Life

CHAPTER 1

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It is usually easy to decide whether or not something is alive. This is because living things share many common attributes, such as the capacity to extract energy from nutrients to drive their various functions, the power to actively respond to changes in their environment, and the ability to grow, to differentiate, and—perhaps most telling of all—to reproduce. Of course, a given organism may not have all of these traits. For example, mules, which are obviously alive, rarely reproduce. Conversely, inanimate matter may exhibit some lifelike properties. For instance, crystals may grow larger when immersed in a supersaturated solution of the crystalline material. Therefore, life, as are many other complex phenomena, is perhaps impossible to define in a precise fashion. Norman Horowitz, however, proposed a useful set of criteria for living systems: *Life possesses the properties of replication, catalysis, and mutability*. Much of this text is concerned with the manner in which living organisms exhibit these properties.

Biochemistry is the study of life on the molecular level. The significance of such studies is greatly enhanced if they are related to the biology of the corresponding organisms or even communities of such organisms. This introductory chapter therefore begins with a synopsis of the biological realm. This is followed by an outline of biochemistry, a review of genetics, a discussion of the origin of life, and finally, an introduction to the biochemical literature.

1 PROKARYOTES

It has long been recognized that life is based on morphological units known as **cells.** The formulation of this concept is generally attributed to an 1838 paper by Matthias Schleiden and Theodor Schwann, but its origins may be traced to the seventeenth century observations of early microscopists such as Robert Hooke. There are two major classifications of cells: the **eukaryotes** (Greek: *eu,* good or true + *karyon,* kernel or nut), which have a membrane-enclosed **nucleus** encapsulating their **DNA (deoxyribonucleic acid);** and the **prokaryotes** (Greek: *pro,* before), which lack this organelle. Prokaryotes, which comprise the various types of bacteria, have relatively simple structures and are invariably unicellular (although they may form filaments or colonies of independent cells). They are estimated to represent about half of Earth's biomass. Eukaryotes, which may be multicellular as well as unicellular, are vastly more complex than prokaryotes. (**Viruses,** which are much simpler entities than cells, are not classified as living because they lack the metabolic apparatus to reproduce outside their host cells. They are essentially large molecular aggregates.) This section is a discussion of prokaryotes. Eukaryotes are considered in the following section.

A. *Form and Function*

Prokaryotes are the most numerous and widespread organisms on Earth. This is because their varied and often highly adaptable metabolisms suit them to an enormous variety of habitats. Besides inhabiting our familiar temperate and aerobic environment, certain types of bacteria may thrive in or even require conditions that are hostile to eukaryotes such as unusual chemical environments, high temperatures (as high as 130°C), and lack of oxygen. Moreover, the rapid reproductive rate of prokaryotes (optimally <20 min per cell division for many species) permits them to take advantage of transiently favorable conditions, and

conversely, the ability of many bacteria to form resistant **spores** allows them to survive adverse conditions.

a. Prokaryotes Have Relatively Simple Anatomies

Prokaryotes, which were first observed in 1683 by the inventor of the microscope, Antonie van Leeuwenhoek, have sizes that are mostly in the range 1 to 10 μm. They have one of three basic shapes (Fig. 1-1): spheroidal **(cocci),** rodlike **(bacilli),** and helically coiled **(spirilla),** but all have the same general design (Fig. 1-2). They are bounded, as are all cells, by an ~70-Å-thick **cell membrane (plasma membrane),** which consists of a lipid bilayer containing embedded proteins that control the passage of molecules in and out of the cell and catalyze a variety of reactions. The cells of most prokaryotic species are surrounded by a rigid, 30- to 250-Å-thick polysaccharide **cell wall** that mainly functions to protect the cell from mechanical injury and to prevent it from bursting in media more osmotically dilute than its contents. Some bacteria further encase themselves in a gelatinous polysaccharide **capsule** that protects them from the defenses of higher organisms. Although prokaryotes lack the membranous subcellular organelles characteristic of eukaryotes (Section 1-2), their plasma membranes may be infolded to form multilayered structures known as **mesosomes.** The mesosomes are thought to serve as the site of DNA replication and other specialized enzymatic reactions.

The prokaryotic **cytoplasm** (cell contents) is by no means a homogeneous soup. Its single **chromosome** (DNA molecule, several copies of which may be present in a rapidly growing cell) is condensed to form a body known as a **nucleoid.** The cytoplasm also contains numerous species of **RNA (ribonucleic acid),** a variety of soluble **enzymes** (proteins that catalyze specific reactions), and many thousands of 250-Å-diameter particles known as **ribosomes,** which are the sites of protein synthesis.

