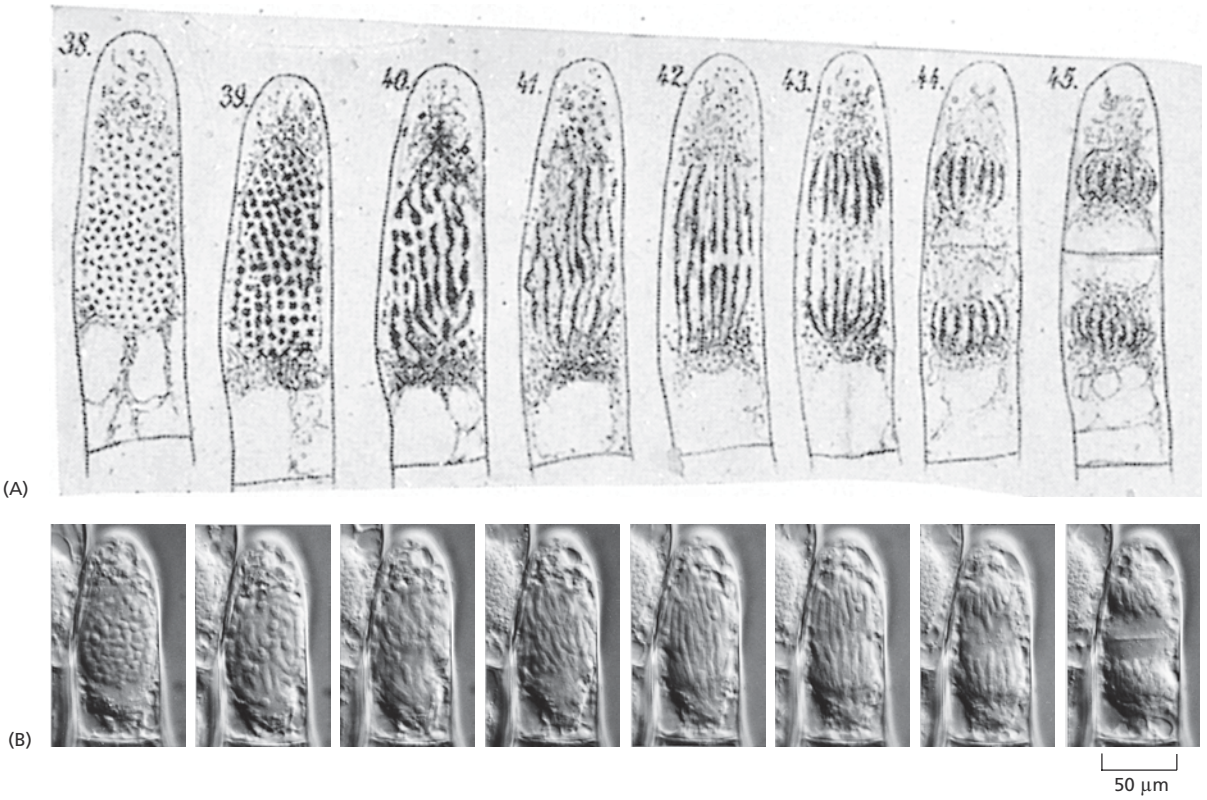


Figure 1–4 New cells form by growth and division of existing cells. (A) In 1880, Eduard Strasburger drew a living plant cell (a hair cell from a *Tradescantia* flower), which he observed dividing into two daughter cells over a period of 2.5 hours. (B) A comparable living plant cell photographed recently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

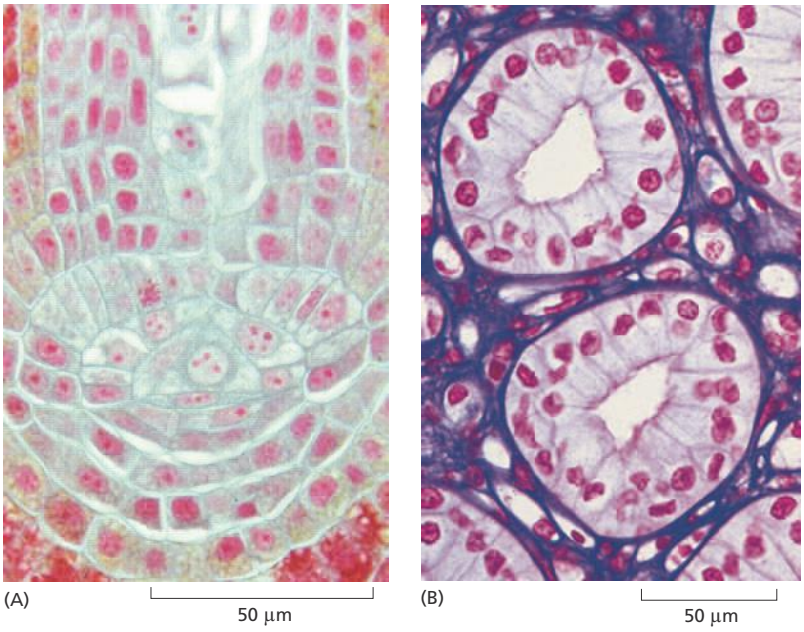


Figure 1–5 Cells form tissues in plants and animals. (A) Cells in the root tip of a fern. The nuclei are stained *red*, and each cell is surrounded by a thin cell wall (*light blue*). (B) Cells in the urine-collecting ducts of the kidney. Each duct appears in this cross section as a ring of closely packed 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.)

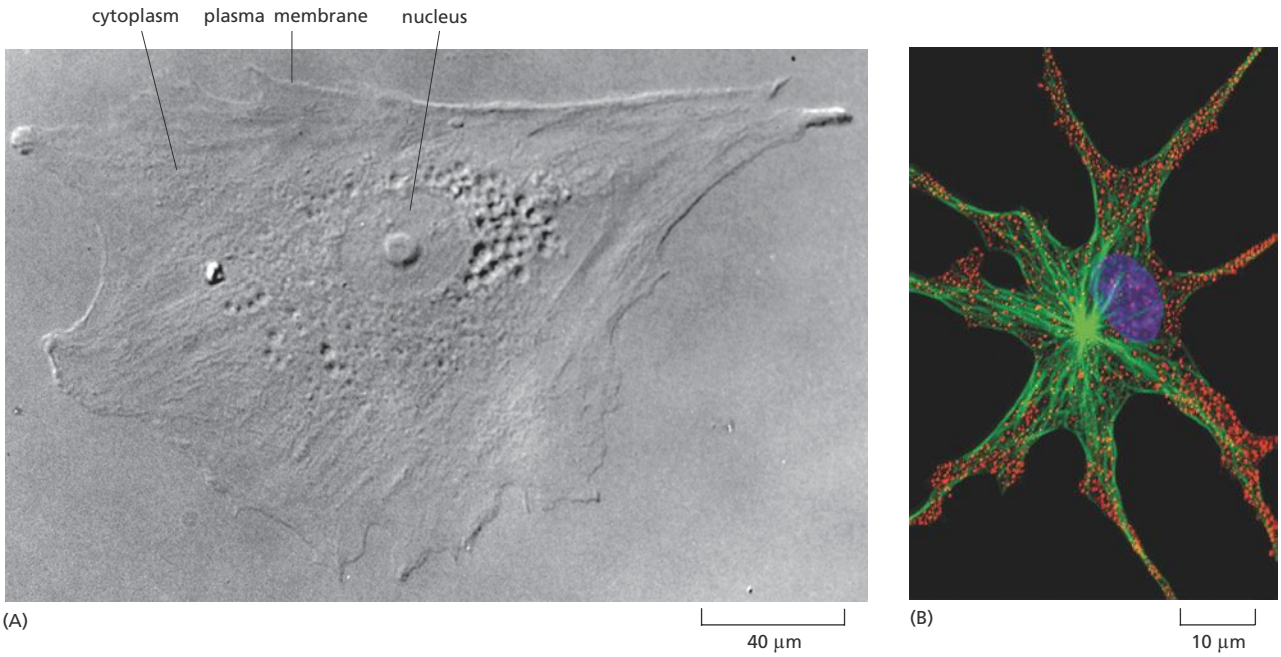


Figure 1–6 Some of the internal structures of a living cell can be seen with a light microscope. (A) A cell taken from human skin and grown in culture was photographed through a light microscope using interference-contrast optics (see Panel 1–1, pp. 10–11). The nucleus is especially prominent. (B) A 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.)

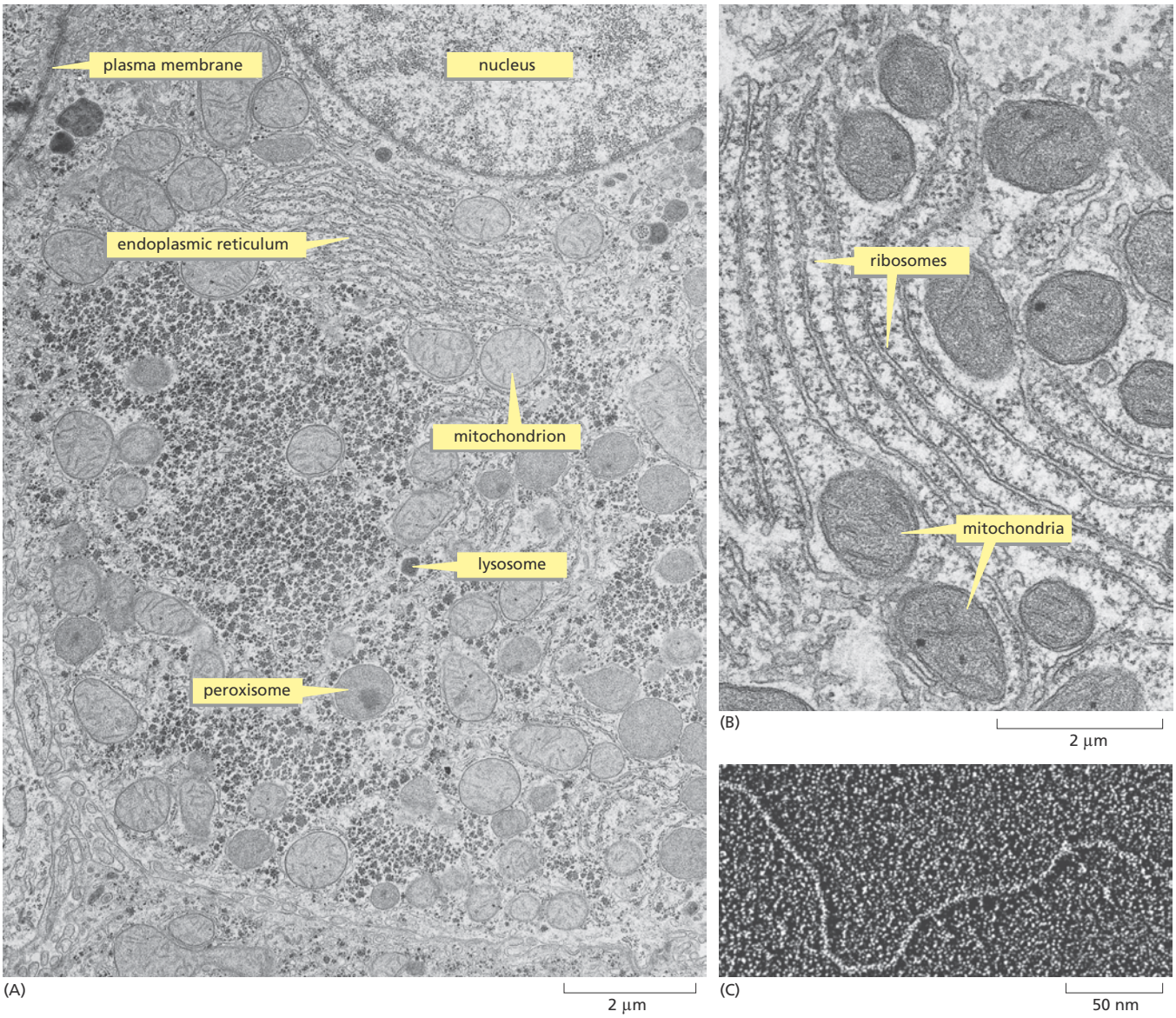
refractive index, just as glass differs in refractive index from water, causing light rays to be deflected as they pass from the one medium into the other. The small differences in refractive index can be made visible by specialized optical techniques, and the resulting images can be enhanced further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



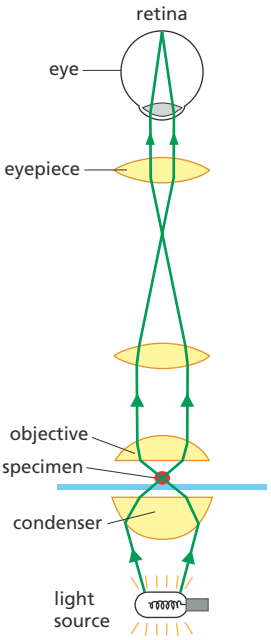
When thin sections are cut, stained, and placed in the electron microscope, much of the jumble of cell components becomes sharply resolved into distinct **organelles**—separate, recognizable substructures with specialized functions that are often only hazily defined with a light microscope. A delicate 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.)

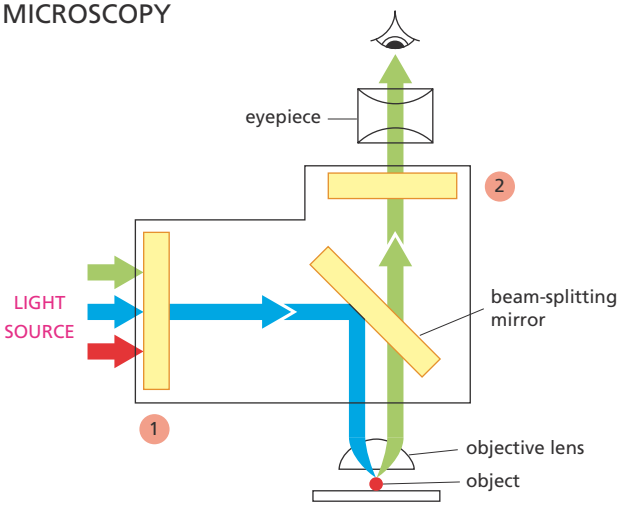
THE LIGHT MICROSCOPE

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.

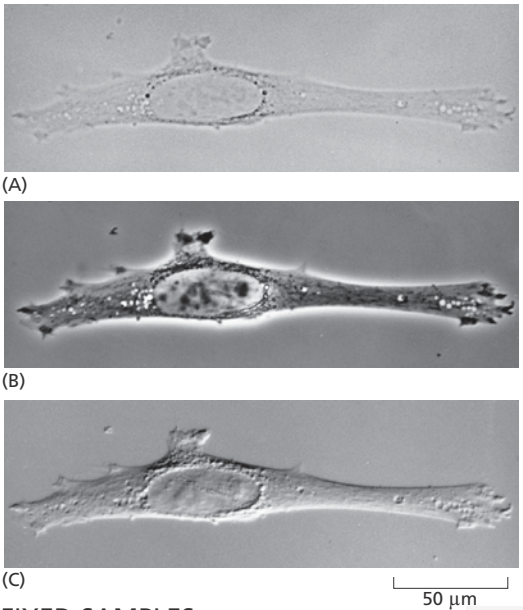


the light path in a light microscope

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.

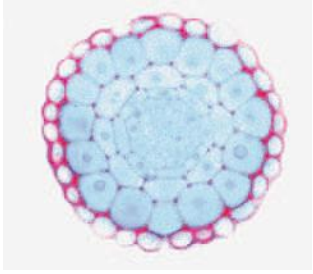


LOOKING AT LIVING CELLS

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.

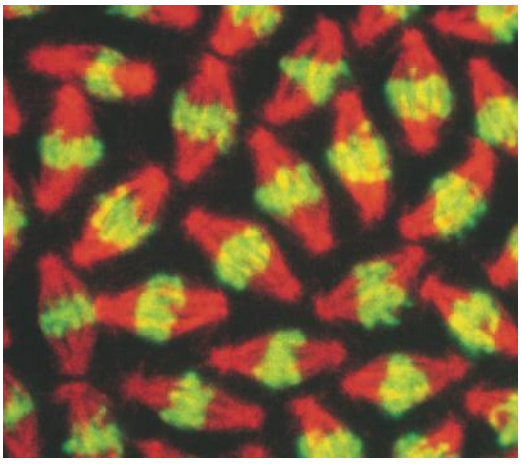
FIXED SAMPLES

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

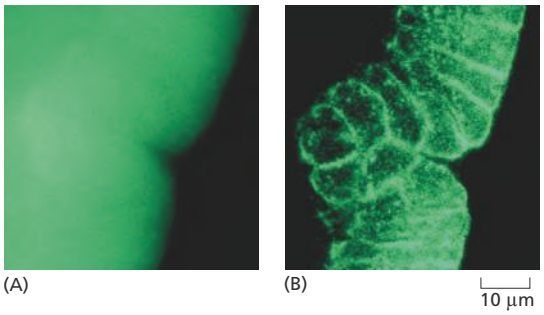
Dividing nuclei in a fly embryo seen with a fluorescence microscope after staining with specific fluorescent dyes.



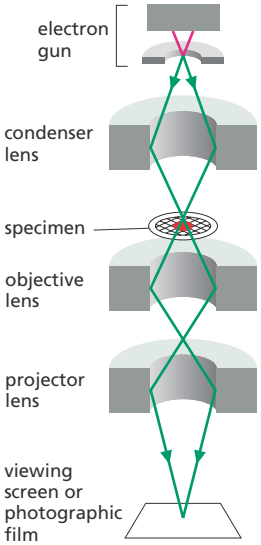
Fluorescent dyes absorb light at one wavelength and emit it at another, longer wavelength. Some such dyes bind specifically to particular molecules in cells and can reveal their location when examined with a fluorescence microscope. An example is the stain for DNA shown here (*green*). Other dyes can 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.)

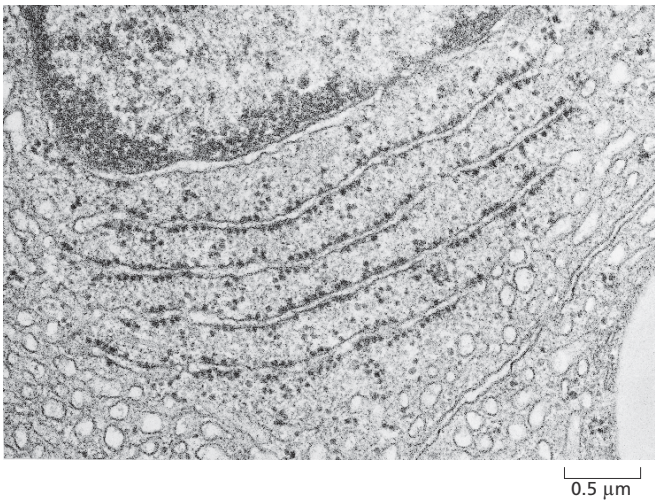


TRANSMISSION ELECTRON MICROSCOPY



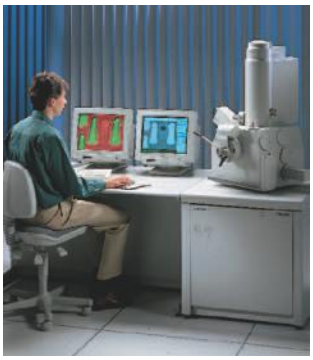
Courtesy of Philips Electron Optics, with permission from FEI Co.

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.)



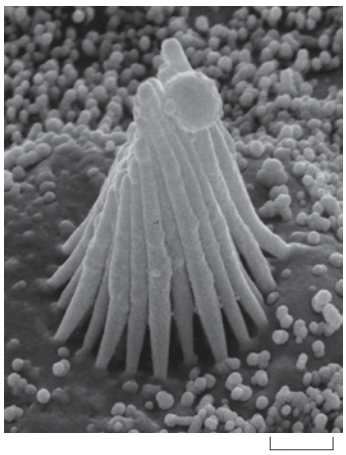
The transmission electron microscope (TEM) is in principle similar to a light microscope, but it uses a beam of electrons instead of a beam of light, and magnetic coils to focus the beam instead of glass lenses. The specimen, which is placed in a vacuum, must be very thin. Contrast is usually introduced 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.

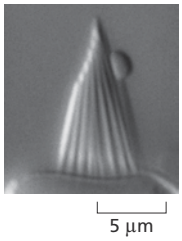
SCANNING ELECTRON MICROSCOPY



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.)

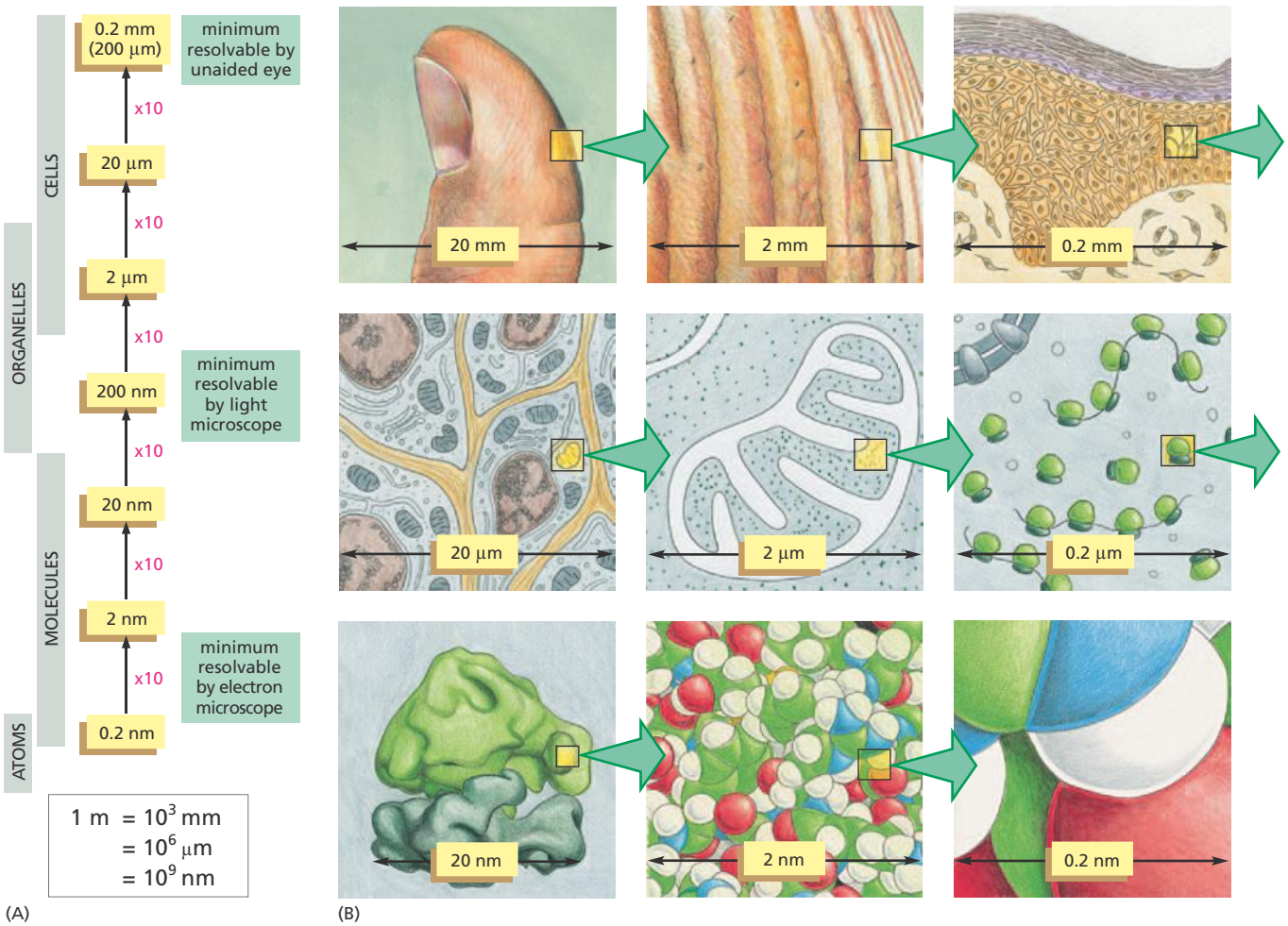


Figure 1–8 How big is a cell and its components? (A) The sizes of cells and of their component parts, plus the units in which they are measured. (B) Drawings to convey a sense of scale between living cells and atoms. Each panel shows an image that is magnified by a factor of 10 compared to its predecessor—producing 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

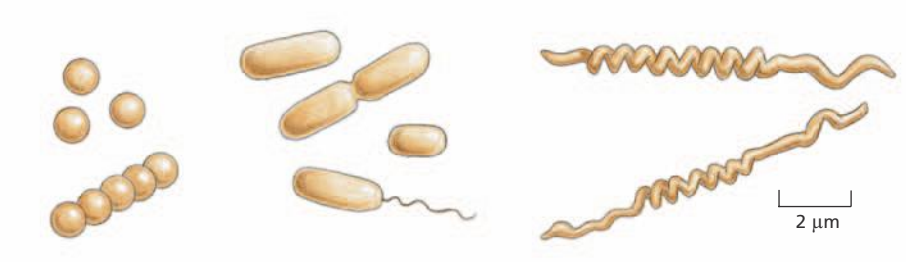


Figure 1–9 Bacteria come in different shapes and sizes. Typical spherical, rodlike, and spiral-shaped bacteria are drawn to scale. The spiral cells shown are the organisms that cause syphilis.

"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

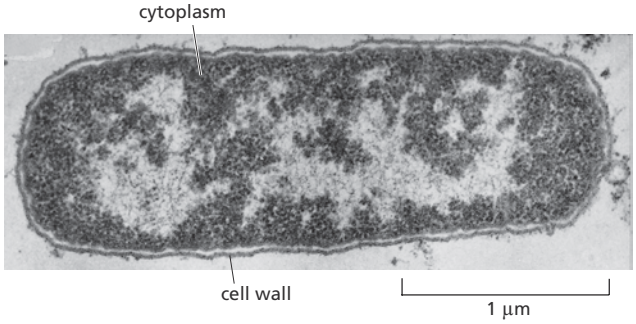


Figure 1–10 The bacterium *Escherichia coli* (*E. coli*) has served as an important model organism. An electron micrograph of a longitudinal section is shown here; the cell's DNA is concentrated in the lightly stained region. (Courtesy of E. Kellenberger.)

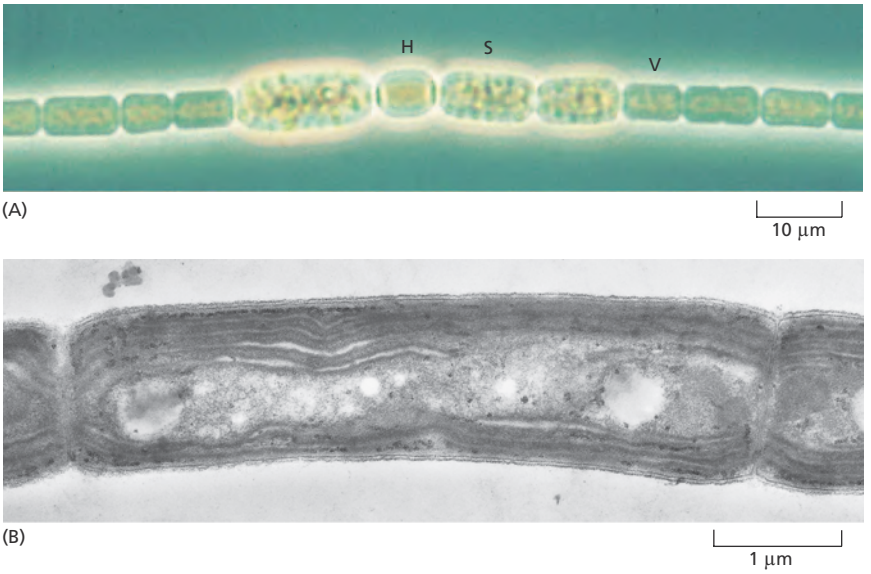


Figure 1–11 Some bacteria are photosynthetic. (A) *Anabaena cylindrica* forms long, multicellular filaments. This light micrograph shows specialized cells that either fix nitrogen (that is, capture N_2 from the atmosphere and incorporate it into organic compounds; labeled *H*), fix CO_2 through photosynthesis (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

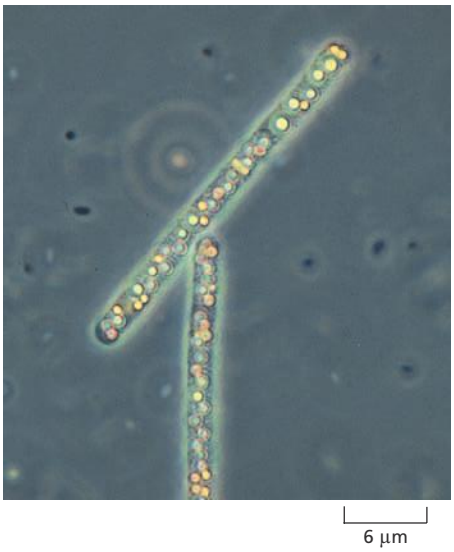


Figure 1–12 A sulfur bacterium gets its energy from H_2S. *Beggiatoa*, a prokaryote that lives in sulfurous environments, oxidizes H_2S to produce sulfur and can fix carbon even in the dark. In this light micrograph, yellow deposits of sulfur can be seen inside both of the cells. (Courtesy of Ralph W.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

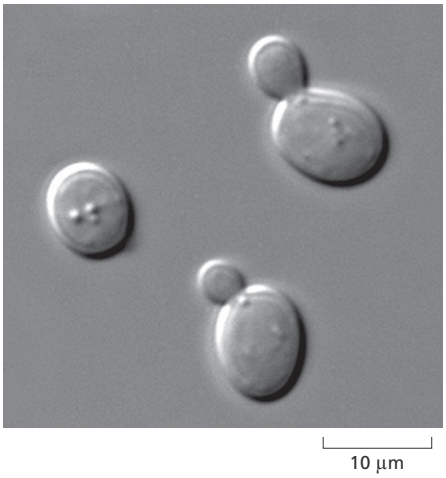


Figure 1–13 Yeasts are simple free-living eukaryotes. The cells shown in this micrograph belong to the species of yeast, *Saccharomyces cerevisiae*, used to make dough rise and turn malted barley juice into beer. As can be seen in this image, the cells reproduce by growing a bud and then dividing asymmetrically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

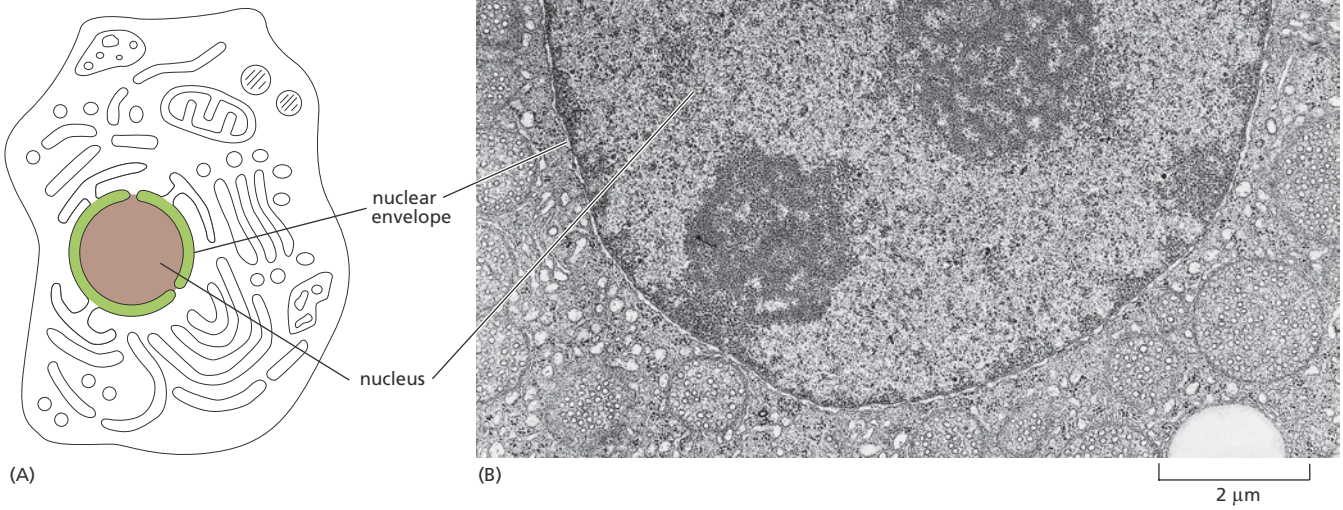


Figure 1–14 The nucleus contains most of the DNA in a eukaryotic cell. (A) This drawing of a typical animal cell shows its extensive system of membrane-enclosed organelles. The nucleus is colored *brown*, the nuclear envelope is *green*, and the cytoplasm (the interior of the cell outside the nucleus) 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

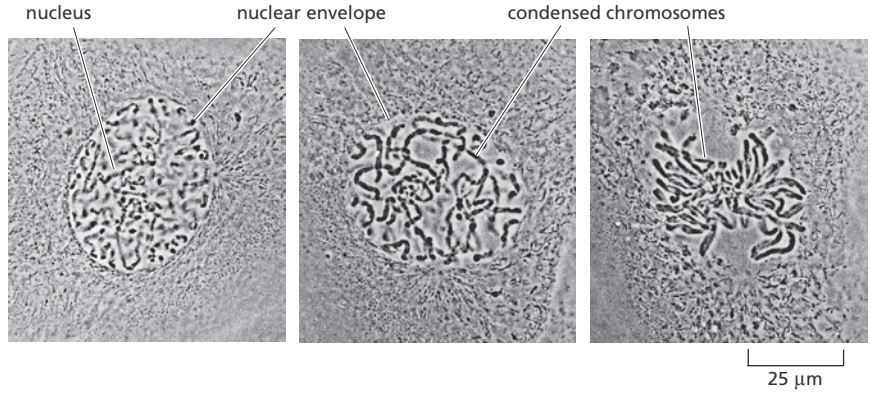
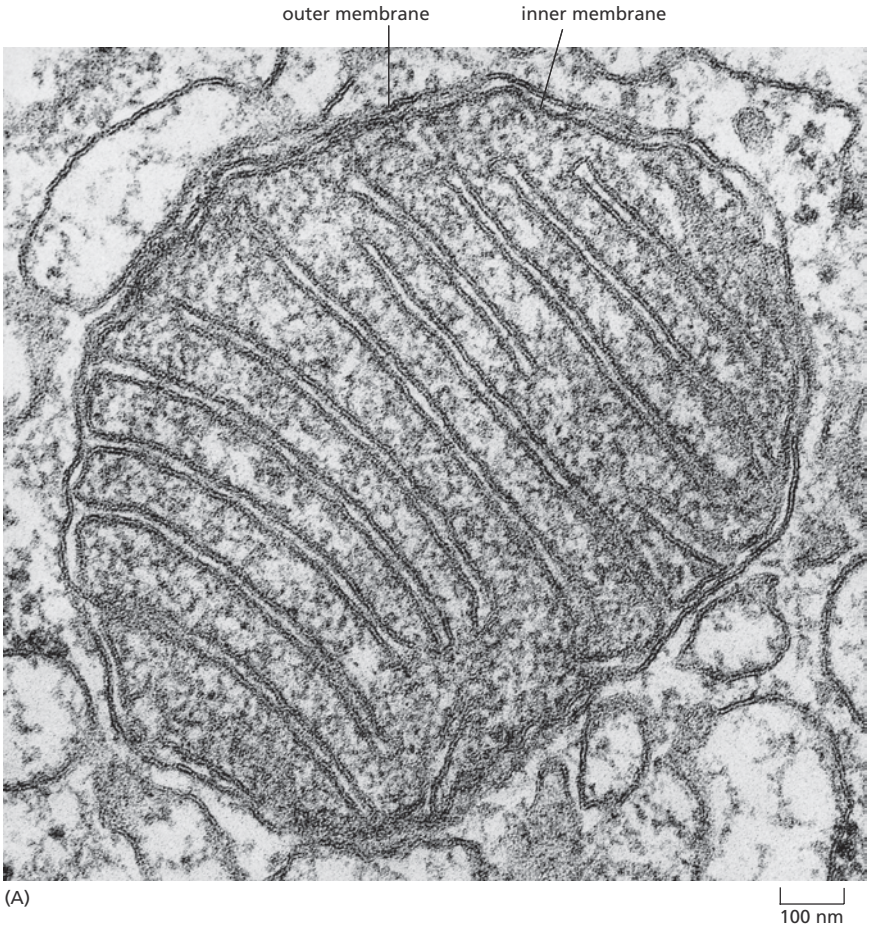
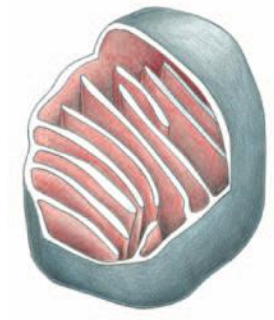


Figure 1–15 Chromosomes become visible when a cell is about to divide. As a eukaryotic cell prepares to divide, its DNA molecules become progressively more compacted (condensed), forming wormlike chromosomes that can be distinguished in the light microscope. The photographs show three successive steps 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.





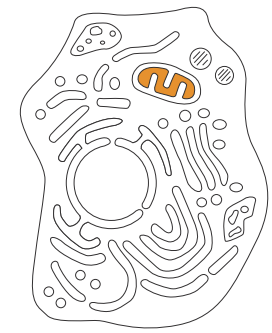


Figure 1–17 Mitochondria have a distinctive structure. (A) An electron micrograph of a cross section of a mitochondrion reveals the extensive infolding of the inner membrane. (B) This three-dimensional representation of the arrangement of the mitochondrial membranes shows the smooth outer membrane (*gray*) 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.)

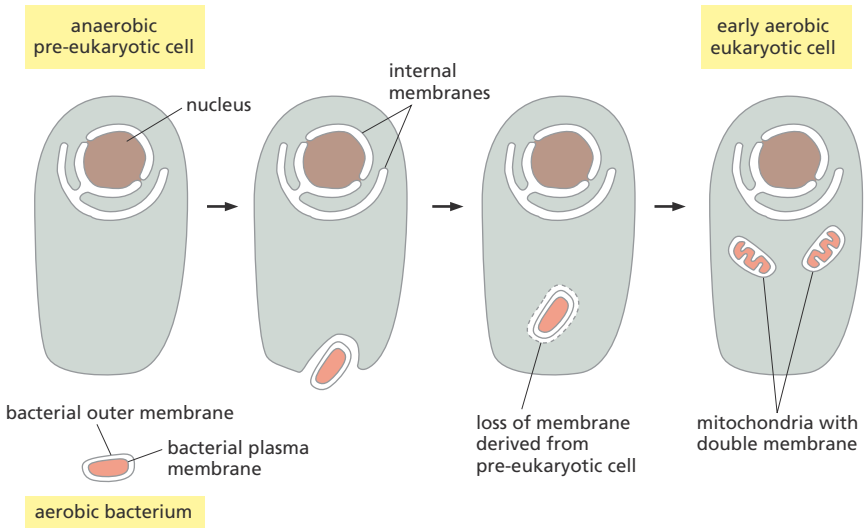


Figure 1–18 Mitochondria most likely evolved from engulfed bacteria. It is virtually certain that mitochondria originate from bacteria that were engulfed by an ancestral pre-eukaryotic cell and survived inside it, living in symbiosis with their host. Note that the double membrane of present-day mitochondria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

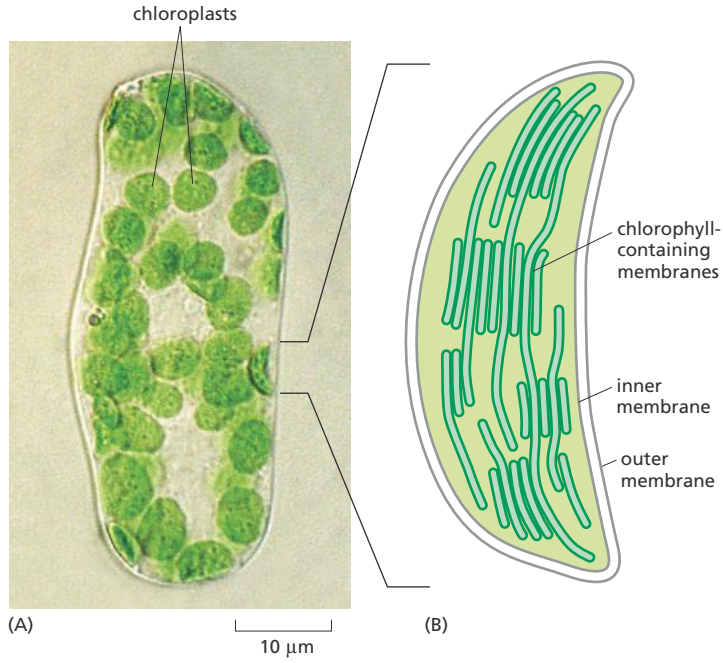


Figure 1–19 Chloroplasts in plant cells capture the energy of sunlight. (A) A single cell isolated from a leaf of a flowering plant, seen in the light microscope, showing many green chloroplasts. (B) A drawing of one of the chloroplasts, showing the inner and outer membranes, as well as the highly folded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

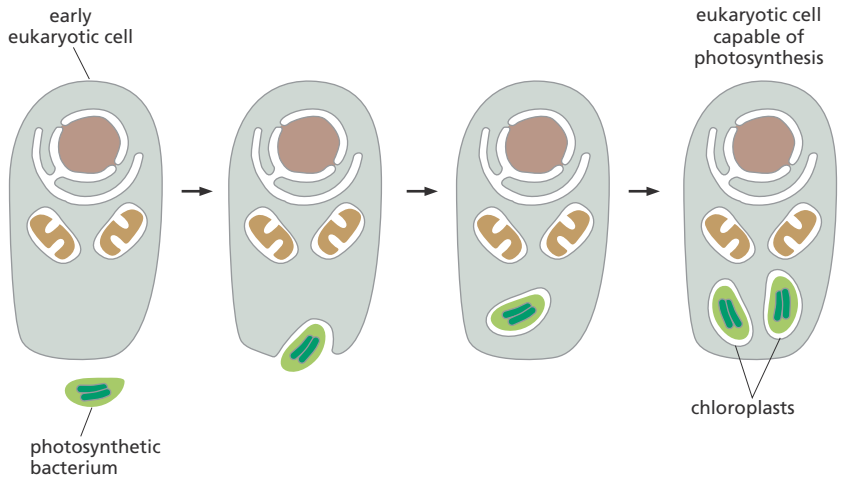


Figure 1–20 Chloroplasts almost certainly evolved from engulfed photosynthetic bacteria. The bacteria are thought to have been taken up by early eukaryotic cells that already contained mitochondria.

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**.

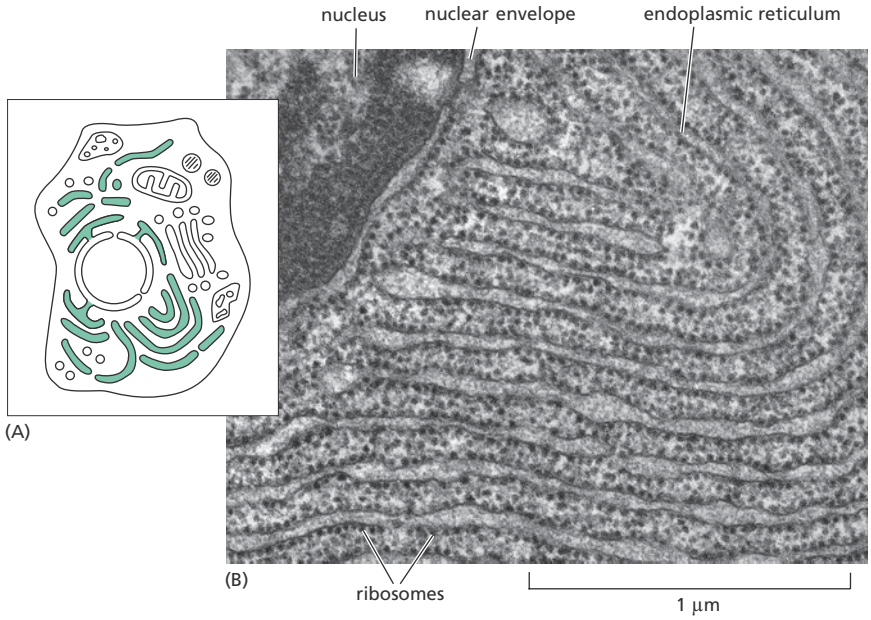


Figure 1–21 The endoplasmic reticulum produces many of the components of a eukaryotic cell. (A) Schematic diagram of an animal cell shows the endoplasmic reticulum (ER) in *green.* (B) Electron micrograph of a thin section of a mammalian pancreatic cell shows a small part of the ER, of which there are 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

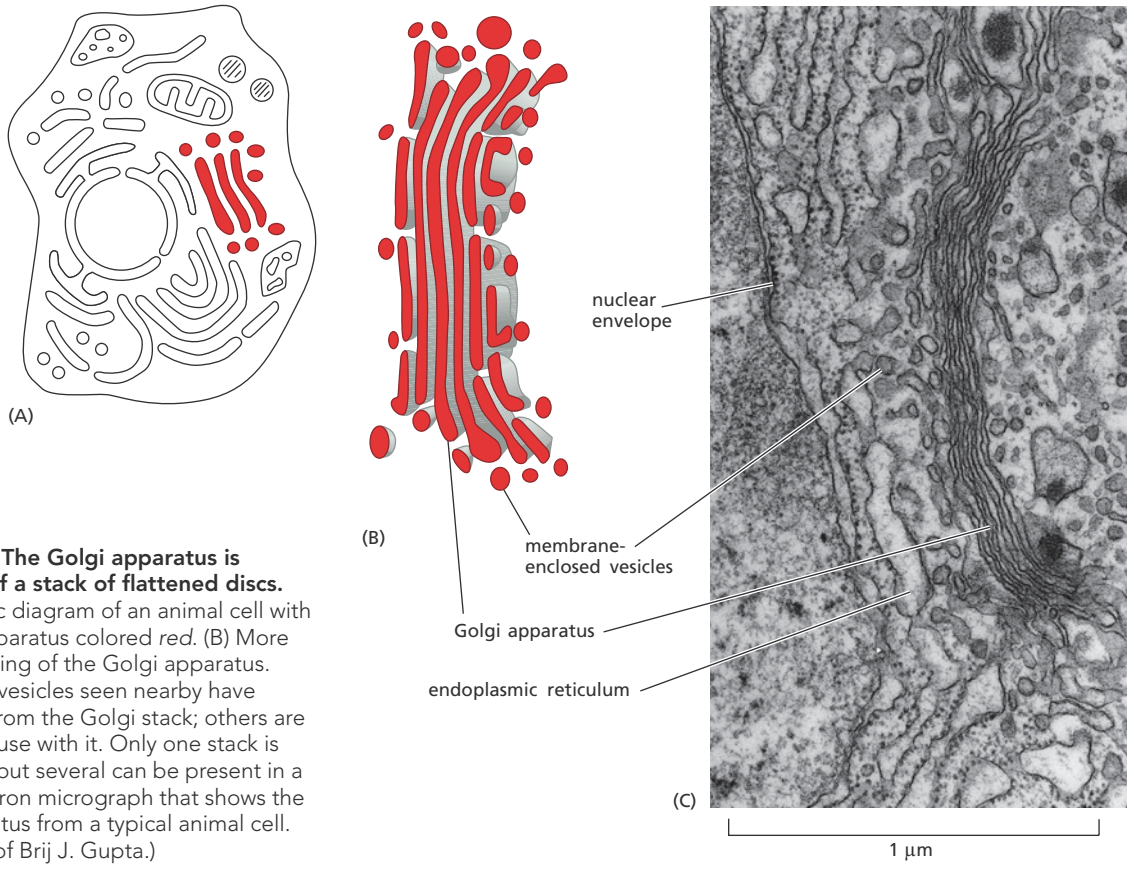


Figure 1–22 The Golgi apparatus is composed of a stack of flattened discs. (A) Schematic diagram of an animal cell with the Golgi apparatus colored *red.* (B) More realistic drawing of the Golgi apparatus. Some of the vesicles seen nearby have pinched off from the Golgi stack; others are destined to 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.)

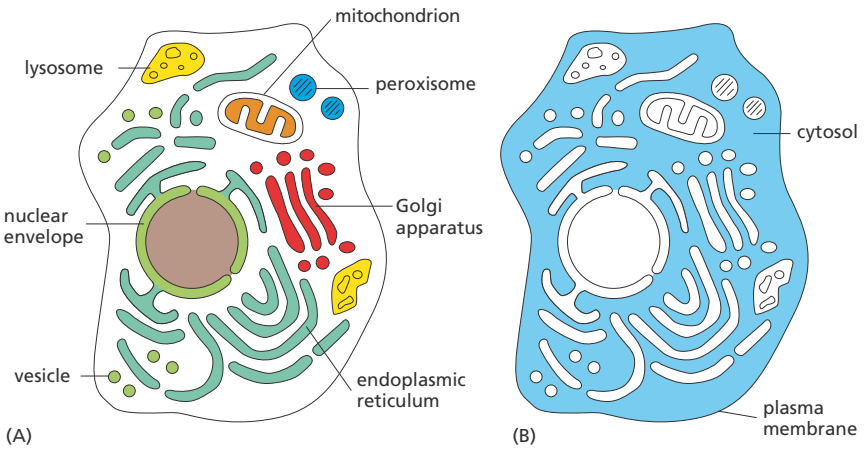


Figure 1–23 Membrane-enclosed organelles are distributed throughout the eukaryotic cell cytoplasm. (A) The membrane-enclosed organelles, shown in different colors, are each specialized to perform a different function. (B) The cytoplasm that fills the space outside of these organelles is called the cytosol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

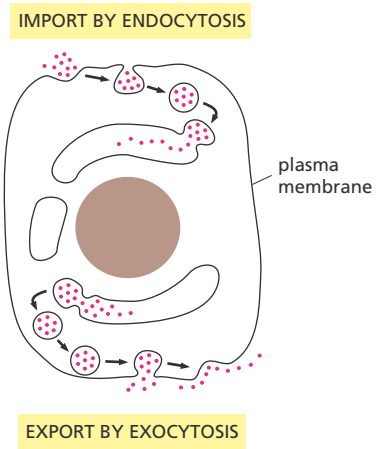


Figure 1–24 Eukaryotic cells engage in continual endocytosis and exocytosis. They import extracellular materials by endocytosis and secrete intracellular materials by exocytosis.

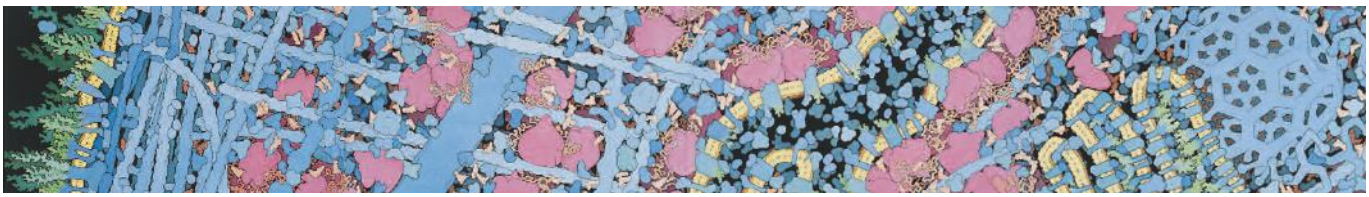


Figure 1–25 The cytoplasm is stuffed with organelles and a host of large and small molecules. This schematic drawing, which extends across two pages and is based on the known sizes and concentrations of molecules in the cytosol, shows how crowded the cytoplasm is. Proteins are *blue*, membrane lipids 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**).

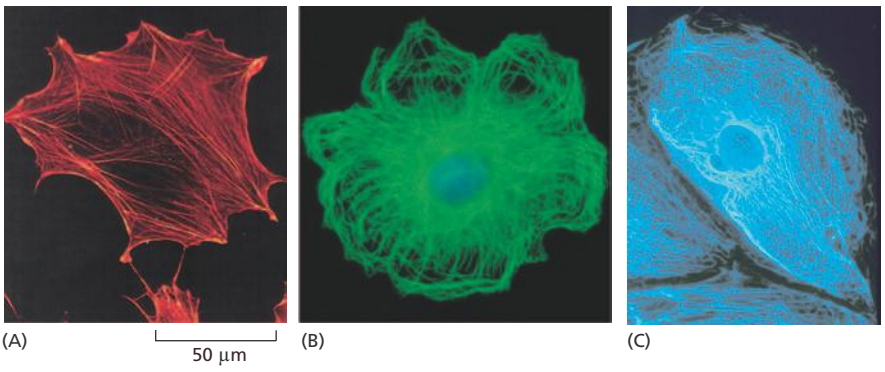
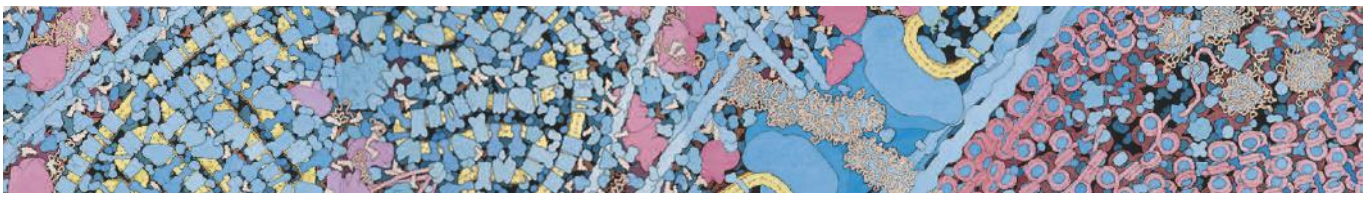


Figure 1–26 The cytoskeleton is a network of protein filaments that criss-crosses the cytoplasm of eukaryotic cells. The three major types of filaments can be detected using different fluorescent stains. Shown here are (A) actin filaments, (B) microtubules, and (C) intermediate filaments. (A, courtesy 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?

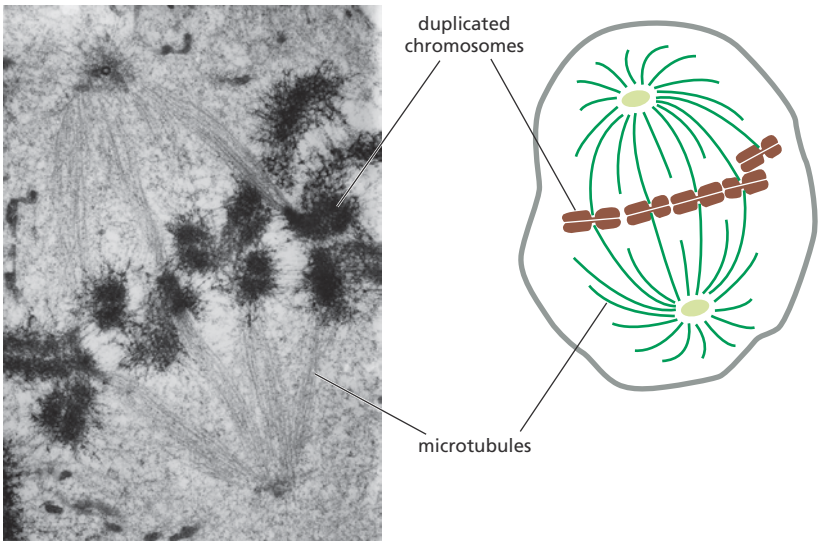


Figure 1–27 Microtubules help distribute the chromosomes in a dividing cell. When a cell divides, its nuclear envelope breaks down and its DNA condenses into visible chromosomes, each of which has duplicated to form a pair of conjoined chromosomes that will ultimately be pulled apart into separate cells 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

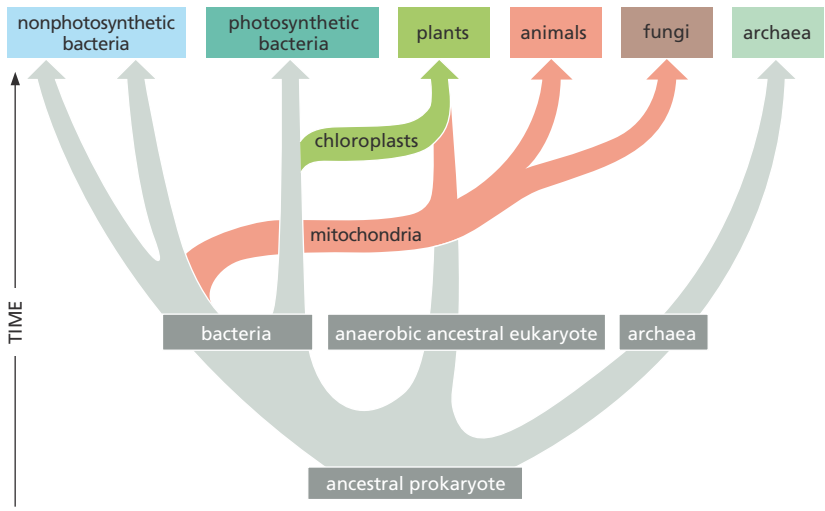
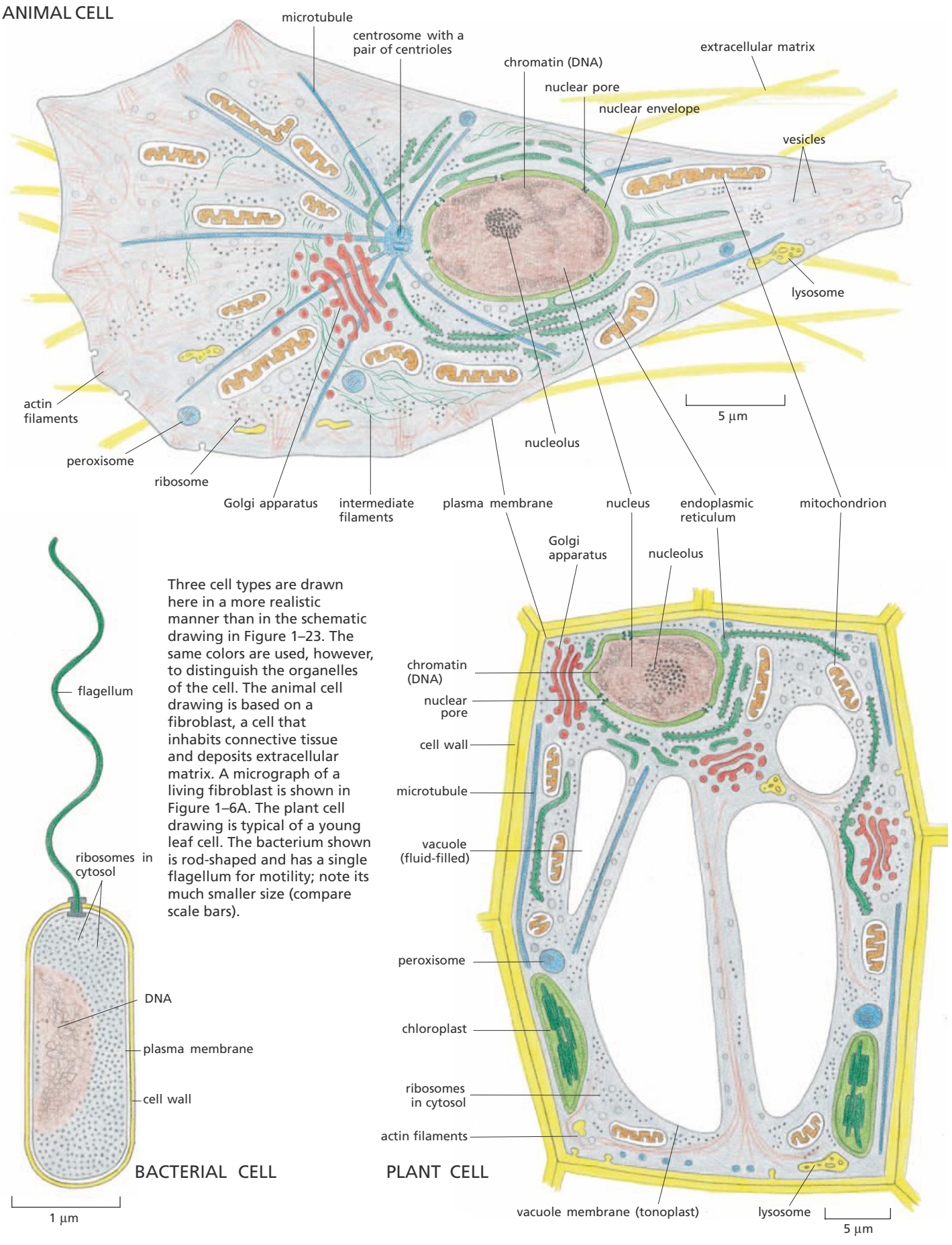


Figure 1–28 Where did eukaryotes come from? The eukaryotic, bacterial, and archaean lineages diverged from one another very early in the evolution of life on Earth. Some time later, eukaryotes are thought to have acquired mitochondria; later still, a subset of eukaryotes acquired chloroplasts. Mitochondria 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).

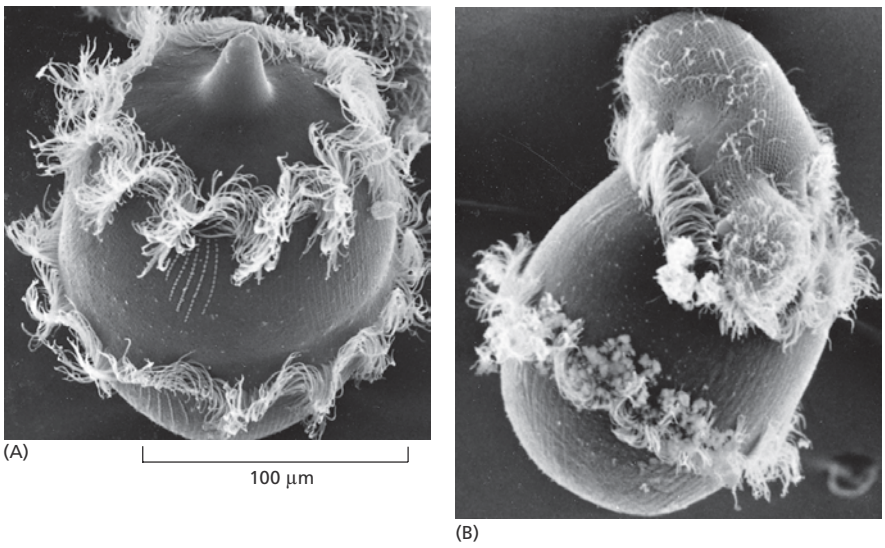


Figure 1–29 One protozoan eats another. (A) The scanning electron micrograph shows *Didinium* on its own, with its circumferential rings of beating cilia and its "snout" at the top. (B) *Didinium* is seen ingesting another ciliated protozoan, a *Paramecium*. (Courtesy of D. Barlow.)

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.

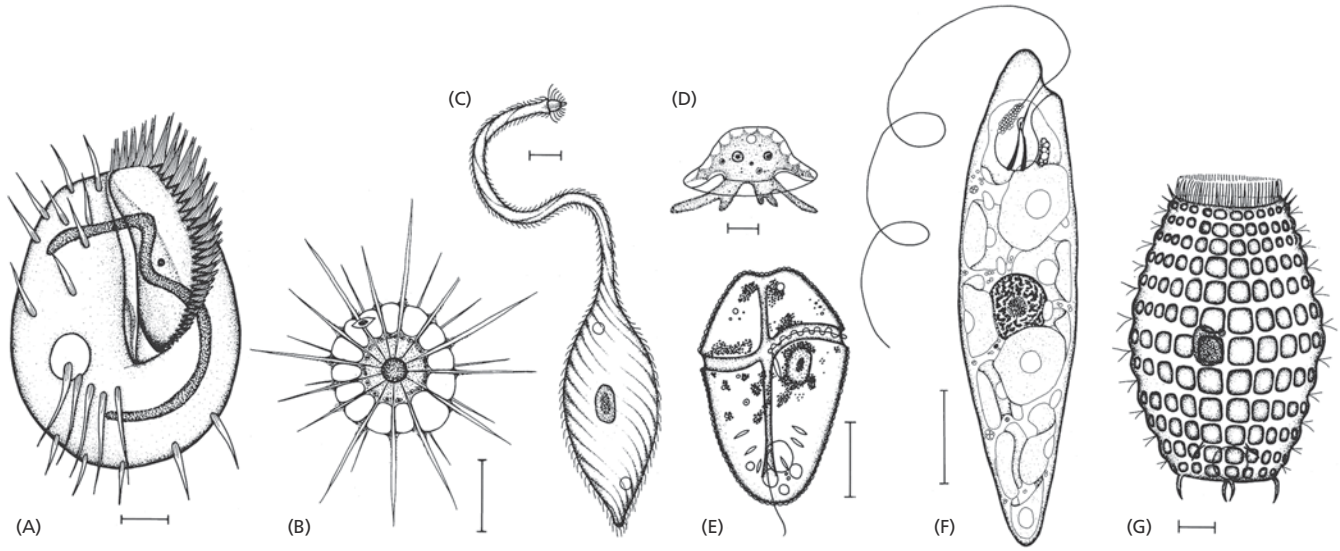


Figure 1–30 An assortment of protozoans illustrates the enormous variety within this class of single-celled microorganisms. These drawings are done to different scales, but in each case the scale bar represents 10 μm. The organisms in (A), (C), and (G) are ciliates; (B) is a heliozoan; (D) is an amoeba; (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?

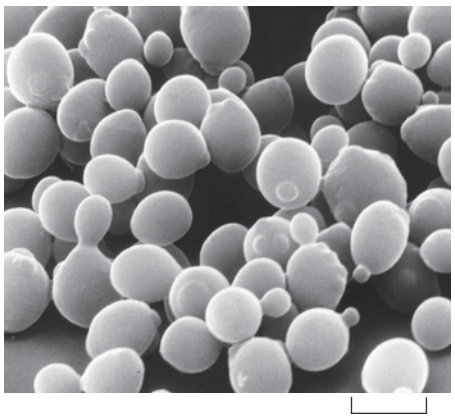


Figure 1–31 The yeast *Saccharomyces cerevisiae* is a model eukaryote. In this scanning electron micrograph, a few yeast cells are seen in the process of dividing, which they do by budding. Another micrograph of the same species is shown in Figure 1–13. (Courtesy of Ira Herskowitz and Eric Schabatach.)

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

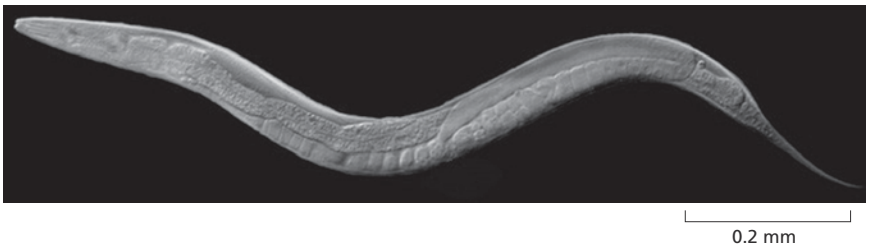


Figure 1–34 *Caenorhabditis elegans* is a small nematode worm that normally lives in the soil. Most individuals are hermaphrodites, producing both sperm and eggs (the latter of which can be seen along the underside of the animal). *C. elegans* was the first multicellular organism to have its complete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

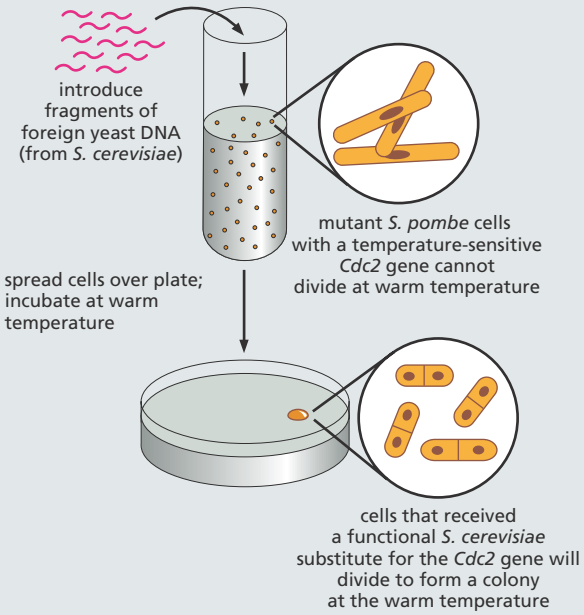


Figure 1–35 *S. pombe* mutants defective in a cell-cycle gene can be rescued by the equivalent gene from *S. cerevisiae*. DNA is collected from *S. cerevisiae* and broken into large fragments, which are introduced into a culture of mutant *S. pombe* cells dividing at room temperature. We discuss how 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.

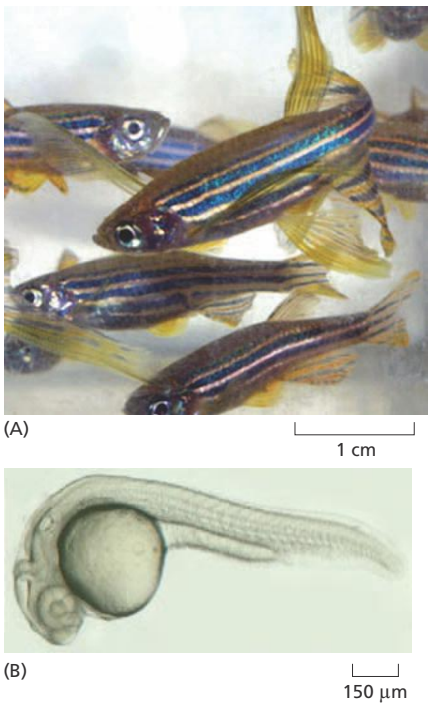


Figure 1–37 Zebrafish are popular models for studies of vertebrate development. (A) These small, hardy, tropical fish are a staple in many home aquaria. But they are also ideal for developmental studies, as their transparent embryos (B) make it easy to observe cells moving and changing their characters 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.

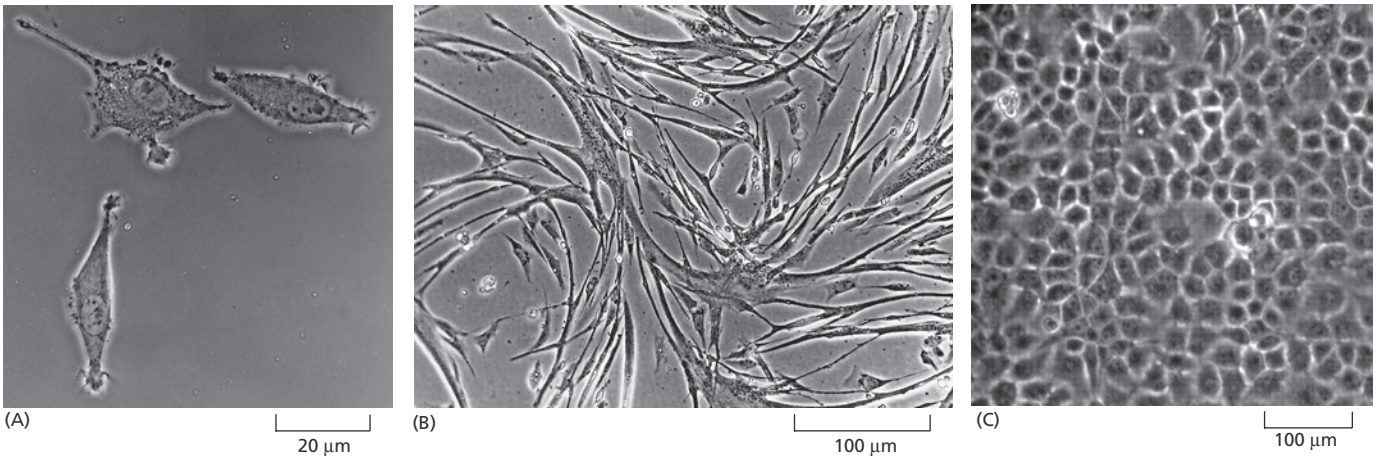
Biologists Also Directly Study Human Beings and Their Cells

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.)

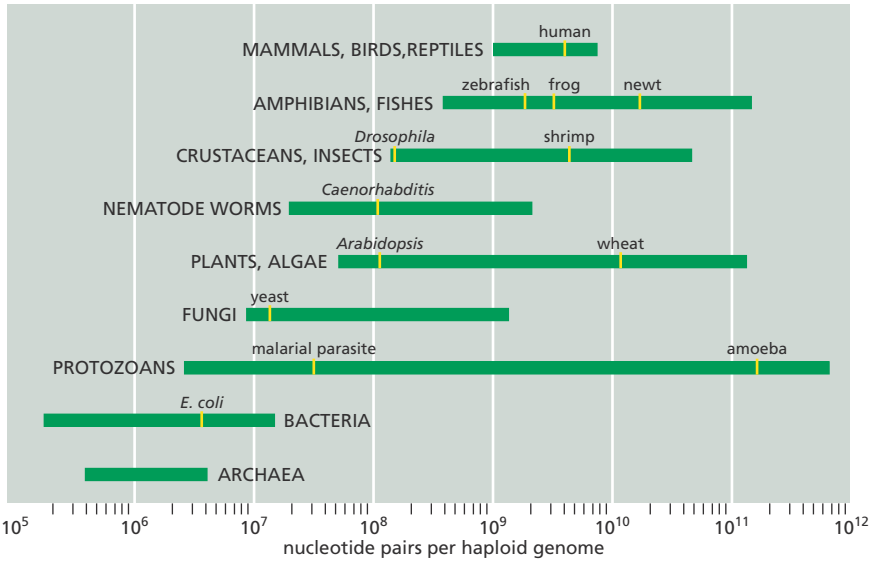


Figure 1–40 Organisms vary enormously in the size of their genomes. Genome size is measured in nucleotide pairs of DNA per haploid genome, that is, per single copy of the genome. (The body cells of sexually reproducing organisms such as ourselves are generally diploid: they contain two copies of the 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*.

KEY TERMS

archaeon
bacterium
cell
chloroplast
chromosome
cytoplasm
cytoskeleton
cytosol
DNA
electron microscope
eukaryote
evolution
fluorescence microscope
genome
homologous
micrometer
microscope
mitochondrion
model organism
nucleus
organelle
photosynthesis
plasma membrane
prokaryote
protein
protozoan
ribosome
RNA

QUESTIONS

QUESTION 1–8

By now you should be familiar with the following cellular components. Briefly define what they are and what function they provide for cells.

A. cytosol

B. cytoplasm

C. mitochondria

D. nucleus

E. chloroplasts

F. lysosomes

G. chromosomes

H. Golgi apparatus

I. peroxisomes

J. plasma membrane

K. endoplasmic reticulum

L. cytoskeleton

QUESTION 1–9

Which of the following statements are correct? Explain your answers.

A. The hereditary information of a cell is passed on by its proteins.

B. Bacterial DNA is found in the cytosol.

C. Plants are composed of prokaryotic cells.

D. All cells of the same organism have the same number of chromosomes (with the exception of egg and sperm cells).

E. The cytosol contains membrane-enclosed organelles, such as lysosomes.

F. The nucleus and mitochondria are surrounded by a double membrane.

G. Protozoans are complex organisms with a set of specialized cells that form tissues, such as flagella, mouthparts, stinging darts, and leglike appendages.

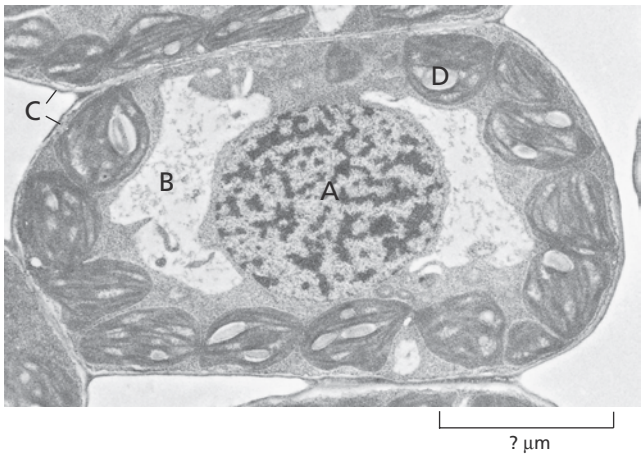
H. Lysosomes and peroxisomes are the sites of degradation of unwanted materials.

QUESTION 1–10

To get a feeling for the size of cells (and to practice the use of the metric system), consider the following: the human brain weighs about 1 kg and contains about 10^{12} cells. Calculate the average size of a brain cell (although we know that their sizes vary widely), assuming that each cell is entirely filled with water (1 cm^3 of water weighs 1 g). What would be the length of one side of this average-sized brain cell if it were a simple cube? If the cells were spread out as a thin layer that is only a single cell thick, how many pages of this book would this layer cover?

QUESTION 1–11

Identify the different organelles indicated with letters in the electron micrograph of a plant cell shown below. Estimate the length of the scale bar in the figure.



QUESTION 1–12

There are three major classes of filaments that make up the cytoskeleton. What are they, and what are the differences in

their functions? Which cytoskeletal filaments would be most plentiful in a muscle cell or in an epidermal cell making up the outer layer of the skin? Explain your answers.

QUESTION 1–13

Natural selection is such a powerful force in evolution because cells with even a small proliferation advantage quickly outgrow their competitors. To illustrate this process, consider a cell culture that contains 1 million bacterial cells that double every 20 minutes. A single cell in this culture acquires a mutation that allows it to divide faster, with a generation time of only 15 minutes. Assuming that there is an unlimited food supply and no cell death, how long would it take before the progeny of the mutated cell became predominant in the culture? (Before you go through the calculation, make a guess: do you think it would take about a day, a week, a month, or a year?) How many cells of either type are present in the culture at this time? (The number of cells N in the 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 generation time.)

QUESTION 1–14

When bacteria are grown under adverse conditions, i.e., in the presence of a poison such as an antibiotic, most cells grow and proliferate slowly. But it is not uncommon that the growth rate of a bacterial culture kept in the presence of the poison is restored after a few days to that observed in its absence. Suggest why this may be the case.

QUESTION 1–15

Apply the principle of exponential growth of a culture as described in Question 1–13 to the cells in a multicellular organism, such as yourself. There are about 10^{13} cells in your body. Assume that one cell acquires a mutation that allows it to divide in an uncontrolled manner (i.e., it becomes a cancer cell). Some cancer cells can proliferate with a generation time of about 24 hours. If none of the cancer cells died, how long would it take before 10^{13} cells in your body would be cancer cells? (Use the equation $N = N_0 \times 2^{t/G}$, with t, the time, and G, the length of each generation. Hint: $10^{13} \approx 2^{43}$.)

QUESTION 1–16

Discuss the following statement: "The structure and function of a living cell are dictated by the laws of physics and chemistry."

QUESTION 1–17

What, if any, are the advantages in being multicellular?

QUESTION 1–18

Draw to scale the outline of two spherical cells, one a bacterium with a diameter of 1 μm, the other an animal cell with a diameter of 15 μm. Calculate the volume, surface area, and surface-to-volume ratio for each cell. How would the latter ratio change if you included the internal membranes of the cell in the calculation of surface area (assume internal membranes have 15 times the area of the plasma membrane)? (The volume of a sphere is given by $4\pi r^3/3$ and its surface by $4\pi r^2$, where r is its radius.) Discuss the following hypothesis: "Internal membranes allowed bigger cells to evolve."

QUESTION 1–19

What are the arguments that all living cells evolved from a common ancestor cell? Imagine the very early days of evolution of life on Earth. Would you assume that the primordial ancestor cell was the first and only cell to form?

QUESTION 1–20

In Figure 1–25, proteins are blue, nucleic acids are pink, lipids are yellow, and polysaccharides are green. Identify the major organelles and other important cellular structures shown in this slice through a eukaryotic cell.

QUESTION 1–21

Looking at some pond water under the microscope, you notice an unfamiliar rod-shaped cell about 200 μm long. Knowing that some exceptional bacteria can be as big as this or even bigger, you wonder whether your cell is a bacterium or a eukaryote. How will you decide? If it is not a eukaryote, how will you discover whether it is a bacterium or an archaeon?

CHAPTER **TWO** 2

Chemical Components of Cells

It is at first sight difficult to accept that living creatures are merely chemical systems. Their incredible diversity of form, their seemingly purposeful behavior, and their ability to grow and reproduce all seem to set them apart from the world of solids, liquids, and gases that chemistry normally describes. Indeed, until the nineteenth century, it was widely believed that animals contained a vital force—an "animus"—that was responsible for their distinctive properties.

We now know that there is nothing in living organisms that disobeys chemical or physical laws. However, the chemistry of life is indeed a special kind. First, it is based overwhelmingly on carbon compounds, the study of which is known as *organic chemistry*. Second, it depends almost exclusively on chemical reactions that take place in a watery, or *aqueous*, solution and in the relatively narrow range of temperatures experienced on Earth. Third, it is enormously complex: even the simplest cell is vastly more complicated in its chemistry than any other chemical system known. Fourth, it is dominated and coordinated by collections of enormous *polymeric molecules*—chains of chemical **subunits** linked end-to-end—whose unique properties enable cells and organisms to grow and reproduce and to do all the other things that are characteristic of life. Finally, the chemistry of life is tightly regulated: cells deploy a variety of mechanisms to make sure that all their chemical reactions occur at the proper place and time.

Because chemistry lies at the heart of all biology, in this chapter, we briefly survey the chemistry of the living cell. We will meet the molecules from which cells are made and examine their structures, shapes, and chemical properties. These molecules determine the size, structure, and functions

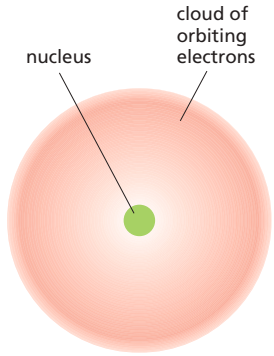


Figure 2–1 An atom consists of a nucleus surrounded by an electron cloud. The dense, positively charged nucleus contains most of the atom's mass. The much lighter and negatively charged electrons occupy space around the nucleus, as governed by the laws of quantum mechanics. The electrons are depicted as a continuous cloud, as there is no way of predicting exactly where an electron is at any given instant. The density of shading of the cloud is an indication of the probability that electrons will be found there. The diameter of the electron cloud ranges from about 0.1 nm (for hydrogen) to about 0.4 nm (for atoms of high atomic number). The nucleus is very much smaller: about 5×10^{-6} nm for carbon, for example.

of living cells. By understanding how they interact, we can begin to see how cells exploit the laws of chemistry and physics to survive, thrive, and reproduce.

CHEMICAL BONDS

Matter is made of combinations of *elements*—substances such as hydrogen or carbon that cannot be broken down or interconverted by chemical means. The smallest particle of an element that still retains its distinctive chemical properties is an *atom*. The characteristics of substances other than pure elements—including the materials from which living cells are made—depend on which atoms they contain and the way these atoms are linked together in groups to form *molecules*. To understand living organisms, therefore, it is crucial to know how the chemical bonds that hold atoms together in molecules are formed.

Cells Are Made of Relatively Few Types of Atoms

Each **atom** has at its center a dense, positively charged nucleus, which is surrounded at some distance by a cloud of negatively charged **electrons**, held there by electrostatic attraction to the nucleus (**Figure 2–1**). The nucleus consists of two kinds of subatomic particles: **protons**, which are positively charged, and *neutrons*, which are electrically neutral. The number of protons present in an atom's nucleus determines its *atomic number*. An atom of hydrogen has a nucleus composed of a single proton; so hydrogen, with an atomic number of 1, is the lightest element. An atom of carbon has six protons in its nucleus and an atomic number of 6 (**Figure 2–2**). The electric charge carried by each proton is exactly equal and opposite to the charge carried by a single electron. Because the whole atom is electrically neutral, the number of negatively charged electrons surrounding the nucleus is equal to the number of positively charged protons that the nucleus contains; thus the number of electrons in an atom also equals the atomic number. All atoms of a given element have the same atomic number, and we will see shortly that it is this number that dictates each atom's chemical behavior.

Neutrons have essentially the same mass as protons. They contribute to the structural stability of the nucleus—if there are too many or too few, the nucleus may disintegrate by radioactive decay—but they do not alter the chemical properties of the atom. Thus an element can exist in several physically distinguishable but chemically identical forms, called *isotopes*, each having a different number of neutrons but the same number of protons. Multiple isotopes of almost all the elements occur naturally,

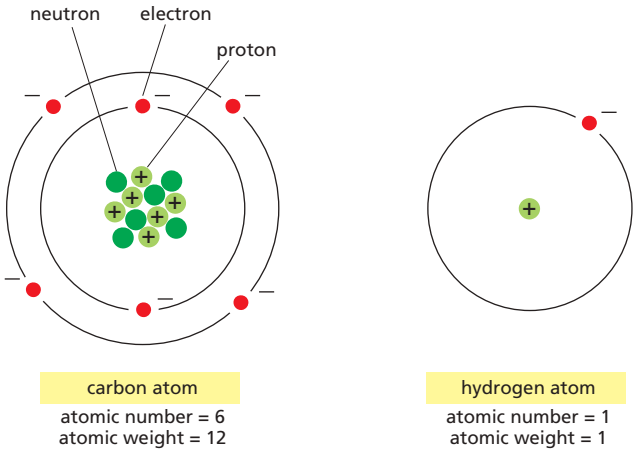


Figure 2–2 The number of protons in an atom determines its atomic number. Schematic representations of an atom of carbon and an atom of hydrogen are shown. The nucleus of every atom except hydrogen consists of both positively charged protons and electrically neutral neutrons; the atomic weight equals the number of protons plus neutrons. The number of electrons in an atom is equal to the number of protons, so that the atom has no net charge. In contrast to Figure 2–1, the electrons are shown here as individual particles. The concentric *black* circles represent in a highly schematic form the "orbits" (that is, the different distributions) of the electrons. The neutrons, protons, and electrons are in reality minute in relation to the atom as a whole; their size is greatly exaggerated here.

including some that are unstable—and thus radioactive. For example, while most carbon on Earth exists as the stable isotope carbon 12, with six protons and six neutrons, also present are small amounts of an unstable isotope, carbon 14, which has six protons and eight neutrons. Carbon 14 undergoes radioactive decay at a slow but steady rate, which allows archaeologists to estimate the age of organic material.

The **atomic weight** of an atom, or the **molecular weight** of a molecule, is its mass relative to that of a hydrogen atom. This is essentially equal to the number of protons plus neutrons that the atom or molecule contains, because the electrons are so light that they contribute almost nothing to the total mass. Thus the major isotope of carbon has an atomic weight of 12 and is written as ^{12}C. The unstable carbon isotope just mentioned has an atomic weight of 14 and is written as ^{14}C. The mass of an atom or a molecule is generally specified in *daltons*, one dalton being an atomic mass unit approximately equal to the mass of a hydrogen atom.

Atoms are so small that it is hard to imagine their size. An individual carbon atom is roughly 0.2 nm in diameter, so that it would take about 5 million of them, laid out in a straight line, to span a millimeter. One proton or neutron weighs approximately $1/(6 \times 10^{23})$ gram. As hydrogen has only one proton—thus an atomic weight of 1—1 gram of hydrogen contains 6×10^{23} atoms. For carbon—which has six protons and six neutrons, and an atomic weight of 12—12 grams contain 6×10^{23} atoms. This huge number, called **Avogadro's number**, allows us to relate everyday quantities of chemicals to numbers of individual atoms or molecules. If a substance has a molecular weight of M, M grams of the substance will contain 6×10^{23} molecules. This quantity is called one *mole* of the substance (**Figure 2–3**). The concept of mole is used widely in chemistry as a way to represent the number of molecules that are available to participate in chemical reactions.

There are about 90 naturally occurring elements, each differing from the others in the number of protons and electrons in its atoms. Living organisms, however, are made of only a small selection of these elements, four of which—carbon (C), hydrogen (H), nitrogen (N), and oxygen (O)—constitute 96% of an organism's weight. This composition differs markedly from that of the nonliving inorganic environment on Earth (**Figure 2–4**) and is evidence of a distinctive type of chemistry.

A mole is X grams of a substance, where X is the molecular weight of the substance. A mole will contain 6×10^{23} molecules of the substance.

1 mole of carbon weighs 12 g
1 mole of glucose weighs 180 g
1 mole of sodium chloride weighs 58 g

A one molar solution has a concentration of 1 mole of the substance in 1 liter of solution. A 1 M solution of glucose, for example, contains 180 g/l, and a one millimolar (1 mM) solution contains 180 mg/l.

The standard abbreviation for gram is g; the abbreviation for liter is L.

Figure 2–3 What's a mole? Some sample calculations of moles and molar solutions.

The Outermost Electrons Determine How Atoms Interact

To understand how atoms come together to form the molecules that make up living organisms, we have to pay special attention to the atoms' electrons. Protons and neutrons are welded tightly to one another in an atom's nucleus, and they change partners only under extreme conditions—during radioactive decay, for example, or in the interior of the sun or of a nuclear reactor. In living tissues, only the electrons of an atom undergo rearrangements. They form the accessible part of the atom and specify the rules of chemistry by which atoms combine to form molecules.

Electrons are in continuous motion around the nucleus, but motions on this submicroscopic scale obey different laws from those we are familiar with in everyday life. These laws dictate that electrons in an atom can exist only in certain discrete regions of movement—roughly speaking, in discrete orbits. Moreover, there is a strict limit to the number of electrons that can be accommodated in an orbit of a given type, a so-called *electron shell*. The electrons closest on average to the positive nucleus are attracted most strongly to it and occupy the inner, most tightly bound shell. This innermost shell can hold a maximum of two electrons. The second shell is farther away from the nucleus, and can hold up to eight

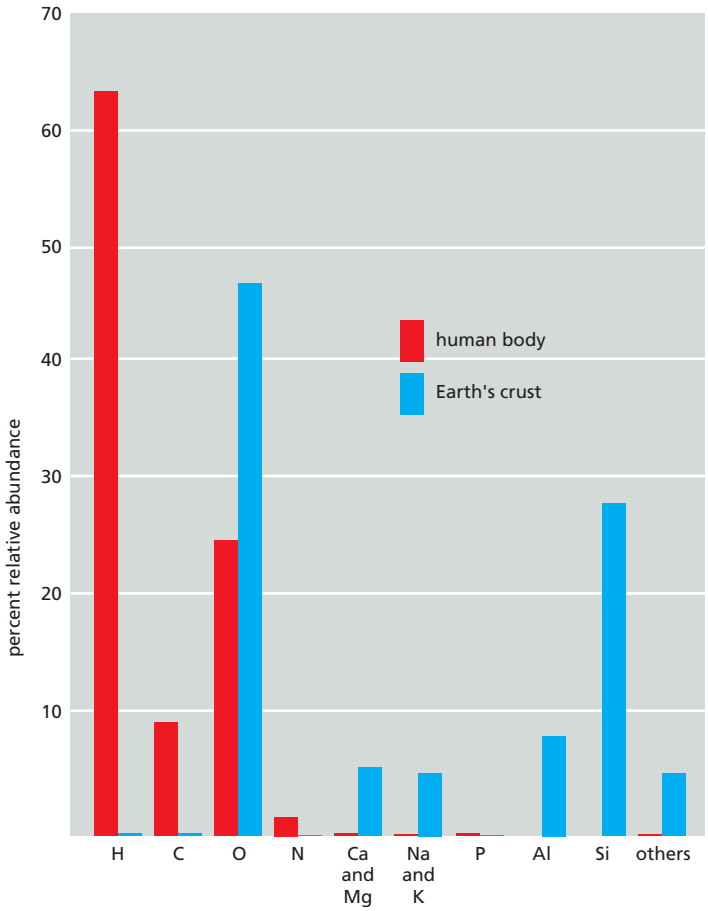


Figure 2–4 The distribution of elements in the Earth's crust differs radically from that in a living organism. The abundance of each element is expressed here as a percentage of the total number of atoms present in a biological or geological sample, including water. Thus, for example, more than 60% of the atoms in the human body are hydrogen atoms, and nearly 30% of the atoms in the Earth's crust are silicon atoms (Si). The relative abundance of elements is similar in all living things.

QUESTION 2–1

A cup of water, containing exactly 18 g, or 1 mole, of water, was emptied into the Aegean Sea 3000 years ago. What are the chances that the same quantity of water, scooped today from the Pacific Ocean, would include at least one of these ancient water molecules? Assume perfect mixing and an approximate volume for the world's oceans of 1.5 billion cubic kilometers (1.5×10^9 km^3).

electrons. The third shell can also hold up to eight electrons, which are even less tightly bound. The fourth and fifth shells can hold 18 electrons each. Atoms with more than four shells are very rare in biological molecules.

The arrangement of electrons in an atom is most stable when all the electrons are in the most tightly bound states that are possible for them—that is, when they occupy the innermost shells, closest to the nucleus. Therefore, with certain exceptions in the larger atoms, the electrons of an atom fill the shells in order—the first before the second, the second before the third, and so on. An atom whose outermost shell is entirely filled with electrons is especially stable and therefore chemically unreactive. Examples are helium with 2 electrons (atomic number 2), neon with 2 + 8 electrons (atomic number 10), and argon with 2 + 8 + 8 electrons (atomic number 18); these are all inert gases. Hydrogen, by contrast, has only one electron, which leaves its outermost shell half-filled, so it is highly reactive. The atoms found in living organisms all have outermost shells that are incompletely filled, and they are therefore able to react with one another to form molecules (**Figure 2–5**).

Because an incompletely filled electron shell is less stable than one that is completely filled, atoms with incomplete outer shells have a strong tendency to interact with other atoms so as to either gain or lose enough electrons to achieve a completed outermost shell. This electron exchange can be achieved either by transferring electrons from one atom to another or by sharing electrons between two atoms. These two strategies generate the two types of **chemical bonds** that bind atoms to one another: an *ionic bond* is formed when electrons are donated by one atom to another, whereas a *covalent bond* is formed when two atoms share a pair of electrons (**Figure 2–6**).

atomic number

	element	electron shell I	II	III	IV
1	Hydrogen (H)	●			
2	Helium (He)	●●			
6	Carbon (C)	●●	●●●●		
7	Nitrogen (N)	●●	●●●●●		
8	Oxygen (O)	●●	●●●●●●		
10	Neon (Ne)	●●	●●●●●●●●		
11	Sodium (Na)	●●	●●●●●●●●	●	
12	Magnesium (Mg)	●●	●●●●●●●●	●●	
15	Phosphorus (P)	●●	●●●●●●●●	●●●●●	
16	Sulfur (S)	●●	●●●●●●●●	●●●●●●	
17	Chlorine (Cl)	●●	●●●●●●●●	●●●●●●●	
18	Argon (Ar)	●●	●●●●●●●●	●●●●●●●●	
19	Potassium (K)	●●	●●●●●●●●	●●●●●●●●	●
20	Calcium (Ca)	●●	●●●●●●●●	●●●●●●●●	●●

Figure 2–5 An element's chemical reactivity depends on how its outermost electron shell is filled. All of the elements commonly found in living organisms have outermost shells that are not completely filled with electrons *(red)* and can thus participate in chemical reactions with other atoms. Inert gases *(yellow)*, in contrast, have completely filled outermost shells and are thus chemically unreactive.

An H atom, which needs only one more electron to fill its only shell, generally acquires it by sharing—forming one covalent bond with another atom. The other most common elements in living cells—C, N, and O, which have an incomplete second shell, and P and S, which have an incomplete third shell (see Figure 2–5)—generally share electrons and achieve a filled outer shell of eight electrons by forming several covalent bonds. The number of electrons an atom must acquire or lose (either by sharing or by transfer) to attain a filled outer shell determines the number of bonds the atom can make.

Because the state of the outer electron shell determines the chemical properties of an element, when the elements are listed in order of their atomic number we see a periodic recurrence of elements with similar properties: an element with, say, an incomplete second shell containing one electron will behave in much the same way as an element that has filled its second shell and has an incomplete third shell containing one electron. The metals, for example, have incomplete outer shells with just one or a few electrons, whereas, as we have just seen, the inert gases have full outer shells. This arrangement gives rise to the *periodic table* of the elements, outlined in **Figure 2–7**, which shows elements found in living organisms highlighted in color.

QUESTION 2–2

A carbon atom contains six protons and six neutrons.
A. What are its atomic number and atomic weight?
B. How many electrons does it have?
C. How many additional electrons must it add to fill its outermost shell? How does this affect carbon's chemical behavior?
D. Carbon with an atomic weight of 14 is radioactive. How does it differ in structure from nonradioactive carbon? How does this difference affect its chemical behavior?

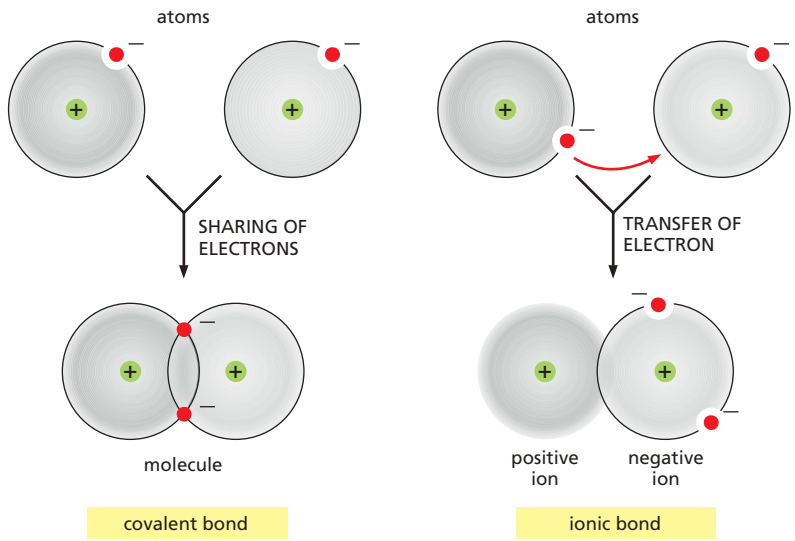


Figure 2–6 Atoms can attain a more stable arrangement of electrons in their outermost shell by interacting with one another. A covalent bond is formed when electrons are shared between atoms. An ionic bond is formed when electrons are transferred from one atom to the other. The two cases shown represent extremes; often, covalent bonds form with a partial transfer (unequal sharing of electrons), resulting in a polar covalent bond, as we discuss shortly.

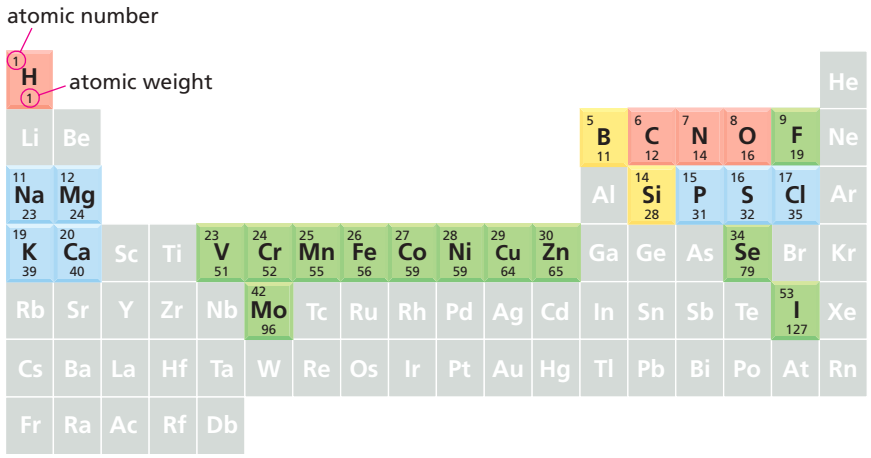


Figure 2–7 The chemistry of life is predominantly the chemistry of lighter elements. When ordered by their atomic number into a *periodic table*, elements fall into groups that show similar properties based on the number of electrons each element possesses in its outer shell. Atoms in the same vertical column must gain or lose the same number of electrons to attain a filled outer shell, and they thus behave similarly. Thus, both magnesium (Mg) and calcium (Ca) tend to give away the two electrons in their outer shells to form ionic bonds with atoms such as chlorine (Cl) that need extra electrons to complete their outer shells.

The four elements highlighted in *red* constitute 99% of the total number of atoms present in the human body and about 96% of our total weight. An additional seven elements, highlighted in *blue*, together represent about 0.9% of the total number of atoms. Other elements, shown in *green*, are required in trace amounts by humans. It remains unclear whether those elements shown in *yellow* are essential in humans or not.

The atomic weights shown here are those of the most common isotope of each element.

Covalent Bonds Form by the Sharing of Electrons

All of the characteristics of a cell depend on the molecules it contains. A **molecule** is a cluster of atoms held together by **covalent bonds**, in which electrons are shared rather than transferred between atoms. The shared electrons complete the outer shells of the interacting atoms. In the simplest possible molecule—a molecule of hydrogen (H_2)—two H atoms, each with a single electron, share their electrons, thus filling their outermost shells. The shared electrons form a cloud of negative charge that is densest between the two positively charged nuclei. This electron density helps to hold the nuclei together by opposing the mutual repulsion between their positive charges that would otherwise force them apart. The attractive and repulsive forces are in balance when the nuclei are separated by a characteristic distance, called the *bond length* (**Figure 2–8**).

Whereas an H atom can form only a single covalent bond, the other common atoms that form covalent bonds in cells—O, N, S, and P, as well as the all-important C—can form more than one. The outermost shells of these atoms, as we have seen, can accommodate up to eight electrons, and they form covalent bonds with as many other atoms as necessary to reach this number. Oxygen, with six electrons in its outer shell, is most stable when it acquires two extra electrons by sharing with other atoms, and it therefore forms up to two covalent bonds. Nitrogen, with five outer electrons, forms a maximum of three covalent bonds, while carbon, with four outer electrons, forms up to four covalent bonds—thus sharing four pairs of electrons (see Figure 2–5).

When one atom forms covalent bonds with several others, these multiple bonds have definite orientations in space relative to one another, reflecting the orientations of the orbits of the shared electrons. Covalent bonds between multiple atoms are therefore characterized by specific bond angles, as well as by specific bond lengths and bond energies (**Figure 2–9**). The four covalent bonds that can form around a carbon

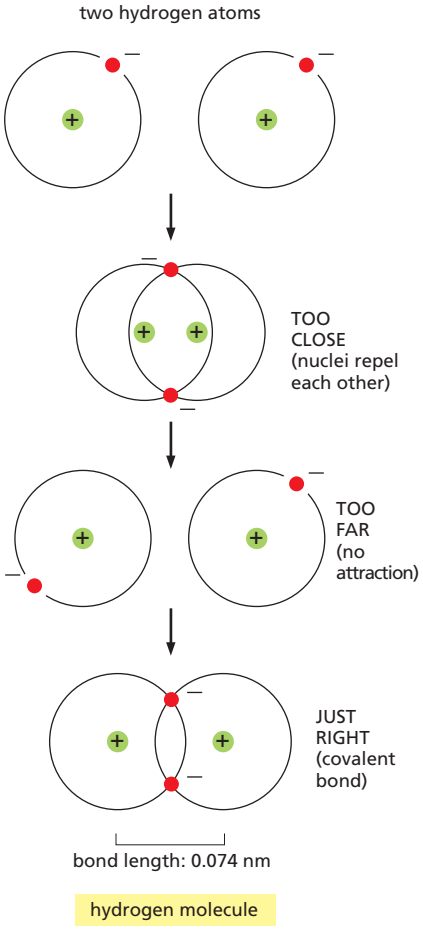


Figure 2–8 The hydrogen molecule is held together by a covalent bond. Each hydrogen atom in isolation has a single electron, which means that its first (and only) electron shell is incompletely filled. By coming together, the two atoms are able to share their electrons, so that each obtains a completely filled first shell, with the shared electrons adopting modified orbits around the two nuclei. The covalent bond between the two atoms has a definite length—0.074 nm, which is the distance between the two nuclei. If the atoms were closer together, the positive nuclei would repel each other; if they were farther apart, they would not be able to share electrons as effectively.

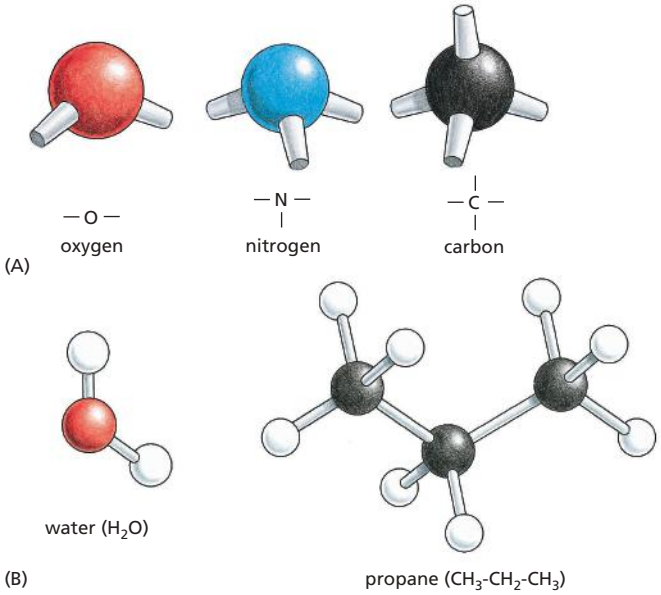


Figure 2–9 Covalent bonds are characterized by particular geometries. (A) The spatial arrangement of the covalent bonds that can be formed by oxygen, nitrogen, and carbon. (B) Molecules formed from these atoms therefore have a precise three-dimensional structure defined by the bond angles and bond lengths for each covalent linkage. A water molecule, for example, forms a "V" shape with an angle close to 109°.

In these ball-and-stick models, the different colored balls represent different atoms, and the sticks represent the covalent bonds. The colors traditionally used to represent the different atoms—*black* for carbon, *white* for hydrogen, *blue* for nitrogen, and *red* for oxygen—were established by the chemist August Wilhelm Hofmann in 1865, when he used a set of colored croquet balls to build molecular models for a public lecture on "the combining power of atoms."

atom, for example, are arranged as if pointing to the four corners of a regular tetrahedron. The precise orientation of the covalent bonds around carbon produces the three-dimensional geometry of organic molecules.

There Are Different Types of Covalent Bonds

Most covalent bonds involve the sharing of two electrons, one donated by each participating atom; these are called *single bonds*. Some covalent bonds, however, involve the sharing of more than one pair of electrons. Four electrons can be shared, for example, two coming from each participating atom; such a bond is called a *double bond*. Double bonds are shorter and stronger than single bonds and have a characteristic effect on the three-dimensional geometry of molecules containing them. A single covalent bond between two atoms generally allows the rotation of one part of a molecule relative to the other around the bond axis. A double bond prevents such rotation, producing a more rigid and less flexible arrangement of atoms (**Figure 2–10**). This restriction has a major influence on the three-dimensional shape of many macromolecules. **Panel 2–1** (pp. 66–67) reviews the covalent bonds commonly encountered in biological molecules.

Some molecules contain atoms that share electrons in a way that produces bonds that are intermediate in character between single and double bonds. The highly stable benzene molecule, for example, is made up of a ring of six carbon atoms in which the bonding electrons are evenly distributed (although the arrangement is sometimes depicted as an alternating sequence of single and double bonds, as shown in Panel 2–1).

When the atoms joined by a single covalent bond belong to different elements, the two atoms usually attract the shared electrons to different degrees. Covalent bonds in which the electrons are shared unequally in this way are known as *polar covalent bonds*. A **polar** structure (in the electrical sense) is one in which the positive charge is concentrated toward one end of the molecule (the positive pole) and the negative charge is concentrated toward the other end (the negative pole). Oxygen and nitrogen atoms, for example, attract electrons relatively strongly, whereas an H atom attracts electrons relatively weakly (because of the relative differences in the positive charges of the nuclei of C, O, N, and H). Thus the

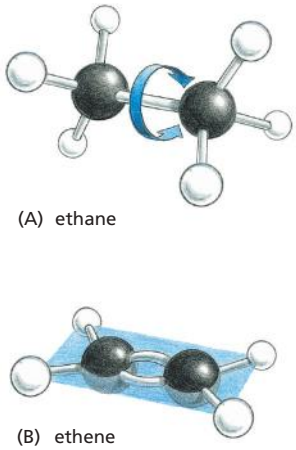


Figure 2–10 Carbon–carbon double bonds are shorter and more rigid than carbon–carbon single bonds. (A) The ethane molecule, with a single covalent bond between the two carbon atoms, shows the tetrahedral arrangement of the three single covalent bonds between each carbon atom and its three attached H atoms. The CH_3 groups, joined by a covalent C–C bond, can rotate relative to one another around the bond axis. (B) The double bond between the two carbon atoms in a molecule of ethene (ethylene) alters the bond geometry of the carbon atoms and brings all the atoms into the same plane; the double bond prevents the rotation of one CH_2 group relative to the other.

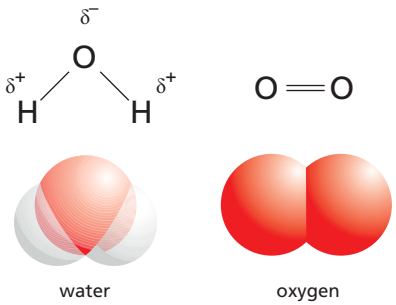


Figure 2–11 In polar covalent bonds, the electrons are shared unequally. Comparison of electron distributions in the polar covalent bonds in a molecule of water (H_2O) and the nonpolar covalent bonds in a molecule of oxygen (O_2). In H_2O, electrons are more strongly attracted to the oxygen nucleus than to the H nucleus, as indicated by the distributions of the partial negative (δ^-) and partial positive (δ^+) charges.

covalent bond between O and H, O–H, or between N and H, N–H, is polar (**Figure 2–11**). An atom of C and an atom of H, by contrast, attract electrons more equally. Thus the bond between carbon and hydrogen, C–H, is relatively nonpolar.

Covalent Bonds Vary in Strength

We have already seen that the covalent bond between two atoms has a characteristic length that depends on the atoms involved. A further crucial property of any chemical bond is its strength. *Bond strength* is measured by the amount of energy that must be supplied to break the bond, usually expressed in units of either kilocalories per mole (kcal/mole) or kilojoules per mole (kJ/mole). A kilocalorie is the amount of energy needed to raise the temperature of 1 liter of water by 1°C. Thus, if 1 kilocalorie of energy must be supplied to break 6×10^{23} bonds of a specific type (that is, 1 mole of these bonds), then the strength of that bond is 1 kcal/mole. One kilocalorie is equal to about 4.2 kJ, which is the unit of energy universally employed by physical scientists and, increasingly, by cell biologists as well.

To get an idea of what bond strengths mean, it is helpful to compare them with the average energies of the impacts that molecules continually undergo owing to collisions with other molecules in their environment—their thermal, or heat, energy. Typical covalent bonds are stronger than these thermal energies by a factor of 100, so they are resistant to being pulled apart by thermal motions. In living organisms, they are normally broken only during specific chemical reactions that are carefully controlled by highly specialized protein catalysts, called *enzymes*.

When water is present, covalent bonds are much stronger than ionic bonds. In ionic bonds, electrons are transferred rather than shared, as we now discuss.

Ionic Bonds Form by the Gain and Loss of Electrons

Ionic bonds are usually formed between atoms that can attain a completely filled outer shell most easily by donating electrons to—or accepting electrons from—another atom, rather than by sharing them. For example, returning to Figure 2–5, we see that a sodium (Na) atom can achieve a filled outer shell by giving up the single electron in its third shell. By contrast, a chlorine (Cl) atom can complete its outer shell by gaining just one electron. Consequently, if a Na atom encounters a Cl atom, an electron can jump from the Na to the Cl, leaving both atoms with filled outer shells. The offspring of this marriage between sodium, a soft and intensely reactive metal, and chlorine, a toxic green gas, is table salt (NaCl).

When an electron jumps from Na to Cl, both atoms become electrically charged **ions**. The Na atom that lost an electron now has one less electron than it has protons in its nucleus; it therefore has a net single positive charge (Na^+). The Cl atom that gained an electron now has one more electron than it has protons and has a net single negative charge (Cl^-). Because of their opposite charges, the Na^+ and Cl^- ions are attracted

QUESTION 2–3

Discuss whether the following statement is correct: "An ionic bond can, in principle, be thought of as a very polar covalent bond. Polar covalent bonds, then, fall somewhere between ionic bonds at one end of the spectrum and nonpolar covalent bonds at the other end."

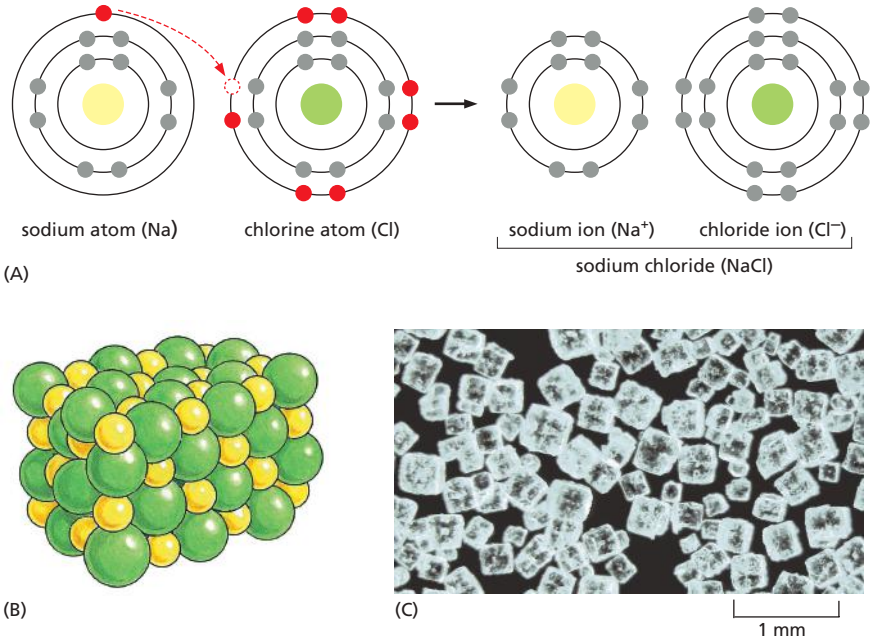


Figure 2–12 Sodium chloride is held together by ionic bonds. (A) An atom of sodium (Na) reacts with an atom of chlorine (Cl). Electrons of each atom are shown in their different shells; electrons in the chemically reactive (incompletely filled) outermost shells are shown in *red*. The reaction takes place with transfer of a single electron from sodium to chlorine, forming two electrically charged atoms, or ions, each with complete sets of electrons in their outermost shells. The two ions have opposite charge and are held together by electrostatic attraction. (B) The product of the reaction between sodium and chlorine, crystalline sodium chloride, contains sodium and chloride ions packed closely together in a regular array in which the charges are exactly balanced. (C) Color photograph of crystals of sodium chloride.

to each other and are thereby held together by an ionic bond (**Figure 2–12A**). Ions held together solely by ionic bonds are generally called *salts* rather than molecules. A NaCl crystal contains astronomical numbers of Na^+ and Cl^- packed together in a precise three-dimensional array with their opposite charges exactly balanced: a crystal only 1 mm across contains about 2×10^{19} ions of each type (**Figure 2–12B and C**).

Because of the favorable interaction between ions and water molecules (which are polar), many salts (including NaCl) are highly soluble in water. They dissociate into individual ions (such as Na^+ and Cl^-), each surrounded by a group of water molecules. Positive ions are called *cations*, and negative ions are called *anions*. Small inorganic ions such as Na^+, Cl^-, K^+, and Ca^{2+} play important parts in many biological processes, including the electrical activity of nerve cells, as we discuss in Chapter 12.

Noncovalent Bonds Help Bring Molecules Together in Cells

In aqueous solution, ionic bonds are 10–100 times weaker than the covalent bonds that hold atoms together in molecules. But this weakness has its place: much of biology depends on specific but transient interactions between one molecule and another. These associations are mediated by **noncovalent bonds**. Although noncovalent bonds are individually quite weak, their energies can sum to create an effective force between two molecules.

The ionic bonds that hold together the Na^+ and Cl^- ions in a salt crystal (see Figure 2–12) are a form of noncovalent bond called an *electrostatic attraction*. Electrostatic attractions are strongest when the atoms involved are fully charged, as are Na^+ and Cl^-. But a weaker electrostatic attraction also occurs between molecules that contain polar covalent bonds (see Figure 2–11). Polar covalent bonds are thus extremely important in biology because they allow molecules to interact through electrical forces. Any large molecule with many polar groups will have a pattern of partial positive and negative charges on its surface. When such a molecule encounters a second molecule with a complementary set of charges, the two will be attracted to each other by electrostatic attraction—even

QUESTION 2–4

What, if anything, is wrong with the following statement: "When NaCl is dissolved in water, the water molecules closest to the ions will tend to preferentially orient themselves so that their oxygen atoms face the sodium ions and face away from the chloride ions"? Explain your answer.

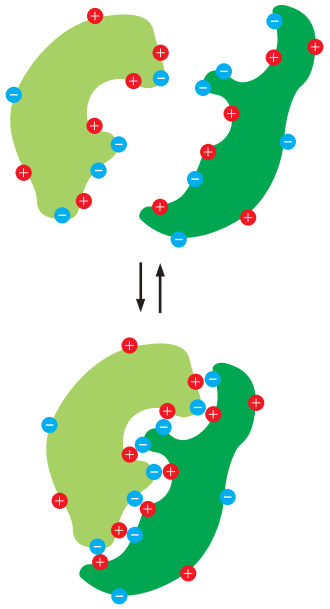


Figure 2–13 A large molecule, such as a protein, can bind to another protein through complementary charges on the surface of each molecule. In the aqueous environment of a cell, the many individual electrostatic attractions shown would help the two proteins stay bound to each other.

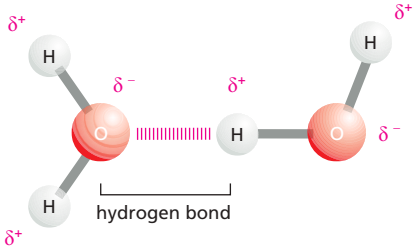


Figure 2–14 A hydrogen bond can form between two water molecules. These bonds are largely responsible for water's life-sustaining properties—including its ability to exist as a liquid at the temperatures inside the typical mammalian body.

though water greatly reduces the attractiveness of these charges in most biological settings. When present in large numbers, however, weak noncovalent bonds on the surfaces of large molecules can promote strong and specific binding (**Figure 2–13**).

Hydrogen Bonds Are Important Noncovalent Bonds For Many Biological Molecules

Water accounts for about 70% of a cell's weight, and most intracellular reactions occur in an aqueous environment. Life on Earth is thought to have begun in the ocean. Thus the properties of water have put a permanent stamp on the chemistry of living things.

In each molecule of water (H_2O), the two H atoms are linked to the O atom by covalent bonds. The two H–O bonds are highly polar because the O is strongly attractive for electrons, whereas the H is only weakly attractive. Consequently, there is an unequal distribution of electrons in a water molecule, with a preponderance of positive charge on the two H atoms and negative charge on the O (see Figure 2–11). When a positively charged region of one water molecule (that is, one of its H atoms) comes close to a negatively charged region (that is, the O) of a second water molecule, the electrical attraction between them can establish a weak bond called a **hydrogen bond** (**Figure 2–14**). These bonds are much weaker than covalent bonds and are easily broken by random thermal motions. Thus each bond lasts only an exceedingly short time. But the combined effect of many weak bonds is far from trivial. Each water molecule can form hydrogen bonds through its two H atoms to two other water molecules, producing a network in which hydrogen bonds are being continually broken and formed. It is because of these interlocking hydrogen bonds that water at room temperature is a liquid—with a high boiling point and high surface tension—and not a gas. Without hydrogen bonds, life as we know it could not exist. The biologically significant properties of water are reviewed in **Panel 2–2** (pp. 68–69).

Hydrogen bonds are not limited to water. In general, a hydrogen bond can form whenever a positively charged H atom held in one molecule by a polar covalent linkage comes close to a negatively charged atom—typically an oxygen or a nitrogen—belonging to another molecule (see Figure 2–14). Hydrogen bonds can also occur between different parts of a single large molecule, where they often help the molecule fold into a particular shape. The length and strength of hydrogen bonds and of ionic bonds are compared to those of covalent bonds in **Table 2–1**.

Molecules, such as alcohols, that contain polar bonds and that can form hydrogen bonds mix well with water. As mentioned previously, molecules carrying positive or negative charges (ions) likewise dissolve readily in water. Such molecules are termed **hydrophilic**, meaning that they are

TABLE 2–1 LENGTH AND STRENGTH OF SOME CHEMICAL BONDS

Bond type	Length* (nm)	Strength (kcal/mole)	
		in vacuum	in water
Covalent	0.10	90 [377]**	90 [377]
Noncovalent: ionic bond	0.25	80 [335]	3 [12.6]
Noncovalent: hydrogen bond	0.17	4 [16.7]	1 [4.2]

*The bond lengths and strengths listed are approximate, because the exact values will depend on the atoms involved.
**Values in brackets are kJ/mole. 1 calorie = 4.184 joules.

"water-loving." A large proportion of the molecules in the aqueous environment of a cell fall into this category, including sugars, DNA, RNA, and a majority of proteins. **Hydrophobic** ("water-fearing") molecules, by contrast, are uncharged and form few or no hydrogen bonds, and they do not dissolve in water.

Hydrocarbons are important hydrophobic cell constituents (see Panel 2–1, pp. 66–67). In these molecules, the H atoms are covalently linked to C atoms by nonpolar bonds. Because the H atoms have almost no net positive charge, they cannot form effective hydrogen bonds to other molecules. This makes the hydrocarbon as a whole hydrophobic—a property that is exploited by cells, whose membranes are constructed largely from *lipid molecules* that have long hydrocarbon tails. Because lipids do not dissolve in water, they can form the thin membrane barriers that keep the aqueous interior of the cell separate from the surrounding aqueous environment, as we discuss later.

Some Polar Molecules Form Acids and Bases in Water

One of the simplest kinds of chemical reaction, and one that has profound significance in cells, takes place when a molecule possessing a highly polar covalent bond between a hydrogen and another atom dissolves in water. The hydrogen atom in such a bond has given up its electron almost entirely to the companion atom, so it exists as an almost naked positively charged hydrogen nucleus—in other words, a *proton* (H^+). When the polar molecule becomes surrounded by water molecules, the proton will be attracted to the partial negative charge on the oxygen atom of an adjacent water molecule (see Figure 2–11); this proton can dissociate from its original partner and associate instead with the oxygen atom of the water molecule, generating a **hydronium ion** (H_3O^+) (**Figure 2–15A**). The reverse reaction also takes place very readily, so one has to imagine an equilibrium state in which billions of protons are constantly flitting to and fro between one molecule and another in an aqueous solution.

Substances that release protons when they dissolve in water, thus forming H_3O^+, are termed **acids**. The higher the concentration of H_3O^+, the more acidic the solution. H_3O^+ is present even in pure water, at a concentration of 10^{-7} M, as a result of the movement of protons from one water molecule to another (**Figure 2–15B**). By tradition, the H_3O^+ concentration

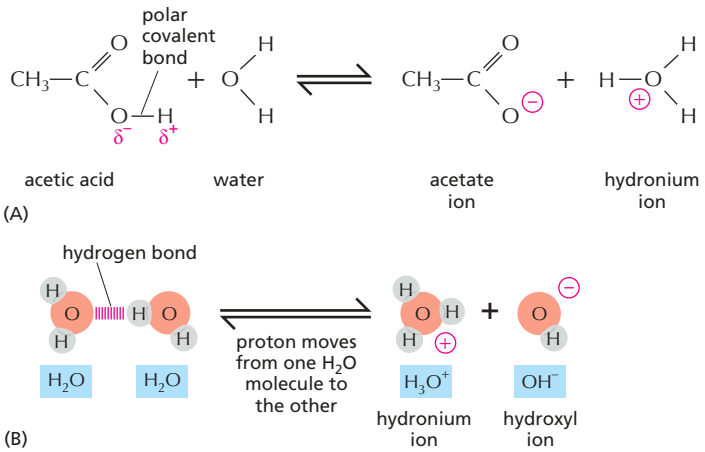


Figure 2–15 Protons move continuously from one water molecule to another in aqueous solutions. (A) The reaction that takes place when a molecule of acetic acid dissolves in water. At pH 7, nearly all of the acetic acid molecules are present as acetate ions. (B) Water molecules are continually exchanging protons with each other to form hydronium and hydroxyl ions. These ions in turn rapidly recombine to form water molecules.

is usually referred to as the H^+ concentration, even though most protons in an aqueous solution are present as H_3O^+. To avoid the use of unwieldy numbers, the concentration of H^+ is expressed using a logarithmic scale called the **pH scale**, as illustrated in Panel 2–2. Pure water has a pH of 7.0 and is thus neutral—that is, neither acidic (pH < 7) nor basic (pH > 7).

Acids are characterized as being strong or weak, depending on how readily they give up their protons to water. Strong acids, such as hydrochloric acid (HCl), lose their protons easily. Acetic acid, on the other hand, is a weak acid because it holds on to its proton more tightly when dissolved in water. Many of the acids important in the cell—such as molecules containing a carboxyl (COOH) group—are weak acids (see Panel 2–2, pp. 68–69). Their tendency to give up a proton with some reluctance is a useful characteristic, as it renders the molecules sensitive to changes in pH in the cell—a property that can be exploited to regulate function.

Because protons can be passed readily to many types of molecules in cells, thus altering the molecules' character, the H^+ concentration inside a cell (the pH) must be closely controlled. Acids—especially weak acids—will give up their protons more readily if the H^+ concentration is low and will tend to accept them back if the concentration is high.

The opposite of an acid is a **base**, which includes any molecule that accepts a proton when dissolved in water. Just as the defining property of an acid is that it raises the concentration of H_3O^+ ions by donating a proton to a water molecule, so the defining property of a base is that it raises the concentration of hydroxyl (OH^-) ions by removing a proton from a water molecule. Thus sodium hydroxide (NaOH) is basic (the term *alkaline* is also used) because it dissociates in aqueous solution to form Na^+ ions and OH^- ions; because it does so readily, NaOH is called a strong base. Weak bases—which have a weak tendency to accept a proton from water—however, are actually more important in cells. Many biologically important weak bases contain an amino (NH_2) group, which can generate OH^- by taking a proton from water: $-NH_2 + H_2O \rightarrow -NH_3^+ + OH^-$ (see Panel 2–2, pp. 68–69).

Because an OH^- ion combines with a proton to form a water molecule, an increase in the OH^- concentration forces a decrease in the H^+ concentration, and vice versa. A pure solution of water thus contains an equal concentration (10^{-7} M) of both ions, rendering it neutral (pH 7). The interior of a cell is also kept close to neutral by the presence of **buffers**: mixtures of weak acids and bases that can adjust proton concentrations around pH 7 by releasing protons (acids) or taking them up (bases). This give-and-take keeps the pH of the cell relatively constant under a variety of conditions.

QUESTION 2–5

A. Are there any H_3O^+ ions present in pure water at neutral pH (i.e., at pH = 7.0)? If so, how are they formed?
B. If they exist, what is the ratio of H_3O^+ ions to H_2O molecules at neutral pH? (Hint: the molecular weight of water is 18, and 1 liter of water weighs 1 kg.)

SMALL MOLECULES IN CELLS

Having looked at the ways atoms combine to form small molecules and how these molecules behave in an aqueous environment, we now examine the main classes of small molecules found in cells and their biological roles. Amazingly, we will see that a few basic categories of molecules, formed from a handful of different elements, give rise to all the extraordinary richness of form and behavior displayed by living things.

A Cell Is Formed from Carbon Compounds

If we disregard water, nearly all the molecules in a cell are based on carbon. Carbon is outstanding among all the elements in its ability to form large molecules; silicon—an element with the same number of electrons in its outer shell—is a poor second. Because a carbon atom is small and

has four electrons and four vacancies in its outer shell, it can form four covalent bonds with other atoms (see Figure 2–9). Most importantly, one carbon atom can join to other carbon atoms through highly stable covalent C–C bonds to form chains and rings and hence generate large and complex molecules with no obvious upper limit to their size. The small and large carbon compounds made by cells are called **organic molecules**. By contrast, all other molecules, including water, are said to be **inorganic**.

Certain combinations of atoms, such as the methyl ($-CH_3$), hydroxyl (–OH), carboxyl (–COOH), carbonyl (–C=O), phosphoryl ($-PO_3^{2-}$), and amino ($-NH_2$) groups, occur repeatedly in organic molecules. Each such **chemical group** has distinct chemical and physical properties that influence the behavior of the molecule in which the group occurs, including whether the molecule tends to gain or lose protons and with which other molecules it will interact. Knowing these groups and their chemical properties greatly simplifies understanding the chemistry of life. The most common chemical groups and some of their properties are summarized in Panel 2–1 (pp. 67–68).

Cells Contain Four Major Families of Small Organic Molecules

The small organic molecules of the cell are carbon compounds with molecular weights in the range 100–1000 that contain up to 30 or so carbon atoms. They are usually found free in solution in the cytosol and have many different roles. Some are used as *monomer* subunits to construct the cell's giant polymeric *macromolecules*—its proteins, nucleic acids, and large polysaccharides. Others serve as energy sources, which are broken down and transformed into other small molecules in a maze of intracellular metabolic pathways. Many have more than one role in the cell—acting, for example, as both a potential subunit for a macromolecule and as an energy source. The small organic molecules are much less abundant than the organic macromolecules, accounting for only about one-tenth of the total mass of organic matter in a cell. As a rough guess, there may be a thousand different kinds of these small organic molecules in a typical animal cell.

All organic molecules are synthesized from—and are broken down into—the same set of simple compounds. Both their synthesis and their breakdown occur through sequences of simple chemical changes that are limited in variety and follow step-by-step rules. As a consequence, the compounds in a cell are chemically related, and most can be classified into a small number of distinct families. Broadly speaking, cells contain four major families of small organic molecules: the *sugars*, the *fatty acids*, the *amino acids*, and the *nucleotides* (**Figure 2–16**). Although many compounds present in cells do not fit into these categories, these four families of small organic molecules, together with the macromolecules made by linking them into long chains, account for a large fraction of a cell's mass (**Table 2–2**).

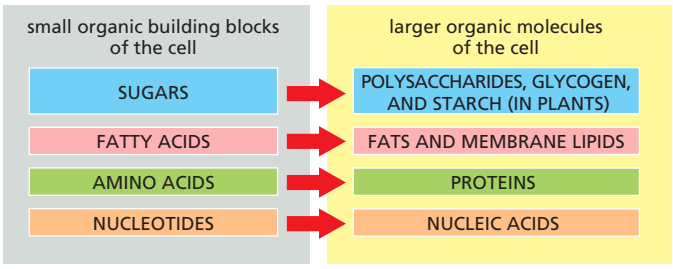


Figure 2–16 Sugars, fatty acids, amino acids, and nucleotides are the four main families of small organic molecules in cells. They form the monomeric building blocks, or subunits, for larger organic molecules, including most of the macromolecules and other molecular assemblies of the cell. Some, like the sugars and the fatty acids, are also energy sources.

TABLE 2–2 THE CHEMICAL COMPOSITION OF A BACTERIAL CELL

	Percent of total cell weight	Approximate number of types of each class of molecule
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	300
Phospholipids	2	4*
Macromolecules (nucleic acids, proteins, and polysaccharides)	24	3000

*There are four classes of phospholipids, each of which exists in many varieties.

Sugars Are Both Energy Sources and Subunits of Polysaccharides

The simplest **sugars**—the *monosaccharides*—are compounds with the general formula $(CH_2O)_n$, where n is usually 3, 4, 5, or 6. Sugars, and the larger molecules made from them, are also called *carbohydrates* because of this simple formula. Glucose, for example, has the formula $C_6H_{12}O_6$ (**Figure 2–17**). The formula, however, does not fully define the molecule: the same set of carbons, hydrogens, and oxygens can be joined together by covalent bonds in a variety of ways, creating structures with different shapes. Thus glucose can be converted into a different sugar—mannose or galactose—simply by switching the orientations of specific –OH groups relative to the rest of the molecule (**Panel 2–3**, pp. 70–71). Each of these sugars, moreover, can exist in either of two forms, called the D-form and the L-form, which are mirror images of each other. Sets of molecules with the same chemical formula but different structures are called *isomers*, and mirror-image pairs of such molecules are called *optical isomers*. Isomers are widespread among organic molecules in general, and they play a

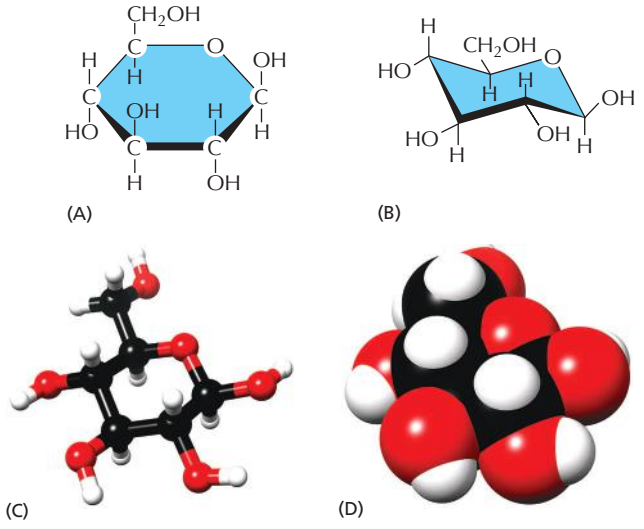


Figure 2–17 The structure of glucose, a monosaccharide, can be represented in several ways. (A) A structural formula in which the atoms are shown as chemical symbols, linked together by solid lines representing the covalent bonds. The thickened lines are used to indicate the plane of the sugar ring and to show that the –H and –OH groups are not in the same plane as the ring. (B) Another kind of structural formula that shows the three-dimensional structure of glucose in the so-called "chair configuration." (C) A ball-and-stick model in which the three-dimensional arrangement of the atoms in space is indicated. (D) A space-filling model, which, as well as depicting the three-dimensional arrangement of the atoms, also gives some idea of their relative sizes and of the surface contours of the molecule (Movie 2.1). The atoms in (C) and (D) are colored as in Figure 2–9: C, *black*; H, *white*; O, *red*. This is the conventional color coding for these atoms and will be used throughout this book.

major part in generating the enormous variety of sugars. A more complete outline of sugar structures and chemistry is presented in Panel 2–3.

Monosaccharides can be linked by covalent bonds—called glycosidic bonds—to form larger carbohydrates. Two monosaccharides linked together make a disaccharide, such as sucrose, which is composed of a glucose and a fructose unit. Larger sugar polymers range from the *oligosaccharides* (trisaccharides, tetrasaccharides, and so on) up to giant *polysaccharides,* which can contain thousands of monosaccharide units. In most cases, the prefix *oligo-* is used to refer to molecules made of a small number of monomers, typically 2 to 10 in the case of oligosaccharides. Polymers, in contrast, can contain hundreds or thousands of subunits.

The way sugars are linked together illustrates some common features of biochemical bond formation. A bond is formed between an –OH group on one sugar and an –OH group on another by a **condensation reaction**, in which a molecule of water is expelled as the bond is formed. The subunits in other biological polymers, including nucleic acids and proteins, are also linked by condensation reactions in which water is expelled. The bonds created by all of these condensation reactions can be broken by the reverse process of **hydrolysis**, in which a molecule of water is consumed (**Figure 2–18**).

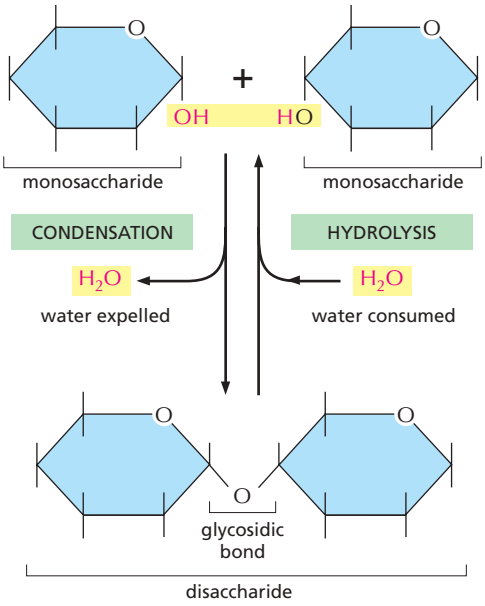


Figure 2–18 Two monosaccharides can be linked by a covalent glycosidic bond to form a disaccharide. This reaction belongs to a general category of reactions termed *condensation reactions*, in which two molecules join together as a result of the loss of a water molecule. The reverse reaction (in which water is added) is termed *hydrolysis*.

Because each monosaccharide has several free hydroxyl groups that can form a link to another monosaccharide (or to some other compound), sugar polymers can be branched, and the number of possible polysaccharide structures is extremely large. For this reason, it is much more difficult to determine the arrangement of sugars in a complex polysaccharide than to determine the nucleotide sequence of a DNA molecule or the amino acid sequence of a protein, in which each unit is joined to the next in exactly the same way.

The monosaccharide *glucose* has a central role as an energy source for cells. It is broken down to smaller molecules in a series of reactions, releasing energy that the cell can harness to do useful work, as we explain in Chapter 13. Cells use simple polysaccharides composed only of glucose units—principally *glycogen* in animals and *starch* in plants—as long-term stores of glucose, held in reserve for energy production.

Sugars do not function exclusively in the production and storage of energy. They are also used, for example, to make mechanical supports. The most abundant organic molecule on Earth—the *cellulose* that forms plant cell walls—is a polysaccharide of glucose. Another extraordinarily abundant organic substance, the *chitin* of insect exoskeletons and fungal cell walls, is also a polysaccharide—in this case, a linear polymer of a sugar derivative called *N*-acetylglucosamine (see Panel 2–3, pp. 70–71). Other polysaccharides, which tend to be slippery when wet, are the main components of slime, mucus, and gristle.

Smaller oligosaccharides can be covalently linked to proteins to form *glycoproteins*, or to lipids to form *glycolipids* (**Panel 2–4**, pp. 72–73), which are both found in cell membranes. The sugar side chains attached to glycoproteins and glycolipids in the plasma membrane are thought to help protect the cell surface and often help cells adhere to one another. Differences in the types of cell-surface sugars form the molecular basis for different human blood groups.

Fatty Acid Chains Are Components of Cell Membranes

A **fatty acid** molecule, such as *palmitic acid*, has two chemically distinct regions. One is a long hydrocarbon chain, which is hydrophobic and not very reactive chemically. The other is a carboxyl (–COOH) group,

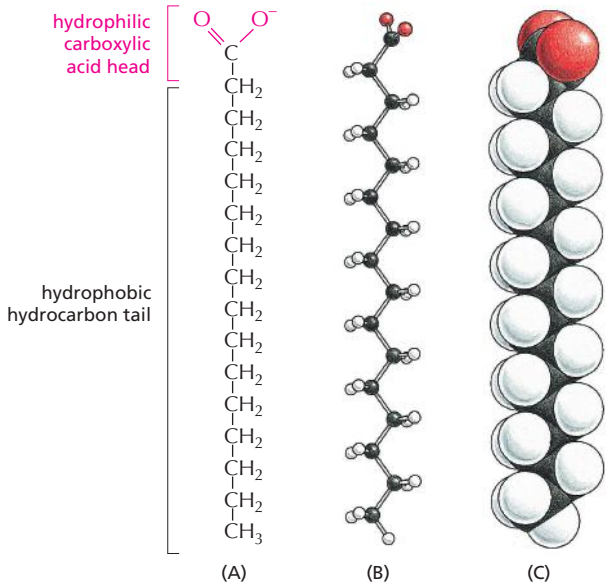


Figure 2–19 Fatty acids have both hydrophobic and hydrophilic components. The hydrophobic hydrocarbon chain is attached to a hydrophilic carboxylic acid group. Different fatty acids have different hydrocarbon tails. Palmitic acid is shown here. (A) Structural formula, showing the carboxylic acid head group in its ionized form, as it exists in water at pH 7. (B) Ball-and-stick model. (C) Space-filling model (Movie 2.2).

which behaves as an acid (carboxylic acid): in an aqueous solution, it is ionized ($-COO^-$), extremely hydrophilic, and chemically reactive (**Figure 2–19**). Almost all the fatty acid molecules in a cell are covalently linked to other molecules by their carboxylic acid group (see Panel 2–4, pp. 72–73). Molecules—such as fatty acids—that possess both hydrophobic and hydrophilic regions are termed *amphipathic*.

The hydrocarbon tail of palmitic acid is *saturated*: it has no double bonds between its carbon atoms and contains the maximum possible number of hydrogens. Some other fatty acids, such as oleic acid, have *unsaturated* tails, with one or more double bonds along their length. The double bonds create kinks in the hydrocarbon tails, interfering with their ability to pack together, and it is the absence or presence of these double bonds that accounts for the difference between hard (saturated) and soft (polyunsaturated) margarine. Fatty acid tails are also found in cell membranes, where the tightness of their packing affects the fluidity of the membrane. The many different fatty acids found in cells differ only in the length of their hydrocarbon chains and in the number and position of the carbon–carbon double bonds (see Panel 2–4).

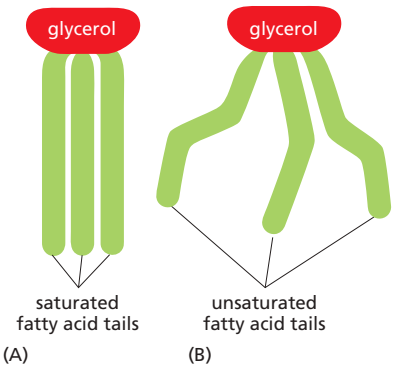


Figure 2–20 The properties of fats depend on the length and saturation of the fatty acid chains they carry. Fatty acids are stored in the cytoplasm of many cells in the form of droplets of *triacylglycerol* molecules made of three fatty acid chains joined to a glycerol molecule. (A) Saturated fats are found in meat and dairy products. (B) Plant oils, such as corn oil, contain unsaturated fatty acids, which may be monounsaturated (containing one double bond) or polyunsaturated (containing multiple double bonds); this is why plant oils are liquid at room temperature. Although fats are essential in the diet, saturated fats are not: they raise the concentration of cholesterol in the blood, which tends to clog the arteries, increasing the risk of heart attacks and strokes.

Fatty acids serve as a concentrated food reserve in cells: they can be broken down to produce about six times as much usable energy, weight for weight, as glucose. Fatty acids are stored in the cytoplasm of many cells in the form of fat droplets composed of *triacylglycerol* molecules—compounds made of three fatty acid chains covalently joined to a glycerol molecule (**Figure 2–20**, and see Panel 2–4). Triacylglycerols are the animal fats found in meat, butter, and cream, and the plant oils such as corn oil and olive oil. When a cell needs energy, the fatty acid chains can be released from triacylglycerols and broken down into two-carbon units. These two-carbon units are identical to those derived from the breakdown of glucose, and they enter the same energy-yielding reaction pathways, as described in Chapter 13.

Fatty acids and their derivatives, including triacylglycerols, are examples of **lipids**. Lipids are loosely defined as molecules that are insoluble in water but soluble in fat and organic solvents such as benzene. They typically contain long hydrocarbon chains, as in the fatty acids, or multiple linked aromatic rings, as in the *steroids* (see Panel 2–4).

The most unique function of fatty acids is in the formation of the **lipid bilayer**, which is the basis for all cell membranes. These thin sheets,

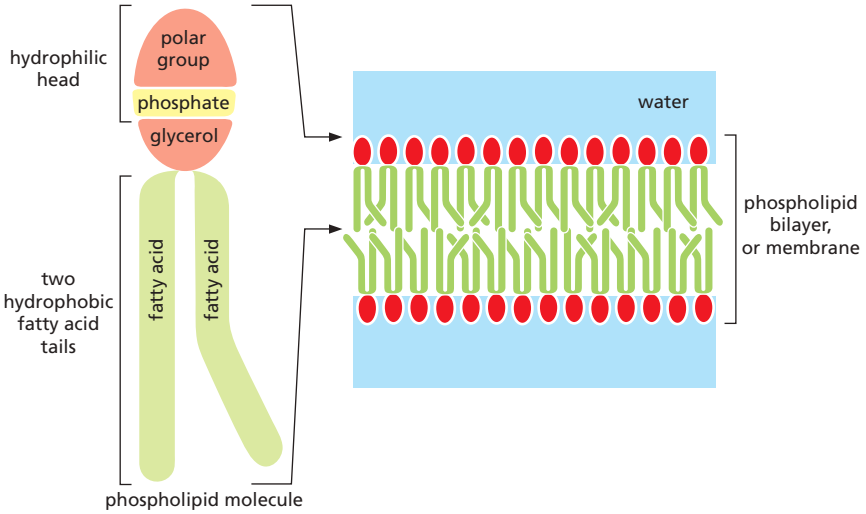


Figure 2–21 Phospholipids can aggregate to form cell membranes. Phospholipids are composed of two hydrophobic fatty acid tails joined to a hydrophilic head. In an aqueous environment, the hydrophobic tails pack together to exclude water, forming a lipid bilayer, with the hydrophilic heads of the phospholipid molecules on the outside, facing the aqueous environment, and the hydrophobic tails on the inside.

which enclose all cells and surround their internal organelles, are composed largely of *phospholipids* (**Figure 2–21**).

Like triacylglycerols, most phospholipids are constructed mainly from fatty acids and glycerol. In these phospholipids, however, the glycerol is joined to two fatty acid chains, rather than to three as in triacylglycerols. The remaining –OH group on the glycerol is linked to a hydrophilic phosphate group, which in turn is attached to a small hydrophilic compound such as choline (see Panel 2–4, pp. 72–73). With their two hydrophobic fatty acid tails and a hydrophilic, phosphate-containing head, phospholipids are strongly amphipathic. This characteristic amphipathic composition and shape gives them different physical and chemical properties from triacylglycerols, which are predominantly hydrophobic. In addition to phospholipids, cell membranes contain differing amounts of other lipids, including *glycolipids*, which contain one or more sugars instead of a phosphate group.

Thanks to their amphipathic nature, phospholipids readily form membranes in water. These lipids will spread over the surface of water to form a monolayer, with their hydrophobic tails facing the air and their hydrophilic heads in contact with the water. Two such molecular layers can readily combine tail-to-tail in water to form the phospholipid sandwich that is the lipid bilayer (see Chapter 11).

Amino Acids Are the Subunits of Proteins

Amino acids are small organic molecules with one defining property: they all possess a carboxylic acid group and an amino group, both linked to their α-carbon atom (**Figure 2–22**). Each amino acid also has a side chain attached to its α-carbon. The identity of this side chain is what distinguishes one amino acid from another.

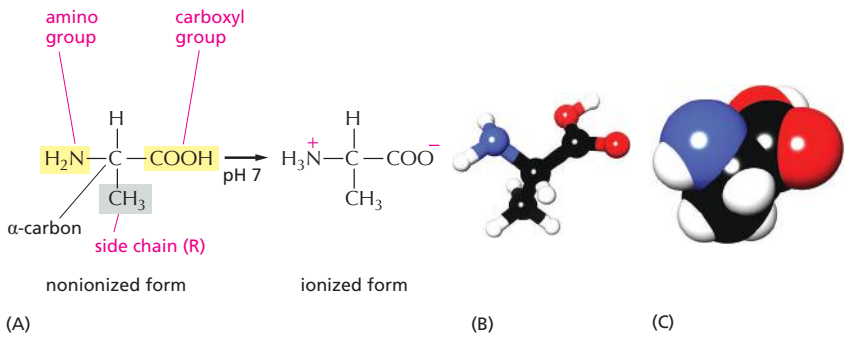


Figure 2–22 All amino acids have an amino group, a carboxyl group, and a side chain (R) attached to their α-carbon atom. In the cell, where the pH is close to 7, free amino acids exist in their ionized form; but, when they are incorporated into a polypeptide chain, the charges on their amino and carboxyl groups disappear. (A) The amino acid shown is alanine, one of the simplest amino acids, which has a methyl group (CH_3) as its side chain. (B) A ball-and-stick model and (C) a space-filling model of alanine. In (B) and (C), the N atom is *blue*.

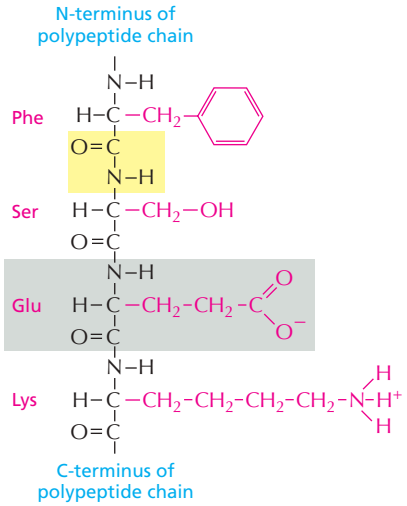


Figure 2–23 Amino acids in a protein are held together by peptide bonds. The four amino acids shown are linked together by three peptide bonds, one of which is highlighted in *yellow*. One of the amino acids, glutamic acid, is shaded in *gray*. The amino acid side chains are shown in *red*. The two ends of a polypeptide chain are chemically distinct. One end, the N-terminus, is capped by an amino group, and the other, the C-terminus, ends in a carboxyl group. The sequence of amino acids in a protein is abbreviated using either a three-letter or a one-letter code, and the sequence is always read from the N-terminus (see Panel 2–5, pp. 74–75). In the example given, the sequence is Phe-Ser-Glu-Lys (or FSEK).

Cells use amino acids to build **proteins**—polymers made of amino acids, which are joined head-to-tail in a long chain that folds up into a three-dimensional structure that is unique to each type of protein. The covalent bond between two adjacent amino acids in a protein chain is called a *peptide bond*; the chain of amino acids is also known as a *polypeptide*. Peptide bonds are formed by condensation reactions that link one amino acid to the next. Regardless of the specific amino acids from which it is made, the polypeptide always has an amino (NH_2) group at one end—its *N-terminus*—and a carboxyl (COOH) group at its other end—its *C-terminus* (**Figure 2–23**). This difference in the two ends gives a polypeptide a definite directionality—a structural (as opposed to electrical) polarity.

Twenty types of amino acids are commonly found in proteins, each with a different side chain attached to the α-carbon atom (**Panel 2–5**, pp. 74–75). The same 20 amino acids are found in all proteins, whether they hail from bacteria, plants, or animals. How this precise set of 20 amino acids came to be chosen is one of the mysteries surrounding the evolution of life; there is no obvious chemical reason why other amino acids could not have served just as well. But once the selection had been locked into place, it could not be changed, as too much chemistry had evolved to exploit it. Switching the types of amino acids used by cells would require a living creature to retool its entire metabolism to cope with the new building blocks.

QUESTION 2–6

Why do you suppose only L-amino acids and not a random mixture of the L- and D-forms of each amino acid are used to make proteins?

Like sugars, all amino acids (except glycine) exist as optical isomers in D- and L-forms (see Panel 2–5). But only L-forms are ever found in proteins (although D-amino acids occur as part of bacterial cell walls and in some antibiotics, and D-serine is used as a signal molecule in the brain). The origin of this exclusive use of L-amino acids to make proteins is another evolutionary mystery.

The chemical versatility that the 20 standard amino acids provide is vitally important to the function of proteins. Five of the 20 amino acids—including lysine and glutamic acid, shown in Figure 2–23—have side chains that can form ions in solution and can therefore carry a charge. The others are uncharged. Some amino acids are polar and hydrophilic, and some are nonpolar and hydrophobic (see Panel 2–5). As we discuss in Chapter 4, the collective properties of the amino acid side chains underlie all the diverse and sophisticated functions of proteins.

Nucleotides Are the Subunits of DNA and RNA

DNA and RNA are built from subunits called **nucleotides**. *Nucleosides* are made of a nitrogen-containing ring compound linked to a five-carbon sugar, which can be either ribose or deoxyribose (**Panel 2–6**, pp. 76–77). Nucleotides are nucleosides that contain one or more phosphate groups attached to the sugar, and they come in two main forms: those containing ribose are known as *ribonucleotides*, and those containing deoxyribose are known as *deoxyribonucleotides*.

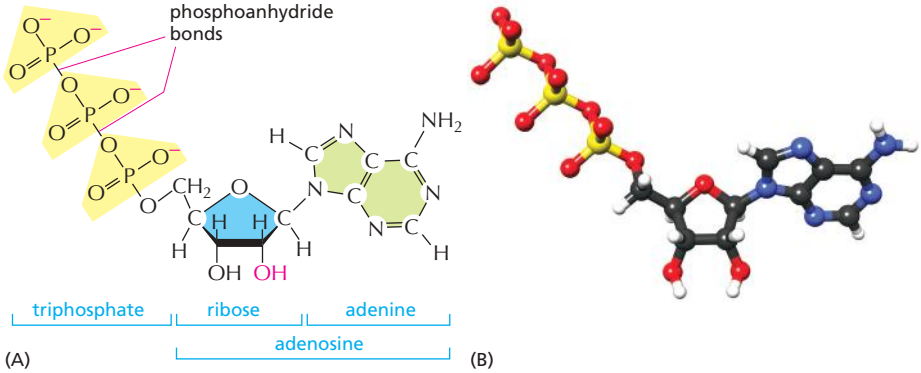


Figure 2–24 Adenosine triphosphate (ATP) is a crucially important energy carrier in cells. (A) Structural formula, in which the three phosphate groups are shaded in *yellow*. (B) Ball-and-stick model (Movie 2.3). In (B), the P atoms are *yellow*.

The nitrogen-containing rings of all these molecules are generally referred to as *bases* for historical reasons: under acidic conditions, they can each bind an H^+ (proton) and thereby increase the concentration of OH^- ions in aqueous solution. There is a strong family resemblance between the different nucleotide bases. *Cytosine* (C), *thymine* (T), and *uracil* (U) are called *pyrimidines*, because they all derive from a six-membered pyrimidine ring; *guanine* (G) and *adenine* (A) are *purines*, which bear a second, five-membered ring fused to the six-membered ring. Each nucleotide is named after the base it contains (see Panel 2–6, pp. 76–77).

Nucleotides can act as short-term carriers of chemical energy. Above all others, the ribonucleotide **adenosine triphosphate**, or **ATP** (**Figure 2–24**), participates in the transfer of energy in hundreds of metabolic reactions. ATP is formed through reactions that are driven by the energy released by the breakdown of foodstuffs. Its three phosphates are linked in series by two *phosphoanhydride bonds* (see Panel 2–6). Rupture of these phosphate bonds releases large amounts of useful energy. The terminal phosphate group in particular is frequently split off by hydrolysis (**Figure 2–25**). In many situations, transfer of this phosphate to other molecules releases energy that drives energy-requiring biosynthetic reactions. Other nucleotide derivatives serve as carriers for the transfer of other chemical groups. All of this is described in Chapter 3.

Nucleotides also have a fundamental role in the storage and retrieval of biological information. They serve as building blocks for the construction

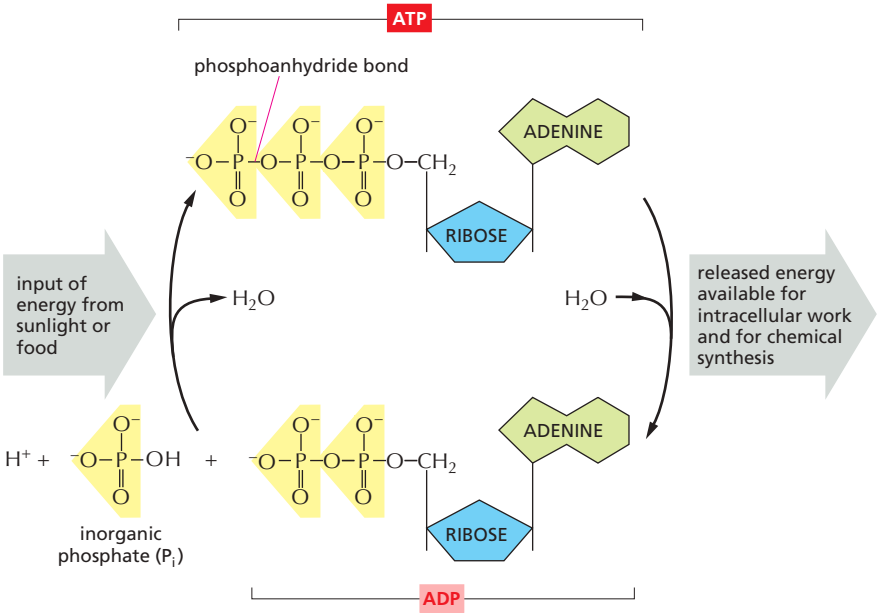


Figure 2–25 ATP is synthesized from ADP and inorganic phosphate, and it releases energy when it is hydrolyzed back to ADP and inorganic phosphate. The energy required for ATP synthesis is derived from either the energy-yielding oxidation of foodstuffs (in animal cells, fungi, and some bacteria) or the capture of light (in plant cells and some bacteria). The hydrolysis of ATP provides the energy to drive many processes inside cells. Together, the two reactions shown form the ATP cycle.

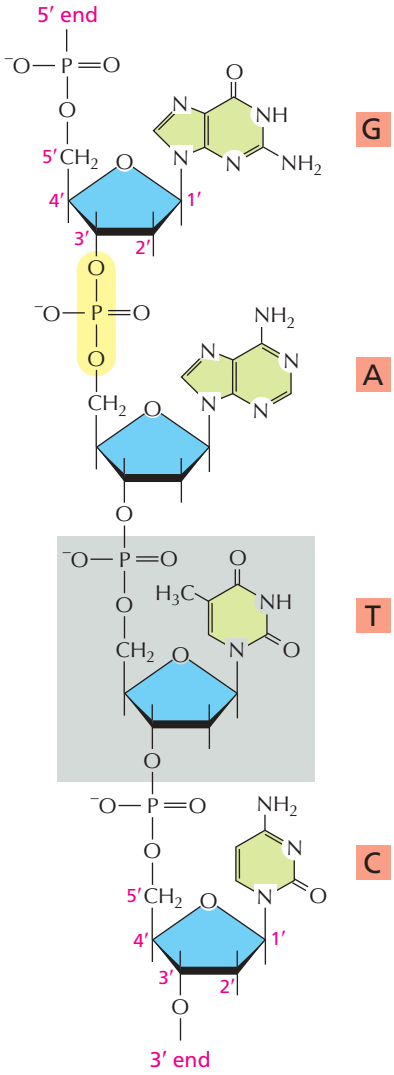


Figure 2–26 A short length of one chain of a deoxyribonucleic acid (DNA) molecule shows the covalent phosphodiester bonds linking four consecutive nucleotides. Because the bonds link specific carbon atoms in the sugar ring—known as the 5′ and 3′ atoms—one end of a polynucleotide chain, the 5′ end, has a free phosphate group and the other, the 3′ end, has a free hydroxyl group. One of the nucleotides, thymine (T), is shaded in *gray*, and one phosphodiester bond is highlighted in *yellow*. The linear sequence of nucleotides in a polynucleotide chain is commonly abbreviated by a one-letter code, and the sequence is always read from the 5′ end. In the example illustrated, the sequence is GATC.

of *nucleic acids*—long polymers in which nucleotide subunits are linked by the formation of covalent *phosphodiester bonds* between the phosphate group attached to the sugar of one nucleotide and a hydroxyl group on the sugar of the next nucleotide (**Figure 2–26**). Nucleic acid chains are synthesized from energy-rich nucleoside triphosphates by a condensation reaction that releases inorganic pyrophosphate during phosphodiester bond formation (see Panel 2–6, pp. 76–77).

There are two main types of nucleic acids, which differ in the type of sugar contained in their sugar–phosphate backbone. Those based on the sugar ribose are known as **ribonucleic acids**, or **RNA**, and contain the bases A, G, C, and U. Those based on deoxyribose (in which the hydroxyl at the 2′ position of the ribose carbon ring is replaced by a hydrogen) are known as **deoxyribonucleic acids**, or **DNA**, and contain the bases A, G, C, and T (T is chemically similar to the U in RNA; see Panel 2–6). RNA usually occurs in cells in the form of a single-stranded polynucleotide chain, but DNA is virtually always in the form of a double-stranded molecule: the DNA double helix is composed of two polynucleotide chains that run in opposite directions and are held together by hydrogen bonds between the bases of the two chains (**Panel 2–7**, pp. 78–79).

The linear sequence of nucleotides in a DNA or an RNA molecule encodes genetic information. The two nucleic acids, however, have different roles in the cell. DNA, with its more stable, hydrogen-bonded helices, acts as a long-term repository for hereditary information, while single-stranded RNA is usually a more transient carrier of molecular instructions. The ability of the bases in different nucleic acid molecules to recognize and pair with each other by hydrogen-bonding (called *base-pairing*)—G with C, and A with either T or U—underlies all of heredity and evolution, as explained in Chapter 5.

MACROMOLECULES IN CELLS

On the basis of weight, macromolecules are by far the most abundant of the organic molecules in a living cell (**Figure 2–27**). They are the principal building blocks from which a cell is constructed and also the components that confer the most distinctive properties on living things. Intermediate in size and complexity between small organic molecules and organelles, **macromolecules** are constructed simply by covalently linking small organic **monomers**, or *subunits*, into long chains, or **polymers** (**Figure 2–28** and **How We Know**, pp. 60–61). Yet they have many unexpected properties that could not have been predicted from their simple constituents. For example, it took a long time to determine that the nucleic acids DNA and RNA store and transmit hereditary information (see How We Know, pp. 174–176).

Proteins are especially versatile and perform thousands of distinct functions in cells. Many proteins act as enzymes that catalyze the chemical

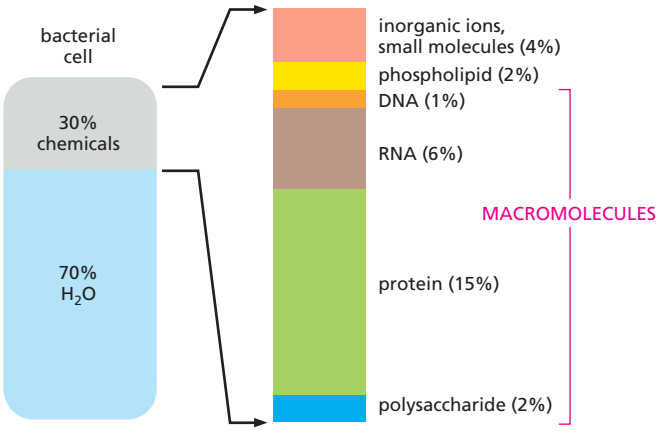


Figure 2–27 Macromolecules are abundant in cells. The approximate composition (by mass) of a bacterial cell is shown. The composition of an animal cell is similar.

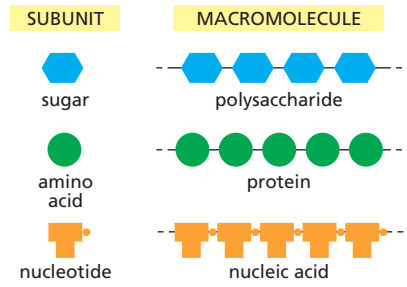


Figure 2–28 Polysaccharides, proteins, and nucleic acids are made from monomeric subunits. Each macromolecule is a polymer formed from small molecules (called monomers or subunits) that are linked together by covalent bonds.

reactions that take place in cells. For example, an enzyme in plants, called ribulose bisphosphate carboxylase, converts CO_2 to sugars, thereby creating most of the organic matter used by the rest of the living world. Other proteins are used to build structural components: tubulin, for example, self-assembles to make the cell's long, stiff microtubules (see Figure 1–27B), and histone proteins assemble into spool-like structures that help wrap up the cell's DNA in chromosomes. Yet other proteins, such as myosin, act as molecular motors to produce force and movement. We examine the molecular basis for many of these wide-ranging functions in later chapters. Here, we consider some of the general principles of macromolecular chemistry that make all of these activities possible.

Each Macromolecule Contains a Specific Sequence of Subunits

Although the chemical reactions for adding subunits to each polymer are different in detail for proteins, nucleic acids, and polysaccharides, they share important features. Each polymer grows by the addition of a monomer onto one end of the polymer chain via a condensation reaction, in which a molecule of water is lost with each subunit added (**Figure 2–29**). In all cases, the reactions are catalyzed by specific enzymes, which ensure that only the appropriate monomer is incorporated.

The stepwise polymerization of monomers into a long chain is a simple way to manufacture a large, complex molecule, because the subunits are added by the same reaction performed over and over again by the same set of enzymes. In a sense, the process resembles the repetitive operation of a machine in a factory—with some important differences. First, apart from some of the polysaccharides, most macromolecules are made from a set of monomers that are slightly different from one another; for example, proteins are constructed from 20 different amino acids (see Panel 2–5, pp. 74–75). Second, and most important, the polymer chain is not assembled at random from these subunits; instead the subunits are added in a particular order, or **sequence**.

The biological functions of proteins, nucleic acids, and many polysaccharides are absolutely dependent on the particular sequence of subunits in the linear chains. By varying the sequence of subunits, the cell can make an enormous diversity of the polymeric molecules. Thus, for a protein chain 200 amino acids long, there are 20^{200} possible combinations ($20 \times 20 \times 20 \times 20...$ multiplied 200 times), while for a DNA molecule

QUESTION 2–7

What is meant by "polarity" of a polypeptide chain and by "polarity" of a chemical bond? How do the meanings differ?

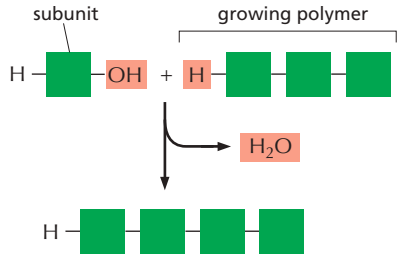


Figure 2–29 Macromolecules are formed by adding subunits to one end. In a condensation reaction, a molecule of water is lost with the addition of each monomer to one end of the growing chain. The reverse reaction—the breakdown of the polymer—occurs by the addition of water (hydrolysis). See also Figure 2–18.

WHAT ARE MACROMOLECULES?

The idea that proteins, polysaccharides, and nucleic acids are large molecules that are constructed from smaller subunits, linked one after another into long molecular chains, may seem fairly obvious today. But this was not always the case. In the early part of the twentieth century, few scientists believed in the existence of such biological polymers built from repeating units held together by covalent bonds. The notion that such "frighteningly large" macromolecules could be assembled from simple building blocks was considered "downright shocking" by chemists of the day. Instead, they thought that proteins and other seemingly large organic molecules were simply heterogeneous aggregates of small organic molecules held together by weak "association forces" (**Figure 2–30**).

The first hint that proteins and other organic polymers are large molecules came from observing their behavior in solution. At the time, scientists were working with various proteins and carbohydrates derived from foodstuffs and other organic materials—albumin from egg whites, casein from milk, collagen from gelatin, and cellulose from wood. Their chemical compositions seemed simple enough: like other organic molecules, they contained carbon, hydrogen, oxygen, and, in the case of proteins, nitrogen. But they behaved oddly in solution, showing, for example, an inability to pass through a fine filter.

Why these molecules misbehaved in solution was a puzzle. Were they really giant molecules, composed of an unusual number of covalently linked atoms? Or were they more like a colloidal suspension of particles—a big, sticky hodgepodge of small organic molecules that associate only loosely?

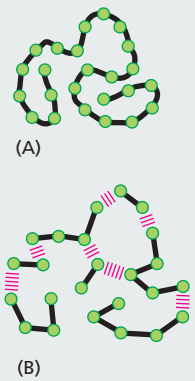


Figure 2–30 What might an organic macromolecule look like? Chemists in the early part of the twentieth century debated whether proteins, polysaccharides, and other apparently large organic molecules were (A) discrete particles made of an unusually large number of covalently linked atoms or (B) a loose aggregation of heterogeneous small organic molecules held together by weak forces.

One way to distinguish between the two possibilities was to determine the actual size of one of these molecules. If a protein such as albumin were made of molecules all identical in size, that would support the existence of true macromolecules. Conversely, if albumin were instead a miscellaneous conglomeration of small organic molecules, these should show a whole range of molecular sizes in solution.

Unfortunately, the techniques available to scientists in the early 1900s were not ideal for measuring the sizes of such large molecules. Some chemists estimated a protein's size by determining how much it would lower a solution's freezing point; others measured the osmotic pressure of protein solutions. These methods were susceptible to experimental error and gave variable results. Different techniques, for example, suggested that cellulose was anywhere from 6000 to 103,000 daltons in mass (where 1 dalton is approximately equal to the mass of a hydrogen atom). Such results helped to fuel the hypothesis that carbohydrates and proteins were loose aggregates of small molecules rather than true macromolecules.

Many scientists simply had trouble believing that molecules heavier than about 4000 daltons—the largest compound that had been synthesized by organic chemists—could exist at all. Take hemoglobin, the oxygen-carrying protein in red blood cells. Researchers tried to estimate its size by breaking it down into its chemical components. In addition to carbon, hydrogen, nitrogen, and oxygen, hemoglobin contains a small amount of iron. Working out the percentages, it appeared that hemoglobin had one atom of iron for every 712 atoms of carbon—and a minimum weight of 16,700 daltons. Could a molecule with hundreds of carbon atoms in one long chain remain intact in a cell and perform specific functions? Emil Fischer, the organic chemist who determined that the amino acids in proteins are linked by peptide bonds, thought that a polypeptide chain could grow no longer than about 30 or 40 amino acids. As for hemoglobin, with its purported 700 carbon atoms, the existence of molecular chains of such "truly fantastic lengths" was deemed "very improbable" by leading chemists.

Definitive resolution of the debate had to await the development of new techniques. Convincing evidence that proteins are macromolecules came from studies using the ultracentrifuge—a device that uses centrifugal force to separate molecules according to their size (see Panel 4–3, pp. 164–165). Theodor Svedberg, who designed the machine in 1925, performed the first studies. If a protein were really an aggregate of smaller molecules, he

reasoned, it would appear as a smear of molecules of different sizes when sedimented in an ultracentrifuge. Using hemoglobin as his test protein, Svedberg found that the centrifuged sample revealed a single, sharp band with a molecular weight of 68,000 daltons. His results strongly supported the theory that proteins are true macromolecules (**Figure 2–31**).

Additional evidence continued to accumulate throughout the 1930s, as other researchers began to prepare crystals of pure protein that could be studied by X-ray diffraction. Only molecules with a uniform size and shape can form highly ordered crystals and diffract X-rays in such a way that their three-dimensional structure can be determined, as we discuss in Chapter 4. A heterogeneous suspension could not be studied in this way.

We now take it for granted that large macromolecules carry out many of the most important activities in living cells. But chemists once viewed the existence of such polymers with the same sort of skepticism that a zoologist might show on being told that "In Africa, there are elephants that are 100 meters long and 20 meters tall." It took decades for researchers to master the techniques required to convince everyone that molecules ten times larger than anything they had ever encountered were a cornerstone of biology. As we shall see throughout this book, such a labored pathway to discovery is not unusual, and progress in science is often driven by advances in technology.

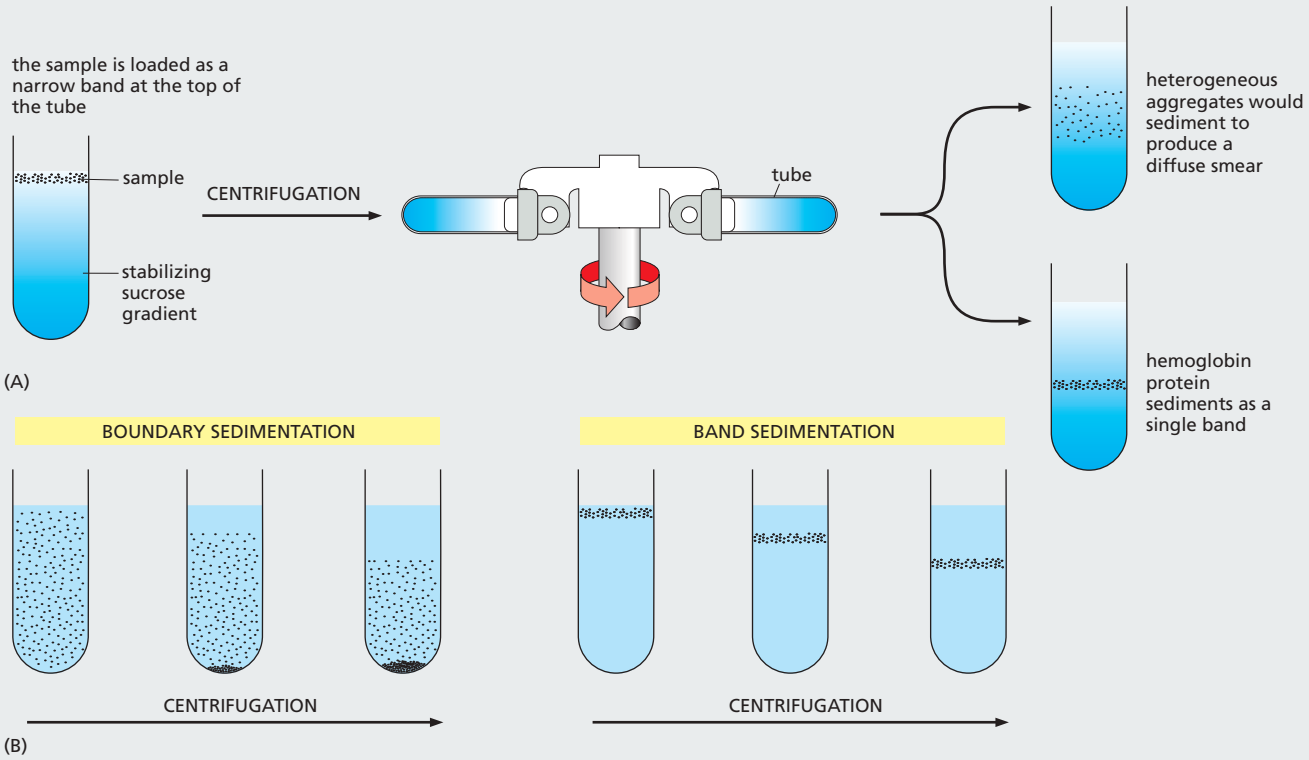


Figure 2–31 The ultracentrifuge helped to settle the debate about the nature of macromolecules. In the ultracentrifuge, centrifugal forces exceeding 500,000 times the force of gravity can be used to separate proteins or other large molecules. (A) In a modern ultracentrifuge, samples are loaded in a thin layer on top of a gradient of sucrose solution formed in a tube. The tube is placed in a metal rotor that is rotated at high speed. Molecules of different sizes sediment at different rates, and these molecules will therefore move as distinct bands in the sample tube. If hemoglobin were a loose aggregate of heterogeneous peptides, it would show a broad smear of sizes after centrifugation (*top* tube). Instead, it appears as a sharp band with a molecular weight of 68,000 daltons (*bottom* tube). Although the ultracentrifuge is now a standard, almost mundane, fixture in most biochemistry laboratories, its construction was a huge technological challenge. The centrifuge rotor must be capable of spinning centrifuge tubes at high speeds for many hours at constant temperature and with high stability; otherwise convection occurs in the sedimenting solution and ruins the experiment. In 1926, Svedberg won the Nobel Prize in Chemistry for his ultracentrifuge design and its application to chemistry. (B) In his actual experiment, Svedberg filled a special tube in the centrifuge with a homogeneous solution of hemoglobin; by shining light through the tube, he then carefully monitored the moving boundary between the sedimenting protein molecules and the clear aqueous solution left behind (so-called boundary sedimentation). The more recently developed method shown in (A) is a form of band sedimentation.

10,000 nucleotides long (small by DNA standards), with its four different nucleotides, there are $4^{10,000}$ different possibilities—an unimaginably large number. Thus the machinery of polymerization must be subject to a sensitive control that allows it to specify exactly which subunit should be added next to the growing polymer end. We discuss the mechanisms that specify the sequence of subunits in DNA, RNA, and protein molecules in Chapters 6 and 7.

Noncovalent Bonds Specify the Precise Shape of a Macromolecule

Most of the single covalent bonds that link together the subunits in a macromolecule allow rotation of the atoms they join; thus the polymer chain has great flexibility. In principle, this allows a single-chain macromolecule to adopt an almost unlimited number of shapes, or **conformations**, as the polymer chain writhes and rotates under the influence of random thermal energy. However, the shapes of most biological macromolecules are highly constrained because of weaker, noncovalent bonds that form between different parts of the molecule. In many cases, these weaker interactions ensure that the polymer chain preferentially adopts one particular conformation, determined by the linear sequence of monomers in the chain. Most protein molecules and many of the RNA molecules found in cells fold tightly into one highly preferred conformation in this way (**Figure 2–32**). These unique conformations—shaped by evolution—determine the chemistry and activity of these macromolecules and dictate their interactions with other biological molecules.

The noncovalent bonds important for the structure and function of macromolecules include two types described earlier: *electrostatic attractions* and *hydrogen bonds* (see Panel 2–7, pp. 78–79). Electrostatic attractions, although strong on their own, are quite weak in water because the charged or partially charged (polar) groups involved in the attraction are shielded by their interactions with water molecules and various inorganic ions present in the aqueous solution. Electrostatic attractions, however, are very important in biological systems. An enzyme that binds a positively charged substrate will often use a negatively charged amino acid side chain to guide its substrate into the proper position.

Earlier, we described the importance of hydrogen bonds in determining the unique properties of water. They are also very important in the folding of a polypeptide chain and in holding together the two strands of a double-stranded DNA molecule.

QUESTION 2–8

In principle, there are many different, chemically diverse ways in which small molecules can be linked to form polymers. For example, the small molecule ethene (CH_2=CH_2) is used commercially to make the plastic polyethylene (...–CH_2–CH_2–CH_2–CH_2–CH_2–...). The individual subunits of the three major classes of biological macromolecules, however, are all linked by similar reaction mechanisms, i.e., by condensation reactions that eliminate water. Can you think of any benefits that this chemistry offers and why it might have been selected in evolution?

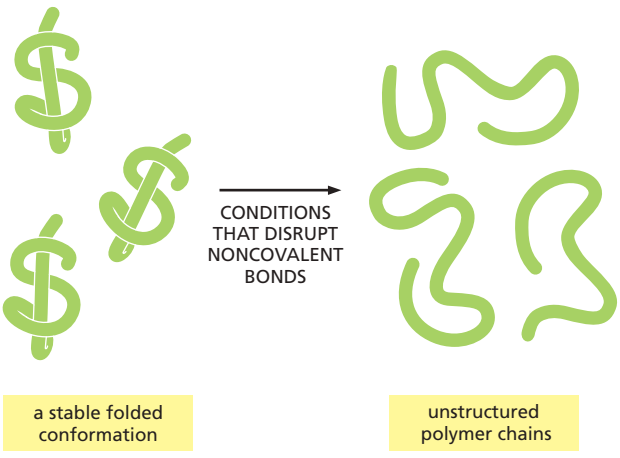


Figure 2–32 Most proteins and many RNA molecules fold into a particularly stable three-dimensional shape, or conformation. This shape is directed mostly by a multitude of weak, noncovalent intramolecular bonds. If the folded macromolecules are subjected to conditions that disrupt noncovalent bonds, the molecule becomes a flexible chain that loses both its conformation and its biological activity.

A third type of noncovalent interaction results from **van der Waals attractions**, which are a form of electrical attraction caused by fluctuating electric charges that arise whenever two atoms come within a very short distance of each other. Although van der Waals attractions are weaker than hydrogen bonds, in large numbers they play an important role in the attraction between macromolecules with complementary shapes. All of these noncovalent bonds are reviewed in Panel 2–7, pp. 78–79.

Another important noncovalent interaction is created by the three-dimensional structure of water, which forces together the hydrophobic portions of dissolved molecules in order to minimize their disruptive effect on the hydrogen-bonded network of water molecules (see Panel 2–7 and Panel 2–2, pp. 68–69). This expulsion from the aqueous solution generates what is sometimes thought of as a fourth kind of noncovalent bond, called a **hydrophobic interaction**. Such interactions hold together phospholipid molecules in cell membranes, for example, and they also play a crucial part in the folding of protein molecules into a compact globular shape.

Noncovalent Bonds Allow a Macromolecule to Bind Other Selected Molecules

As we discussed earlier, although noncovalent bonds are individually weak, they can add up to create a strong attraction between two molecules when these molecules fit together very closely, like a hand in a glove, so that many noncovalent bonds can occur between them (see Panel 2–7). This form of molecular interaction provides for great specificity in the binding of a macromolecule to other small and large molecules, because the multipoint contacts required for strong binding make it possible for a macromolecule to select just one of the many thousands of different molecules present inside a cell. Moreover, because the strength of the binding depends on the number of noncovalent bonds that are formed, associations of almost any strength are possible.

Binding of this type makes it possible for proteins to function as enzymes. It can also stabilize associations between any macromolecules, as long as their surfaces match closely (**Figure 2–33** and **Movie 2.4**). Noncovalent bonds thereby allow macromolecules to be used as building blocks for the formation of much larger structures. For example, proteins often bind

QUESTION 2–9

Why could covalent bonds not be used in place of noncovalent bonds to mediate most of the interactions of macromolecules?

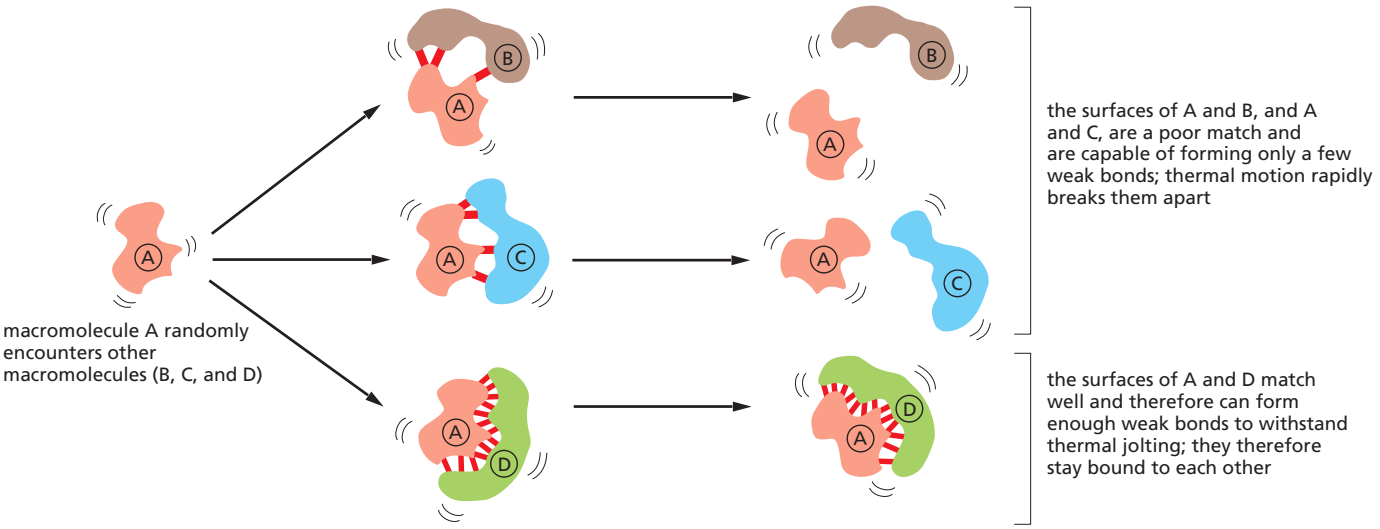


Figure 2–33 Noncovalent bonds mediate interactions between macromolecules. They can also mediate interactions between a macromolecule and small molecules (not shown).

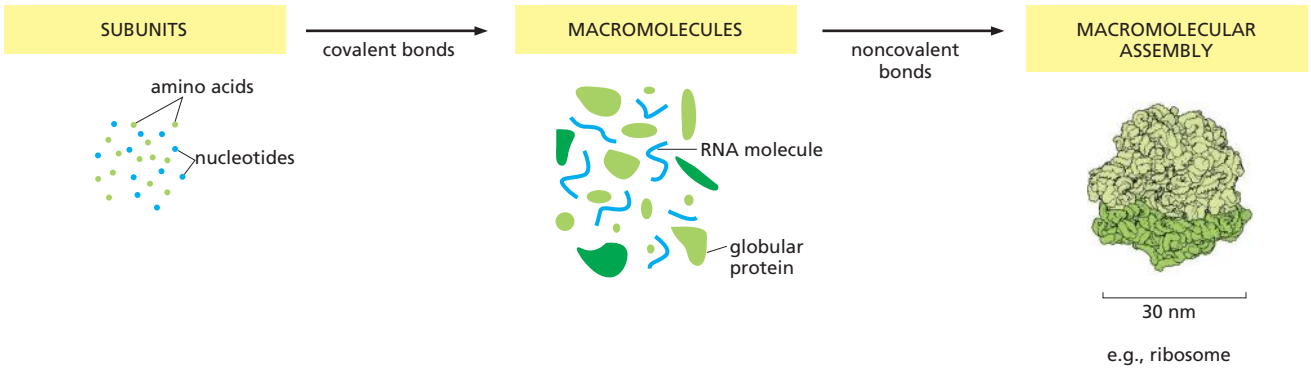


Figure 2–34 Both covalent bonds and noncovalent bonds are needed to form a macromolecular assembly such as a ribosome. Covalent bonds allow small organic molecules to join together to form macromolecules, which can assemble into large macromolecular complexes via noncovalent bonds. Ribosomes are large macromolecular machines that synthesize proteins inside cells. Each ribosome is composed of about 90 macromolecules (proteins and RNA molecules), and it is large enough to see in the electron microscope (see Figure 7–31). The subunits, macromolecules, and the ribosome here are shown roughly to scale.

together into multiprotein complexes that function as intricate machines with multiple moving parts, carrying out such complex tasks as DNA replication and protein synthesis (**Figure 2–34**). In fact, noncovalent bonds account for a great deal of the complex chemistry that makes life possible.

ESSENTIAL CONCEPTS

- Living cells obey the same chemical and physical laws as nonliving things. Like all other forms of matter, they are made of atoms, which are the smallest unit of a chemical element that retain the distinctive chemical properties of that element.
- Cells are made up of a limited number of elements, four of which—C, H, N, O—make up about 96% of a cell's mass.
- Each atom has a positively charged nucleus, which is surrounded by a cloud of negatively charged electrons. The chemical properties of an atom are determined by the number and arrangement of its electrons: it is most stable when its outer electron shell is completely filled.
- A covalent bond forms when a pair of outer-shell electrons is shared between two adjacent atoms; if two pairs of electrons are shared, a double bond is formed. Clusters of two or more atoms held together by covalent bonds are known as molecules.
- When an electron jumps from one atom to another, two ions of opposite charge are generated; these ions are held together by mutual attraction forming a noncovalent ionic bond.
- Living organisms contain a distinctive and restricted set of small carbon-based (organic) molecules, which are essentially the same for every living species. The main categories are sugars, fatty acids, amino acids, and nucleotides.
- Sugars are a primary source of chemical energy for cells and can also be joined together to form polysaccharides or shorter oligosaccharides.
- Fatty acids are an even richer energy source than sugars, but their most essential function is to form lipid molecules that assemble into cell membranes.
- The vast majority of the dry mass of a cell consists of macromolecules—mainly polysaccharides, proteins, and nucleic acids (DNA

and RNA); these macromolecules are formed as polymers of sugars, amino acids, or nucleotides, respectively.

- The most diverse and versatile class of macromolecules are proteins, which are formed from 20 types of amino acids that are covalently linked by peptide bonds into long polypeptide chains.
- Nucleotides play a central part in energy-transfer reactions within cells; they are also joined together to form information-containing RNA and DNA molecules, each of which is composed of only four types of nucleotides.
- Protein, RNA, and DNA molecules are synthesized from subunits by repetitive condensation reactions, and it is the specific sequence of subunits that determines their unique functions.
- Four types of weak noncovalent bonds—hydrogen bonds, electrostatic attractions, van der Waals attractions, and hydrophobic interactions—enable macromolecules to bind specifically to other macromolecules or to selected small molecules.
- The same four types of noncovalent bonds between different regions of a polypeptide or RNA chain allow these chains to fold into unique shapes (conformations).

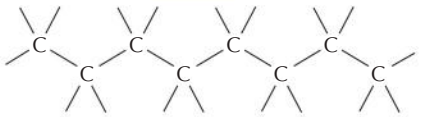
KEY TERMS

acid
amino acid
atom
atomic weight
ATP
Avogadro's number
base
buffer
chemical bond
chemical group
condensation reaction
conformation
covalent bond
DNA
electron
electrostatic attraction
fatty acid
hydrogen bond
hydrolysis
hydronium ion
hydrophilic
hydrophobic
hydrophobic interactions
inorganic molecule
ion
ionic bond
lipid
lipid bilayer
macromolecule
molecule
molecular weight
monomer
noncovalent bond
nucleotide
organic molecule
pH scale
polar
polymer
protein
proton
RNA
sequence
subunit
sugar
van der Waals attractions

CARBON SKELETONS

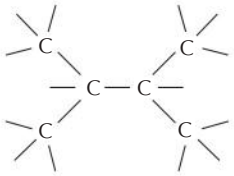
Carbon has a unique role in the cell because of its ability to form strong covalent bonds with other carbon atoms. Thus carbon atoms can join to form:

chains



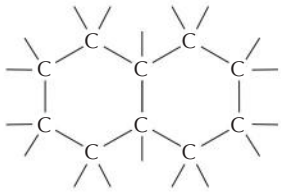
also written as 

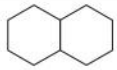
branched trees



also written as 

rings



also written as 

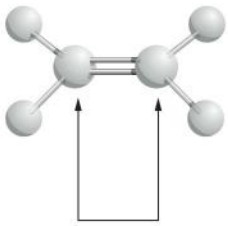
COVALENT BONDS

A covalent bond forms when two atoms come very close together and share one or more of their outer-shell electrons. Each atom forms a fixed number of covalent bonds in a defined spatial arrangement.

SINGLE BONDS: two electrons shared per bond

DOUBLE BONDS: four electrons shared per bond

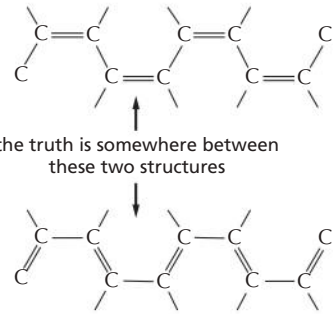
The precise spatial arrangement of covalent bonds influences the three-dimensional structure and chemistry of molecules. In this review panel, we see how covalent bonds are used in a variety of biological molecules.



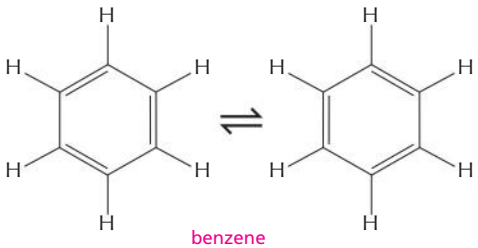
Atoms joined by two or more covalent bonds cannot rotate freely around the bond axis. This restriction has a major influence on the three-dimensional shape of many macromolecules.

ALTERNATING DOUBLE BONDS

A carbon chain can include double bonds. If these are on alternate carbon atoms, the bonding electrons move within the molecule, stabilizing the structure by a phenomenon called *resonance*.



Alternating double bonds in a ring can generate a very stable structure.

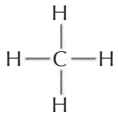


benzene

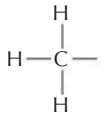
often written as 

C–H COMPOUNDS

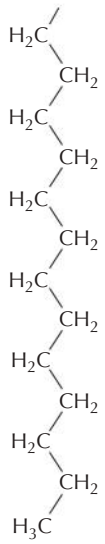
Carbon and hydrogen together make stable compounds (or groups) called hydrocarbons. These are nonpolar, do not form hydrogen bonds, and are generally insoluble in water.



methane



methyl group

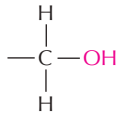


part of the hydrocarbon "tail" of a fatty acid molecule

C–O COMPOUNDS

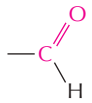
Many biological compounds contain a carbon covalently bonded to an oxygen. For example,

alcohol

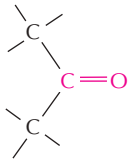


The –OH is called a hydroxyl group.

aldehyde

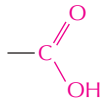


ketone



The C=O is called a carbonyl group.

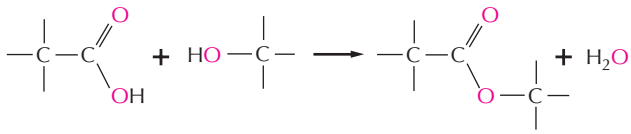
carboxylic acid



The –COOH is called a carboxyl group. In water, this loses an H^+ ion to become $–COO^–$.

esters

Esters are formed by combining an acid and an alcohol.

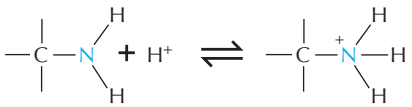


acid alcohol ester

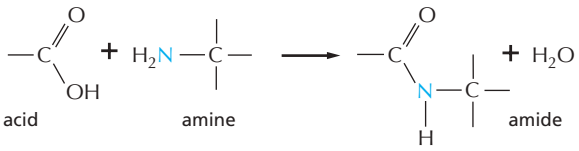
C–N COMPOUNDS

Amines and amides are two important examples of compounds containing a carbon linked to a nitrogen.

Amines in water combine with an H^+ ion to become positively charged.

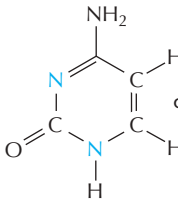


Amides are formed by combining an acid and an amine. Unlike amines, amides are uncharged in water. An example is the peptide bond that joins amino acids in a protein.



acid amine amide

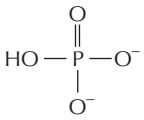
Nitrogen also occurs in several ring compounds, including important constituents of nucleic acids: purines and pyrimidines.



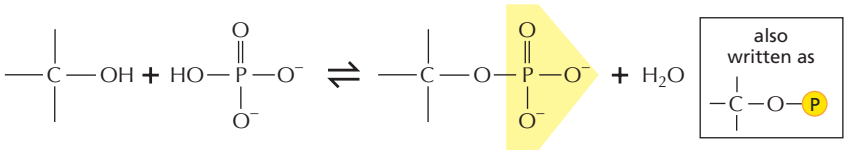
cytosine (a pyrimidine)

PHOSPHATES

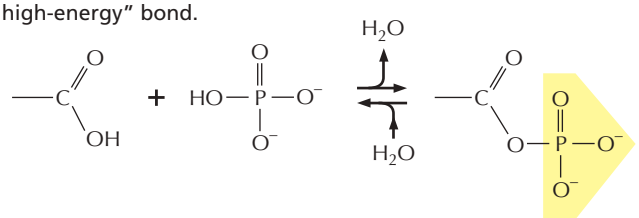
Inorganic phosphate is a stable ion formed from phosphoric acid, H_3PO_4. It is also written as (Pi).



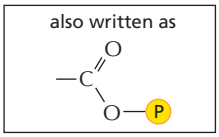
Phosphate esters can form between a phosphate and a free hydroxyl group. Phosphate groups are often covalently attached to proteins in this way.

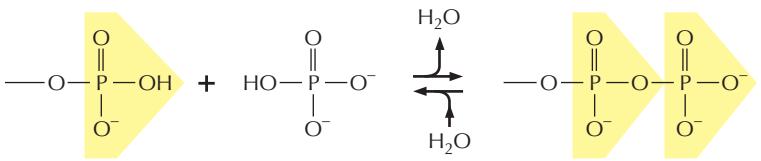


The combination of a phosphate and a carboxyl group, or two or more phosphate groups, gives an acid anhydride. Because compounds of this type release a large amount of energy when hydrolyzed in the cell, they are often said to contain a "high-energy" bond.

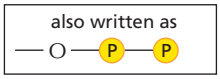


high-energy acyl phosphate bond (carboxylic–phosphoric acid anhydride) found in some metabolites





high-energy phosphoanhydride bond found in molecules such as ATP

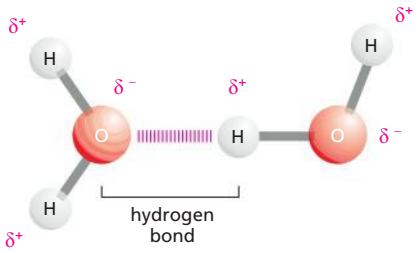


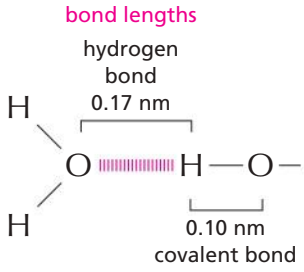
PANEL 2–2 THE CHEMICAL PROPERTIES OF WATER

HYDROGEN BONDS

Because they are polarized, two adjacent H_2O molecules can form a noncovalent linkage known as a hydrogen bond. Hydrogen bonds have only about 1/20 the strength of a covalent bond.

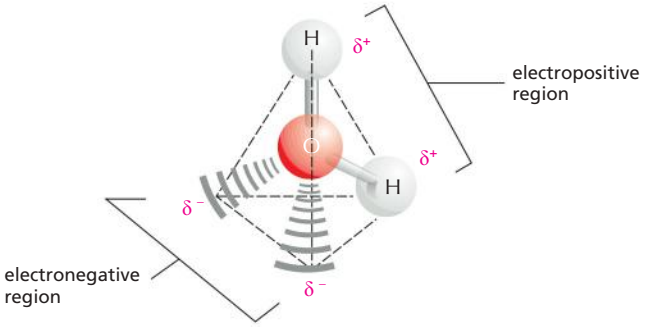
Hydrogen bonds are strongest when the three atoms lie in a straight line.





WATER

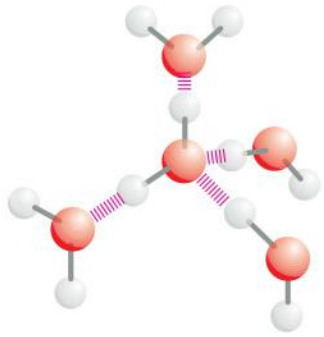
Two atoms connected by a covalent bond may exert different attractions for the electrons of the bond. In such cases, the bond is polar, with one end slightly negatively charged (δ⁻) and the other slightly positively charged (δ⁺).



Although a water molecule has an overall neutral charge (having the same number of electrons and protons), the electrons are asymmetrically distributed, making the molecule polar. The oxygen nucleus draws electrons away from the hydrogen nuclei, leaving the hydrogen nuclei with a small net positive charge. The excess of electron density on the oxygen atom creates weakly negative regions at the other two corners of an imaginary tetrahedron. On these pages, we review the chemical properties of water and see how water influences the behavior of biological molecules.

WATER STRUCTURE

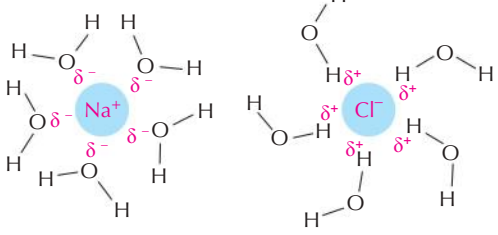
Molecules of water join together transiently in a hydrogen-bonded lattice.



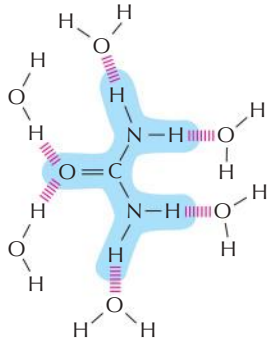
The cohesive nature of water is responsible for many of its unusual properties, such as high surface tension, high specific heat, and high heat of vaporization.

HYDROPHILIC MOLECULES

Substances that dissolve readily in water are termed hydrophilic. They include ions and polar molecules that attract water molecules through electrical charge effects. Water molecules surround each ion or polar molecule and carry it into solution.



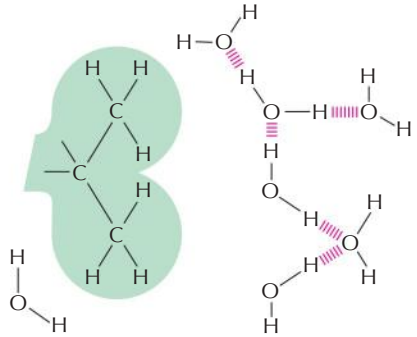
Ionic substances such as sodium chloride dissolve because water molecules are attracted to the positive (Na^+) or negative (Cl^-) charge of each ion.



Polar substances such as urea dissolve because their molecules form hydrogen bonds with the surrounding water molecules.

HYDROPHOBIC MOLECULES

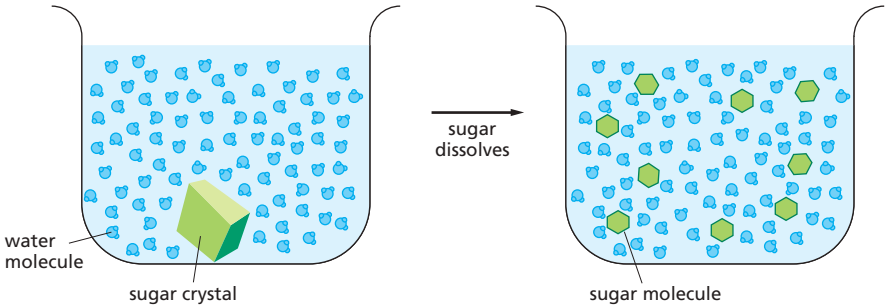
Substances that contain a preponderance of nonpolar bonds are usually insoluble in water and are termed hydrophobic. Water molecules are not attracted to such hydrophobic molecules and so have little tendency to surround them and bring them into solution.



Hydrocarbons, which contain many C–H bonds, are especially hydrophobic.

WATER AS A SOLVENT

Many substances, such as household sugar (sucrose), dissolve in water. That is, their molecules separate from each other, each becoming surrounded by water molecules.



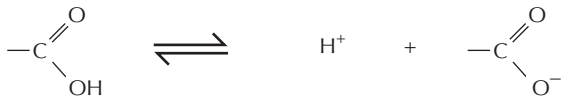
When a substance dissolves in a liquid, the mixture is termed a solution. The dissolved substance (in this case sugar) is the solute, and the liquid that does the dissolving (in this case water) is the solvent. Water is an excellent solvent for hydrophilic substances because of its polar bonds.

ACIDS

Substances that release hydrogen ions (protons) into solution are called acids.

$$\underset{\text{hydrochloric acid (strong acid)}}{HCl} \longrightarrow \underset{\text{hydrogen ion}}{H^+} + \underset{\text{chloride ion}}{Cl^-}$$

Many of the acids important in the cell are not completely dissociated, and they are therefore weak acids—for example, the carboxyl group (–COOH), which dissociates to give a hydrogen ion in solution.

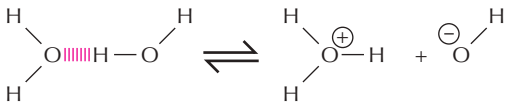


(weak acid)

Note that this is a reversible reaction.

HYDROGEN ION EXCHANGE

Positively charged hydrogen ions (H^+) can spontaneously move from one water molecule to another, thereby creating two ionic species.



hydronium ion hydroxyl ion

often written as: $H_2O \rightleftharpoons \underset{\text{hydrogen ion}}{H^+} + \underset{\text{hydroxyl ion}}{OH^-}$

Because the process is rapidly reversible, hydrogen ions are continually shuttling between water molecules. Pure water contains equal concentrations of hydronium ions and hydroxyl ions (both 10^{-7} M).

pH

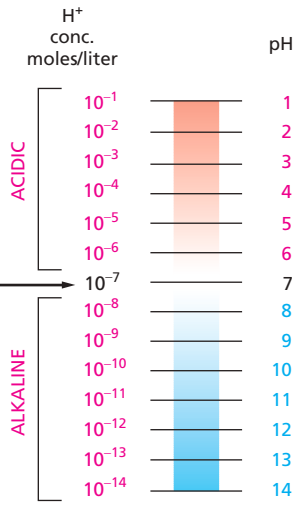
The acidity of a solution is defined by the concentration of hydronium ions (H_3O^+) it possesses, generally abbreviated as H^+. For convenience, we use the pH scale, where

$pH = -\log_{10}[H^+]$

For pure water

$[H^+] = 10^{-7}$ moles/liter

$pH = 7.0$



BASES

Substances that reduce the number of hydrogen ions in solution are called bases. Some bases, such as ammonia, combine directly with hydrogen ions.

$$\underset{\text{ammonia}}{NH_3} + \underset{\text{hydrogen ion}}{H^+} \longrightarrow \underset{\text{ammonium ion}}{NH_4^+}$$

Other bases, such as sodium hydroxide, reduce the number of H^+ ions indirectly, by making OH^- ions that then combine directly with H^+ ions to make H_2O.

$$\underset{\text{sodium hydroxide (strong base)}}{NaOH} \longrightarrow \underset{\text{sodium ion}}{Na^+} + \underset{\text{hydroxyl ion}}{OH^-}$$

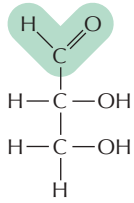
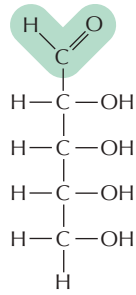
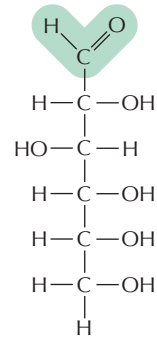
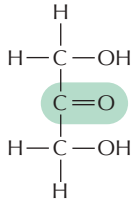
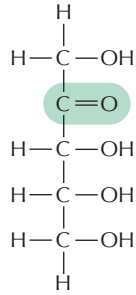
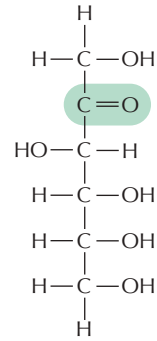
Many bases found in cells are partially associated with H^+ ions and are termed weak bases. This is true of compounds that contain an amino group ($-NH_2$), which has a weak tendency to reversibly accept an H^+ ion from water, thereby increasing the concentration of free OH^- ions.

$$-NH_2 + H^+ \rightleftharpoons -NH_3^+$$

PANEL 2–3 AN OUTLINE OF SOME OF THE TYPES OF SUGARS

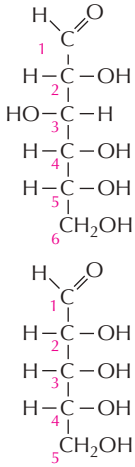
MONOSACCHARIDES

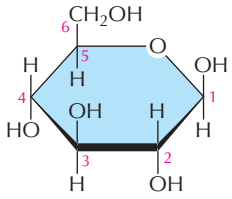
Monosaccharides usually have the general formula $(CH_2O)_n$, where *n* can be 3, 4, 5, or 6, and have two or more hydroxyl groups. They either contain an aldehyde group ($-C\begin{matrix}O\\H\end{matrix}$) and are called aldoses, or a ketone group ($>C=O$) and are called ketoses.

	3-carbon (TRIOSES)	5-carbon (PENTOSES)	6-carbon (HEXOSES)
ALDOSES	 glyceraldehyde	 ribose	 glucose
KETOSES	 dihydroxyacetone	 ribulose	 fructose

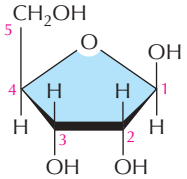
RING FORMATION

In aqueous solution, the aldehyde or ketone group of a sugar molecule tends to react with a hydroxyl group of the same molecule, thereby closing the molecule into a ring.





glucose

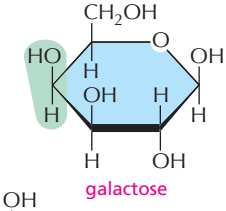


ribose

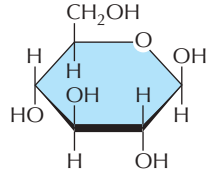
Note that each carbon atom has a number.

ISOMERS

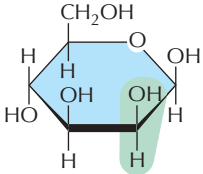
Many monosaccharides differ only in the spatial arrangement of atoms—that is, they are isomers. For example, glucose, galactose, and mannose have the same formula ($C_6H_{12}O_6$) but differ in the arrangement of groups around one or two carbon atoms.



galactose



glucose

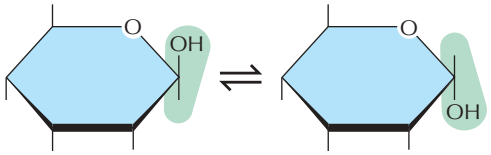


mannose

These small differences make only minor changes in the chemical properties of the sugars. But the differences are recognized by enzymes and other proteins and therefore can have major biological effects.

α AND β LINKS

The hydroxyl group on the carbon that carries the aldehyde or ketone can rapidly change from one position to the other. These two positions are called α and β.

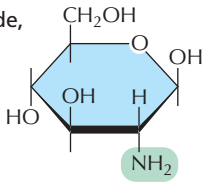


β hydroxyl α hydroxyl

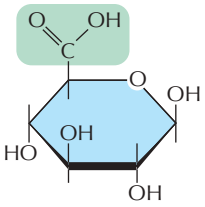
As soon as one sugar is linked to another, the α or β form is frozen.

SUGAR DERIVATIVES

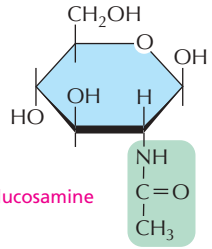
The hydroxyl groups of a simple monosaccharide, such as glucose, can be replaced by other groups.



glucosamine



glucuronic acid



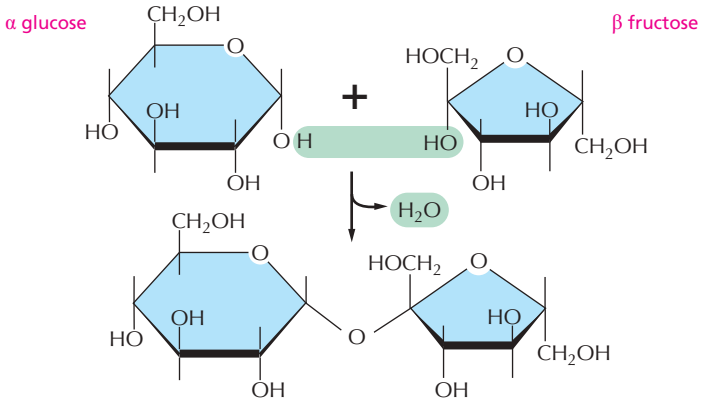
N-acetylglucosamine

DISACCHARIDES

The carbon that carries the aldehyde or the ketone can react with any hydroxyl group on a second sugar molecule to form a disaccharide. Three common disaccharides are

maltose (glucose + glucose)
lactose (galactose + glucose)
sucrose (glucose + fructose)

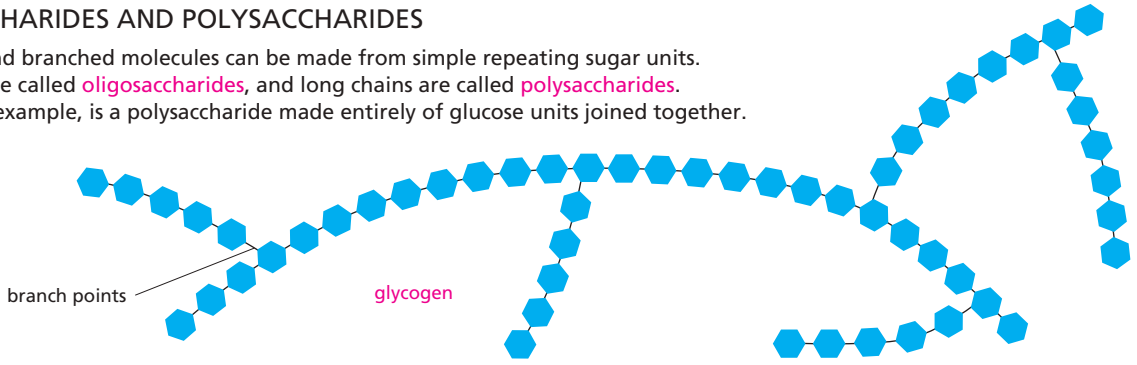
The reaction forming sucrose is shown here.



sucrose

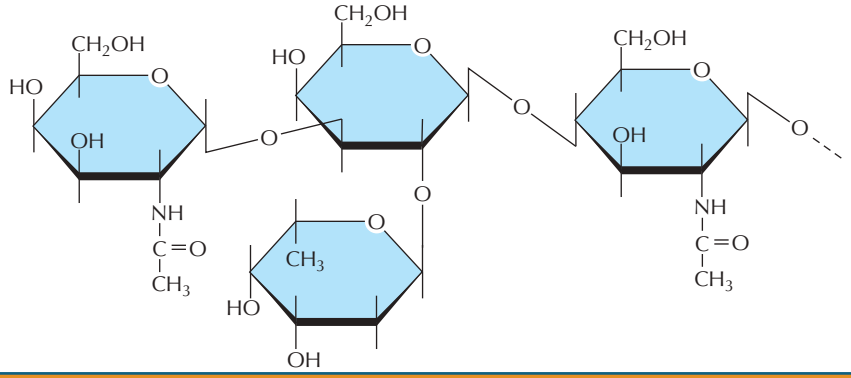
OLIGOSACCHARIDES AND POLYSACCHARIDES

Large linear and branched molecules can be made from simple repeating sugar units. Short chains are called oligosaccharides, and long chains are called polysaccharides. Glycogen, for example, is a polysaccharide made entirely of glucose units joined together.



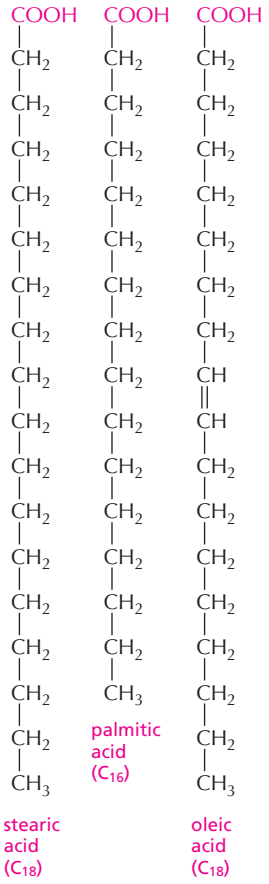
COMPLEX OLIGOSACCHARIDES

In many cases, a sugar sequence is nonrepetitive. Many different molecules are possible. Such complex oligosaccharides are usually linked to proteins or to lipids, as is this oligosaccharide, which is part of a cell-surface molecule that defines a particular blood group.

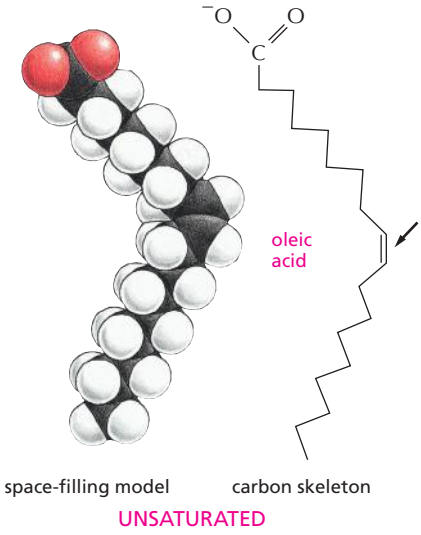


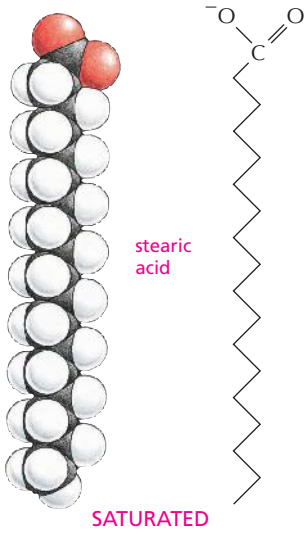
FATTY ACIDS

All fatty acids have carboxyl groups at one end and long hydrocarbon tails at the other.



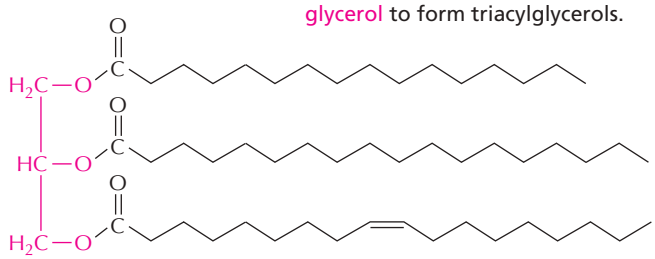
Hundreds of different kinds of fatty acids exist. Some have one or more double bonds in their hydrocarbon tail and are said to be unsaturated. Fatty acids with no double bonds are saturated.

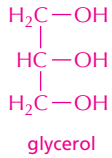




TRIACYLGLYCEROLS

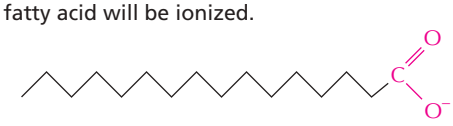
Fatty acids are stored in cells as an energy reserve (fats and oils) through an ester linkage to glycerol to form triacylglycerols.



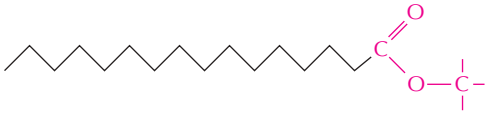


CARBOXYL GROUP

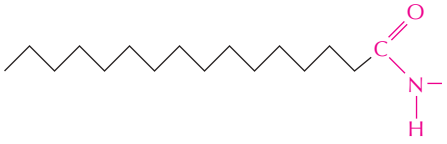
If free, the carboxyl group of a fatty acid will be ionized.



But more often it is linked to other groups to form either esters

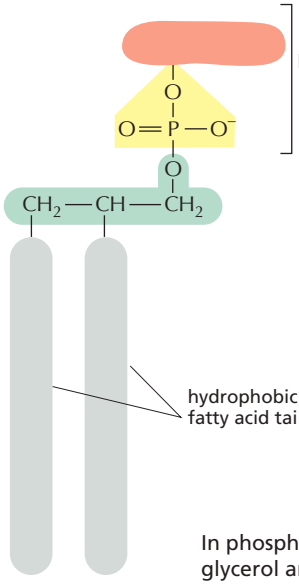


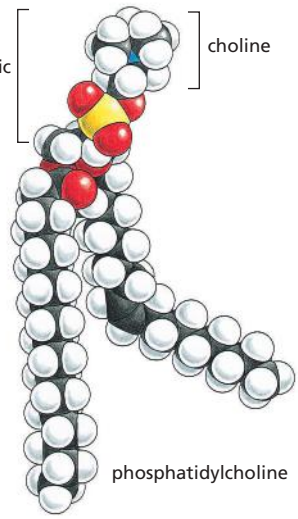
or amides.



PHOSPHOLIPIDS

Phospholipids are the major constituents of cell membranes.

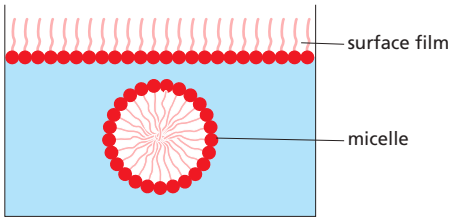




In phospholipids, two of the –OH groups in glycerol are linked to fatty acids, while the third –OH group is linked to phosphoric acid. The phosphate is further linked to one of a variety of small polar groups, such as choline.

LIPID AGGREGATES

Fatty acids have a hydrophilic head and a hydrophobic tail.

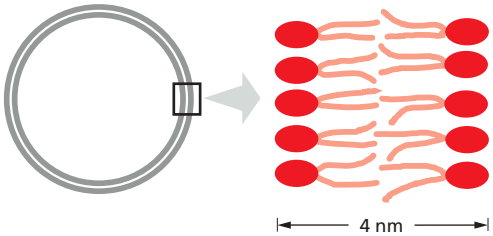


In water, they can form either a surface film or small, spherical micelles.

Their derivatives can form larger aggregates held together by hydrophobic forces:

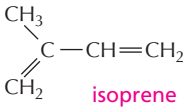
Triacylglycerols form large spherical fat droplets in the cell cytoplasm.

Phospholipids and glycolipids form self-sealing *lipid bilayers*, which are the basis for all cell membranes.



OTHER LIPIDS

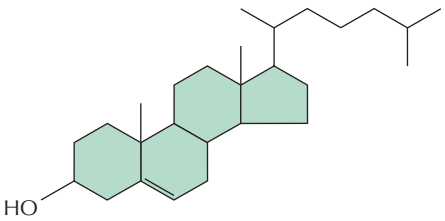
Lipids are defined as water-insoluble molecules that are soluble in organic solvents. Two other common types of lipids are steroids and polyisoprenoids. Both are made from isoprene units.



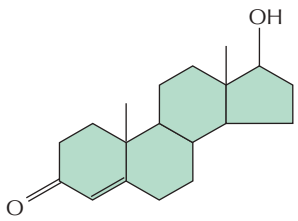
isoprene

STEROIDS

Steroids have a common multiple-ring structure.



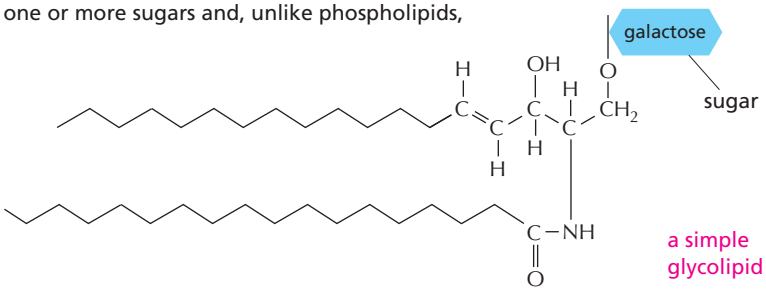
cholesterol—found in many cell membranes



testosterone—male sex hormone

GLYCOLIPIDS

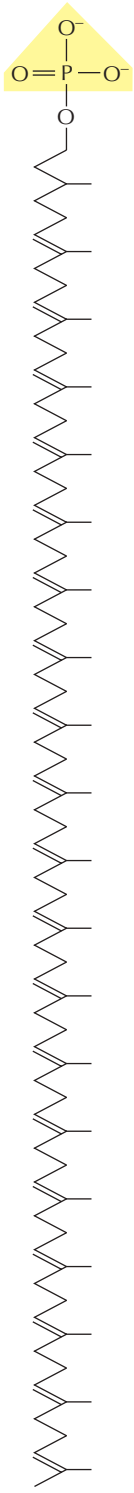
Like phospholipids, these compounds are composed of a hydrophobic region, containing two long hydrocarbon tails, and a polar region, which contains one or more sugars and, unlike phospholipids, no phosphate.



a simple glycolipid

POLYISOPRENOIDS

Long-chain polymers of isoprene



dolichol phosphate—used to carry activated sugars in the membrane-associated synthesis of glycoproteins and some polysaccharides

PANEL 2–5 THE 20 AMINO ACIDS FOUND IN PROTEINS

FAMILIES OF AMINO ACIDS

The common amino acids are grouped according to whether their side chains are

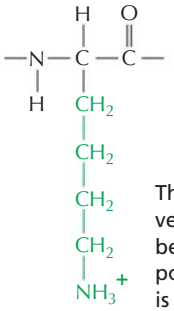
- acidic
- basic
- uncharged polar
- nonpolar

These 20 amino acids are given both three-letter and one-letter abbreviations.

Thus: alanine = Ala = A

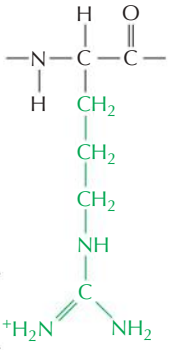
BASIC SIDE CHAINS

lysine (Lys, or K)

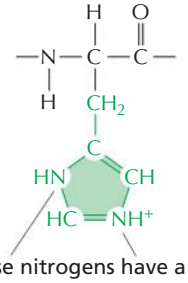


This group is very basic because its positive charge is stabilized by resonance (see Panel 2–1).

arginine (Arg, or R)



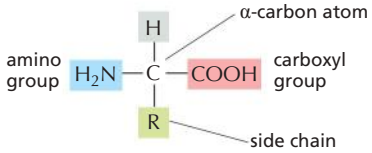
histidine (His, or H)



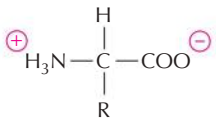
These nitrogens have a relatively weak affinity for an H^+ and are only partly positive at neutral pH.

THE AMINO ACID

The general formula of an amino acid is

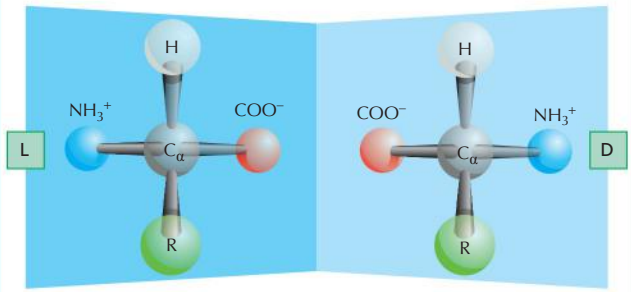


R is commonly one of 20 different side chains. At pH 7, both the amino and carboxyl groups are ionized.



OPTICAL ISOMERS

The α-carbon atom is asymmetric, allowing for two mirror-image (or stereo-) isomers, L and D.

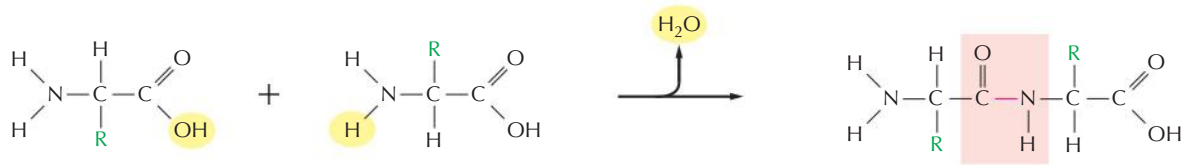


Proteins contain exclusively L-amino acids.

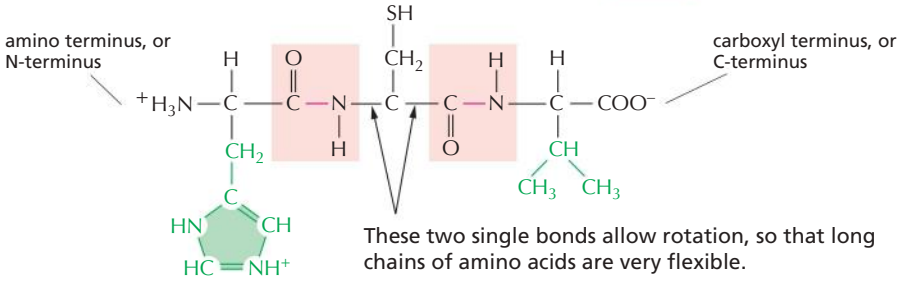
PEPTIDE BONDS

In proteins, amino acids are commonly joined together by an amide linkage, called a peptide bond.

The four atoms in each peptide bond *(red box)* form a rigid planar unit. There is no rotation around the C–N bond.



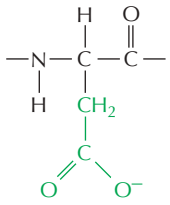
Proteins are long polymers of amino acids linked by peptide bonds, and they are always written with the N-terminus toward the left. Peptides are shorter, usually fewer than 50 amino acids long. The sequence of this tripeptide is histidine-cysteine-valine.



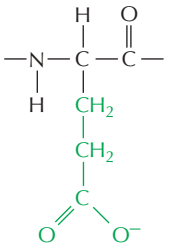
These two single bonds allow rotation, so that long chains of amino acids are very flexible.

ACIDIC SIDE CHAINS

aspartic acid
(Asp, or D)

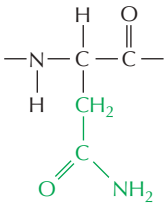


glutamic acid
(Glu, or E)

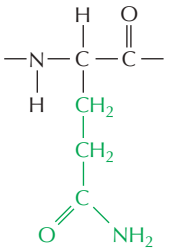


UNCHARGED POLAR SIDE CHAINS

asparagine
(Asn, or N)

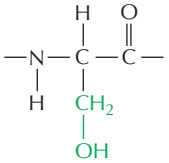


glutamine
(Gln, or Q)

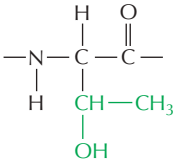


Although the amide N is not charged at neutral pH, it is polar.

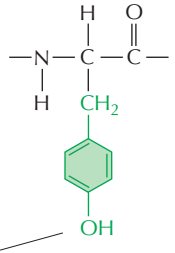
serine
(Ser, or S)



threonine
(Thr, or T)



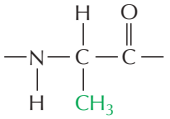
tyrosine
(Tyr, or Y)



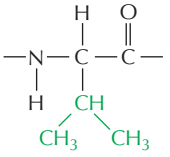
The –OH group is polar.

NONPOLAR SIDE CHAINS

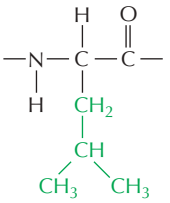
alanine
(Ala, or A)



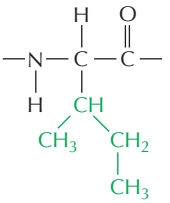
valine
(Val, or V)



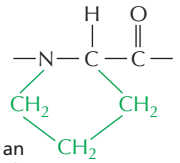
leucine
(Leu, or L)



isoleucine
(Ile, or I)

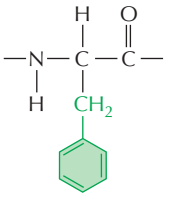


proline
(Pro, or P)

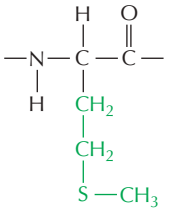


(actually an imino acid)

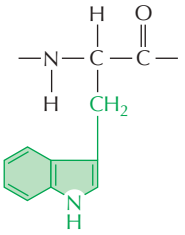
phenylalanine
(Phe, or F)



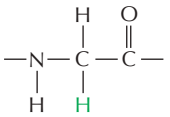
methionine
(Met, or M)



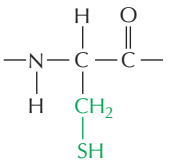
tryptophan
(Trp, or W)



glycine
(Gly, or G)



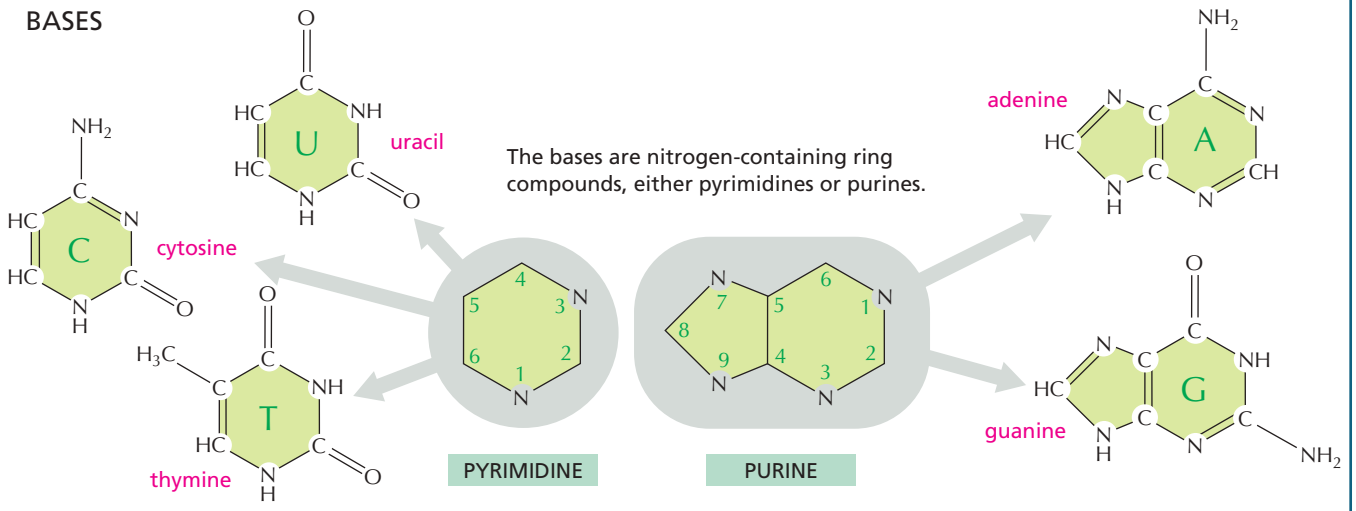
cysteine
(Cys, or C)



Disulfide bonds can form between two cysteine side chains in proteins.

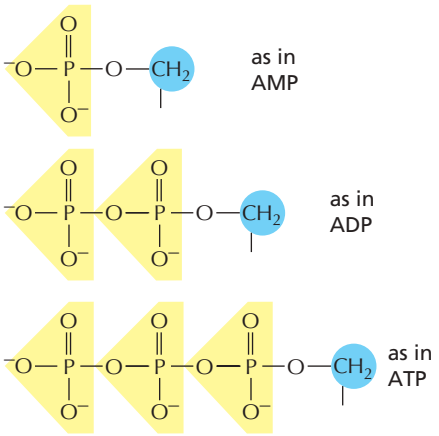
PANEL 2–6 A SURVEY OF THE NUCLEOTIDES

BASES



PHOSPHATES

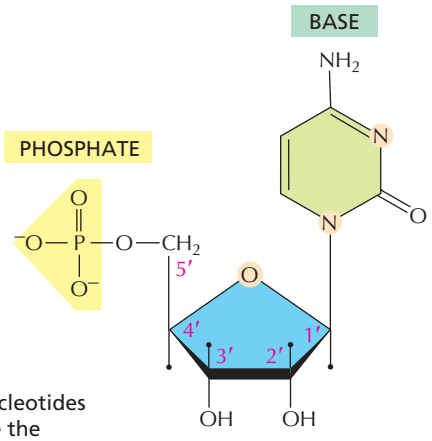
The phosphates are normally joined to the C5 hydroxyl of the ribose or deoxyribose sugar (designated 5'). Mono-, di-, and triphosphates are common.



The phosphate makes a nucleotide negatively charged.

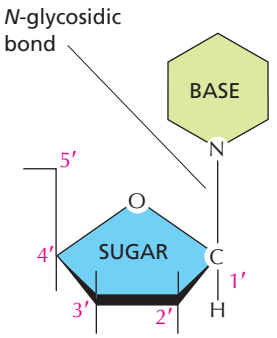
NUCLEOTIDES

A nucleotide consists of a nitrogen-containing base, a five-carbon sugar, and one or more phosphate groups.



Nucleotides are the subunits of the nucleic acids.

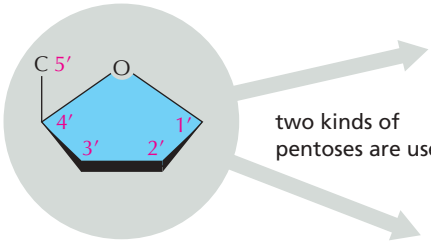
BASE–SUGAR LINKAGE



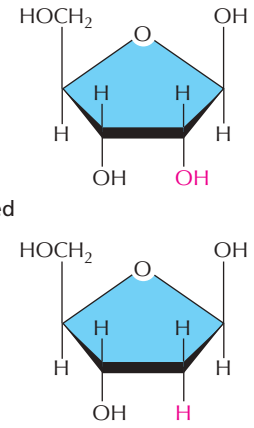
The base is linked to the same carbon (C1) used in sugar–sugar bonds.

SUGARS

PENTOSE
a five-carbon sugar



two kinds of pentoses are used



β-D-ribose
used in ribonucleic acid (RNA)

β-D-2-deoxyribose
used in deoxyribonucleic acid (DNA)

Each numbered carbon on the sugar of a nucleotide is followed by a prime mark; therefore, one speaks of the "5-prime carbon," etc.

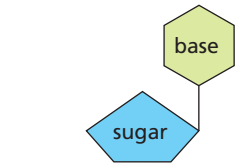
NOMENCLATURE

The names can be confusing, but the abbreviations are clear.

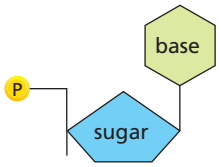
BASE	NUCLEOSIDE	ABBR.
adenine	adenosine	A
guanine	guanosine	G
cytosine	cytidine	C
uracil	uridine	U
thymine	thymidine	T

Nucleotides are abbreviated by three capital letters. Some examples follow:

AMP = adenosine monophosphate
dAMP = deoxyadenosine monophosphate
UDP = uridine diphosphate
ATP = adenosine triphosphate



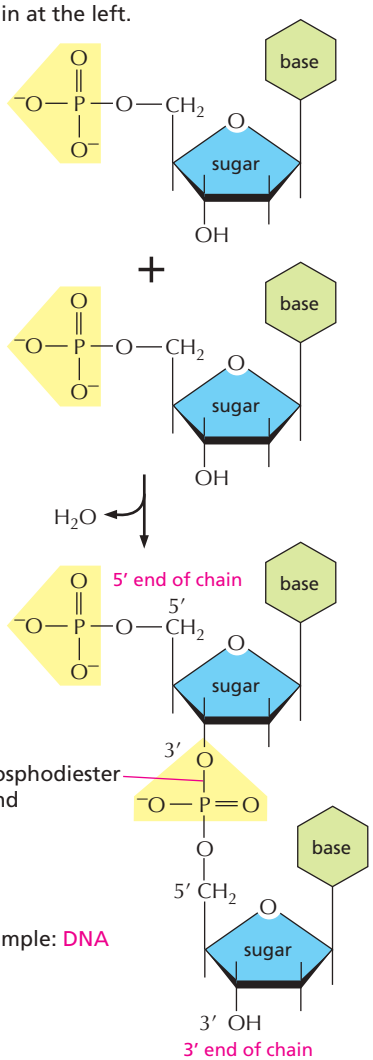
BASE + SUGAR = NUCLEOSIDE



BASE + SUGAR + PHOSPHATE = NUCLEOTIDE

NUCLEIC ACIDS

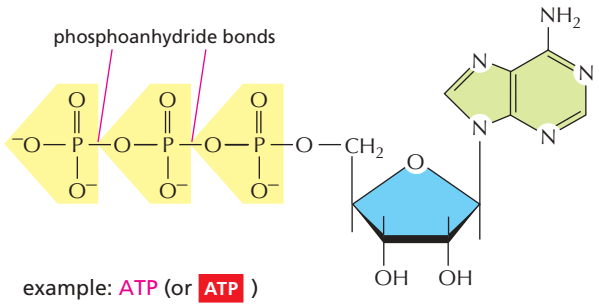
Nucleotides are joined together by phosphodiester bonds between 5′ and 3′ carbon atoms of the sugar ring, via a phosphate group, to form nucleic acids. The linear sequence of nucleotides in a nucleic acid chain is commonly abbreviated by a one-letter code, such as AGCTTACA, with the 5′ end of the chain at the left.



example: DNA

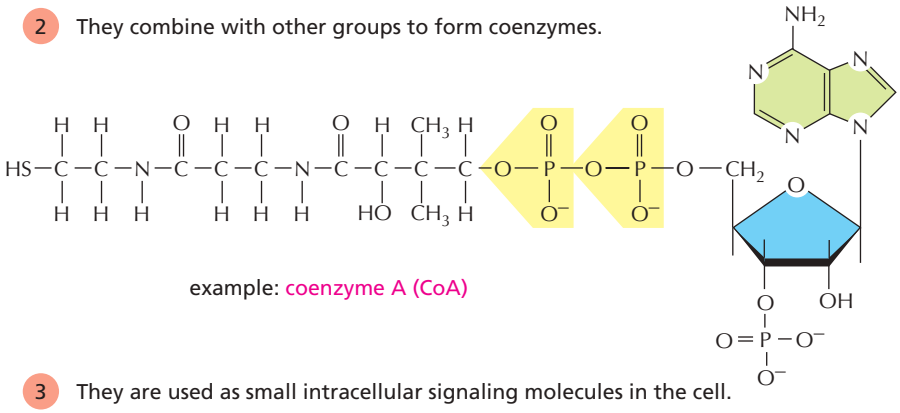
NUCLEOTIDES HAVE MANY OTHER FUNCTIONS

1. They carry chemical energy in their easily hydrolyzed phosphoanhydride bonds.



example: ATP (or ATP)

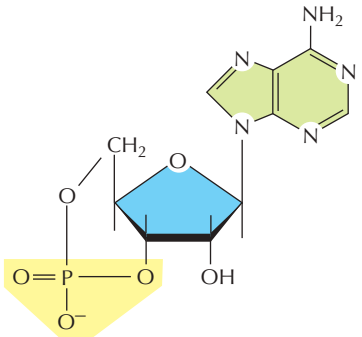
2. They combine with other groups to form coenzymes.



example: coenzyme A (CoA)

3. They are used as small intracellular signaling molecules in the cell.

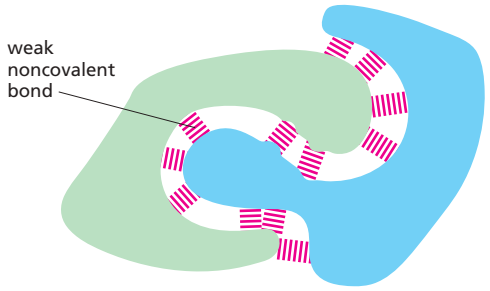
example: cyclic AMP



PANEL 2–7 THE PRINCIPAL TYPES OF WEAK NONCOVALENT BONDS

WEAK NONCOVALENT CHEMICAL BONDS

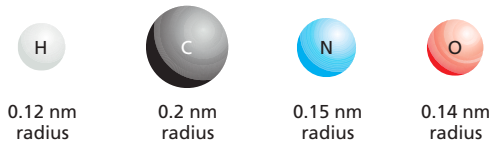
Organic molecules can interact with other molecules through three types of short-range attractive forces known as *noncovalent bonds*: van der Waals attractions, electrostatic attractions, and hydrogen bonds. The repulsion of hydrophobic groups from water is also important for these interactions and for the folding of biological macromolecules.



Weak noncovalent bonds have less than 1/20 the strength of a strong covalent bond. They are strong enough to provide tight binding only when many of them are formed simultaneously.

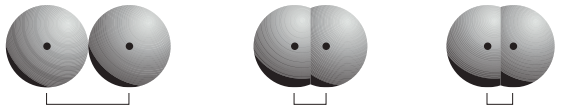
VAN DER WAALS ATTRACTIONS

If two atoms are too close together they repel each other very strongly. For this reason, an atom can often be treated as a sphere with a fixed radius. The characteristic "size" for each atom is specified by a unique van der Waals radius. The contact distance between any two noncovalently bonded atoms is the sum of their van der Waals radii.



At very short distances, any two atoms show a weak bonding interaction due to their fluctuating electrical charges. The two atoms will be attracted to each other in this way until the distance between their nuclei is approximately equal to the sum of their van der Waals radii. Although they are individually very weak, such van der Waals attractions can become important when two macromolecular surfaces fit very close together, because many atoms are involved.

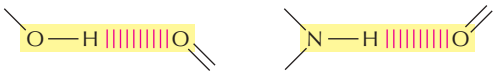
Note that when two atoms form a covalent bond, the centers of the two atoms (the two atomic nuclei) are much closer together than the sum of the two van der Waals radii. Thus,



HYDROGEN BONDS

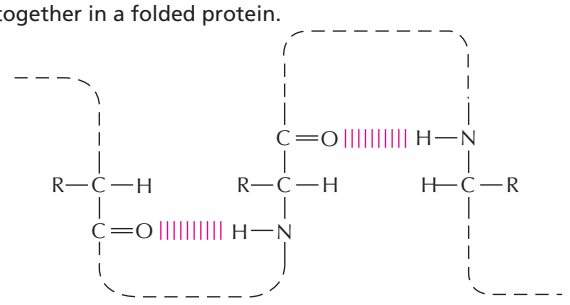
As already described for water (see Panel 2–2, pp. 68–69), hydrogen bonds form when a hydrogen atom is "sandwiched" between two electron-attracting atoms (usually oxygen or nitrogen).

Hydrogen bonds are strongest when the three atoms are in a straight line:

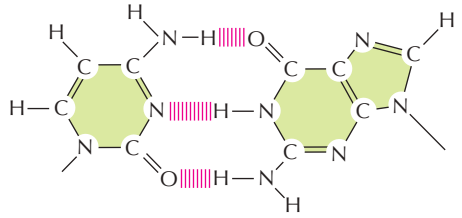


Examples in macromolecules:

Amino acids in a polypeptide chain can be hydrogen-bonded together in a folded protein.

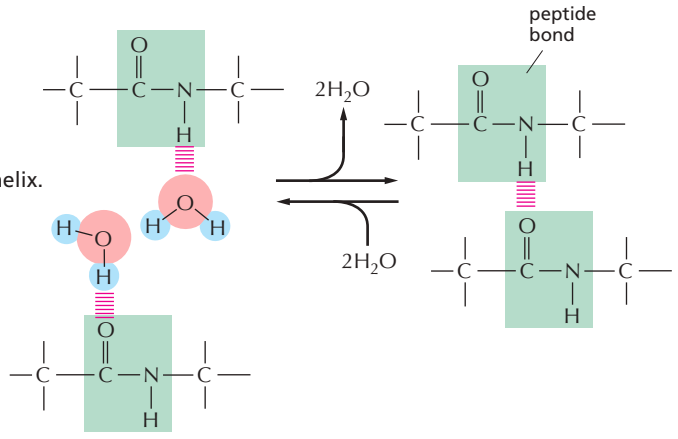


Two bases, G and C, are hydrogen-bonded in a DNA double helix.



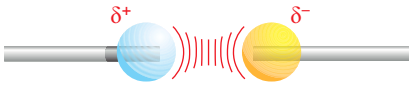
HYDROGEN BONDS IN WATER

Any two atoms that can form hydrogen bonds to each other can alternatively form hydrogen bonds to water molecules. Because of this competition with water molecules, the hydrogen bonds formed in water between two peptide bonds, for example, are relatively weak.



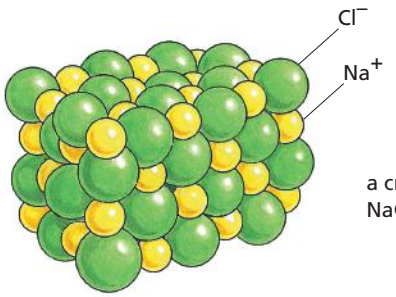
ELECTROSTATIC ATTRACTIONS

Attractive interactions occur both between fully charged groups (ionic bond) and between partially charged groups on polar molecules.



The force of attraction between the two partial charges, δ^+ and δ^-, falls off rapidly as the distance between the charges increases.

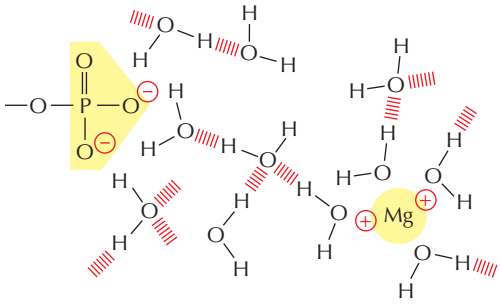
In the absence of water, ionic bonds are very strong. They are responsible for the strength of such minerals as marble and agate, and for crystal formation in common table salt, NaCl.



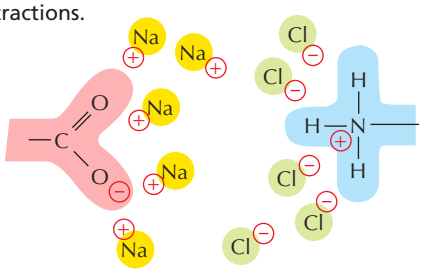
a crystal of NaCl

ELECTROSTATIC ATTRACTIONS IN AQUEOUS SOLUTIONS

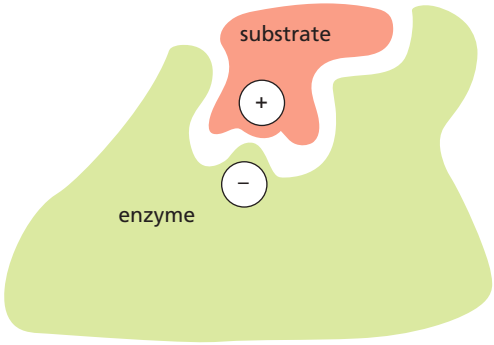
Charged groups are shielded by their interactions with water molecules. Electrostatic attractions are therefore quite weak in water.



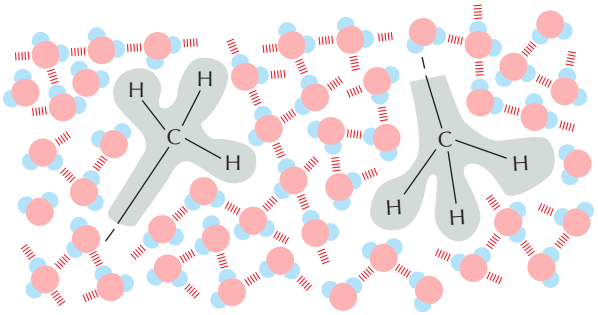
Inorganic ions in solution can also cluster around charged groups and further weaken these electrostatic attractions.

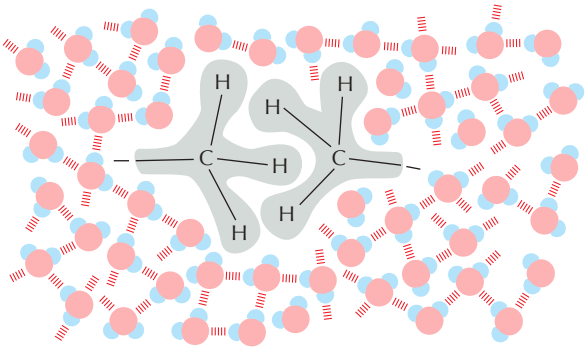


Despite being weakened by water and inorganic ions, electrostatic attractions are very important in biological systems. For example, an enzyme that binds a positively charged substrate will often have a negatively charged amino acid side chain at the appropriate place.



HYDROPHOBIC INTERACTIONS





Water forces hydrophobic groups together in order to minimize their disruptive effects on the water network formed by the H bonds between water molecules. Hydrophobic groups held together in this way are sometimes said to be held together by "hydrophobic bonds," even though the attraction is actually caused by a repulsion from water.

QUESTIONS

QUESTION 2–10

Which of the following statements are correct? Explain your answers.

A. An atomic nucleus contains protons and neutrons.

B. An atom has more electrons than protons.

C. The nucleus is surrounded by a double membrane.

D. All atoms of the same element have the same number of neutrons.

E. The number of neutrons determines whether the nucleus of an atom is stable or radioactive.

F. Both fatty acids and polysaccharides can be important energy stores in the cell.

G. Hydrogen bonds are weak and can be broken by thermal energy, yet they contribute significantly to the specificity of interactions between macromolecules.

QUESTION 2–11

To gain a better feeling for atomic dimensions, assume that the page on which this question is printed is made entirely of the polysaccharide cellulose, whose molecules are described by the formula $(C_nH_{2n}O_n)$, where n can be a quite large number and is variable from one molecule to another. The atomic weights of carbon, hydrogen, and oxygen are 12, 1, and 16, respectively, and this page weighs 5 g.

A. How many carbon atoms are there in this page?

B. In cellulose, how many carbon atoms would be stacked on top of each other to span the thickness of this page (the size of the page is 21.2 cm × 27.6 cm, and it is 0.07 mm thick)?

C. Now consider the problem from a different angle. Assume that the page is composed only of carbon atoms. A carbon atom has a diameter of 2×10^{-10} m (0.2 nm); how many carbon atoms of 0.2 nm diameter would it take to span the thickness of the page?

D. Compare your answers from parts B and C and explain any differences.

QUESTION 2–12

A. How many electrons can be accommodated in the first, second, and third electron shells of an atom?

B. How many electrons would atoms of the elements listed below have to gain or lose to obtain a completely filled outer shell?

helium	gain __	lose __
oxygen	gain __	lose __
carbon	gain __	lose __
sodium	gain __	lose __
chlorine	gain __	lose __

C. What do the answers tell you about the reactivity of helium and the bonds that can form between sodium and chlorine?

QUESTION 2–13

The elements oxygen and sulfur have similar chemical properties because they both have six electrons in their outermost electron shells. Indeed, both elements form molecules with two hydrogen atoms, water (H_2O) and hydrogen sulfide (H_2S). Surprisingly, at room temperature, water is a liquid, yet H_2S is a gas, despite sulfur being much larger and heavier than oxygen. Explain why this might be the case.

QUESTION 2–14

Write the chemical formula for a condensation reaction of two amino acids to form a peptide bond. Write the formula for its hydrolysis.

QUESTION 2–15

Which of the following statements are correct? Explain your answers.

A. Proteins are so remarkably diverse because each is made from a unique mixture of amino acids that are linked in random order.

B. Lipid bilayers are macromolecules that are made up mostly of phospholipid subunits.

C. Nucleic acids contain sugar groups.

D. Many amino acids have hydrophobic side chains.

E. The hydrophobic tails of phospholipid molecules are repelled from water.

F. DNA contains the four different bases A, G, U, and C.

QUESTION 2–16

A. How many different molecules composed of (a) two, (b) three, and (c) four amino acids, linked together by peptide bonds, can be made from the set of 20 naturally occurring amino acids?

B. Assume you were given a mixture consisting of one molecule each of all possible sequences of a smallish protein of molecular weight 4800 daltons. If the average molecular weight of an amino acid is, say, 120 daltons, how much would the sample weigh? How big a container would you need to hold it?

C. What does this calculation tell you about the fraction of possible proteins that are currently in use by living organisms (the average molecular weight of proteins is about 30,000 daltons)?

QUESTION 2–17

This is a biology textbook. Explain why the chemical principles that are described in this chapter are important in the context of modern cell biology.

QUESTION 2–18

A. Describe the similarities and differences between van der Waals attractions and hydrogen bonds.

B. Which of the two bonds would form (a) between two hydrogens bound to carbon atoms, (b) between a nitrogen atom and a hydrogen bound to a carbon atom, and (c) between a nitrogen atom and a hydrogen bound to an oxygen atom?

QUESTION 2–19

What are the forces that determine the folding of a macromolecule into a unique shape?

QUESTION 2–20

Fatty acids are said to be "amphipathic." What is meant by this term, and how does an amphipathic molecule behave in water? Draw a diagram to illustrate your answer.

QUESTION 2–21

Are the formulas in **Figure Q2–21** correct or incorrect? Explain your answer in each case.

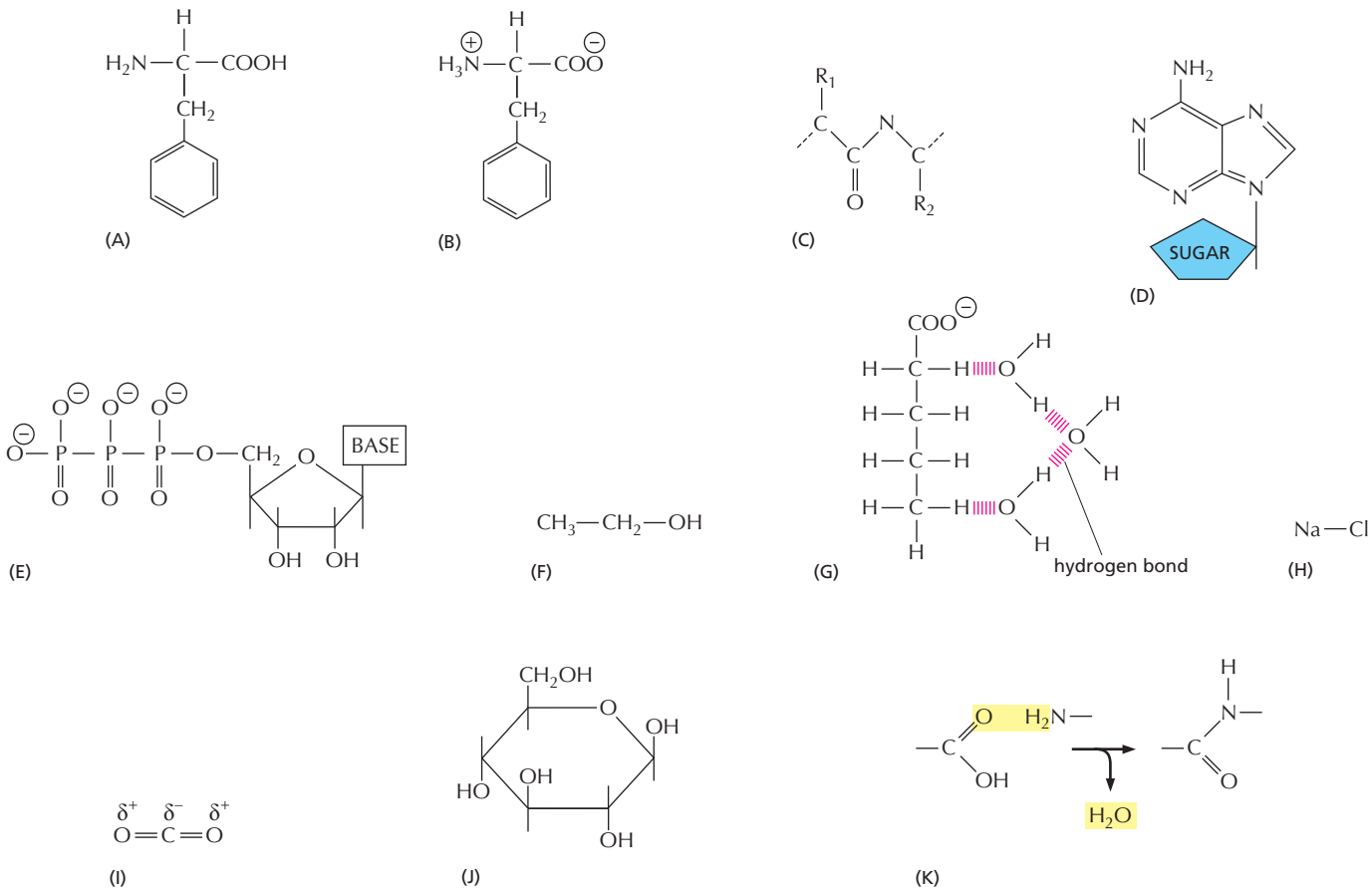


Figure Q2–21

Page left intentionally blank