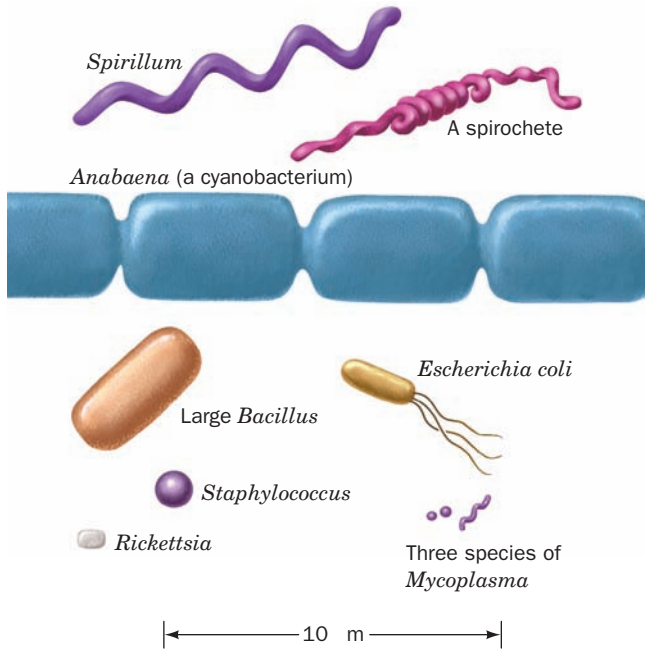


Figure 1-1 **Scale drawings of some prokaryotic cells.**

Many bacterial cells bear one or more whiplike appendages known as **flagella,** which are used for locomotion (Section 35-3I). Certain bacteria also have filamentous projections named **pili,** some types of which function as conduits for DNA during sexual conjugation (a process in which DNA is transferred from one cell to another; prokaryotes usually reproduce by binary fission) or aid in the attachment of the bacterium to a host organism's cells.

The bacterium ***Escherichia coli*** (abbreviated ***E. coli*** and named after its discoverer, Theodor Escherich) is the

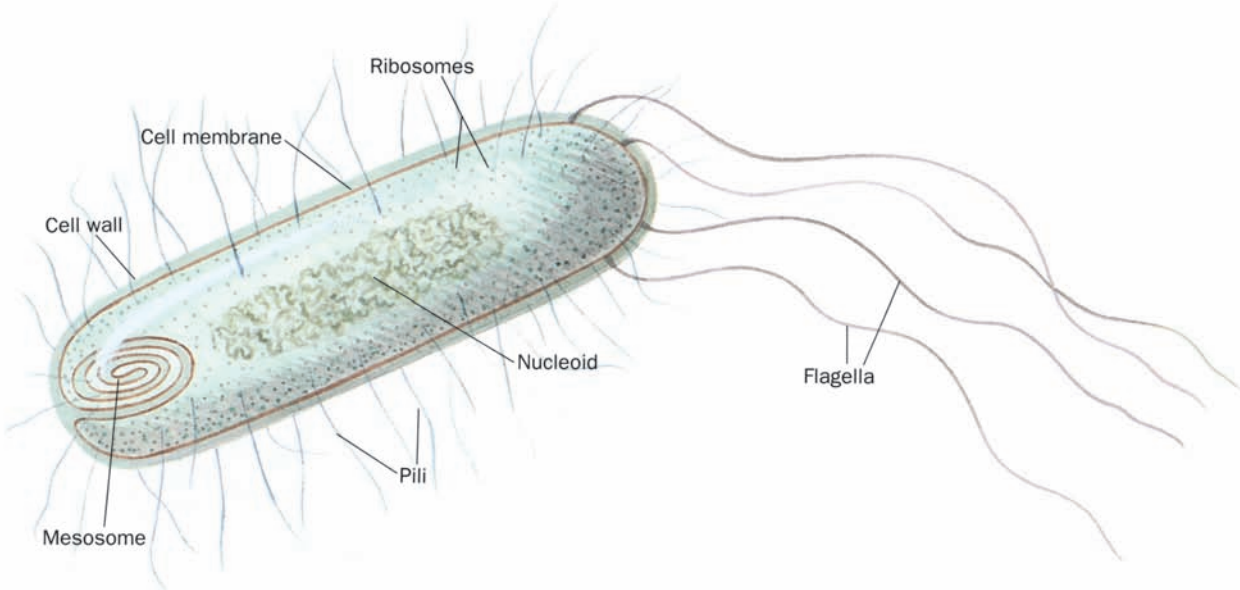
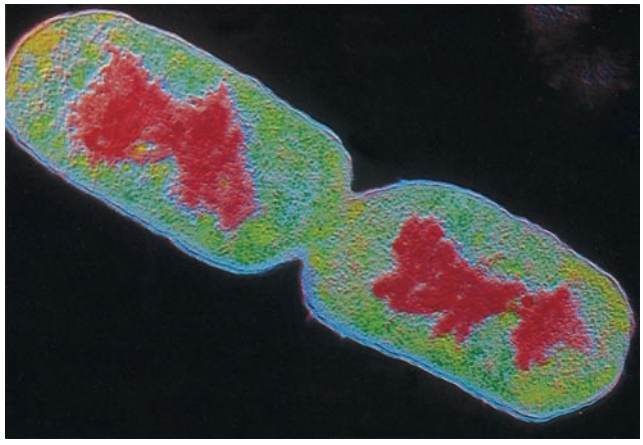
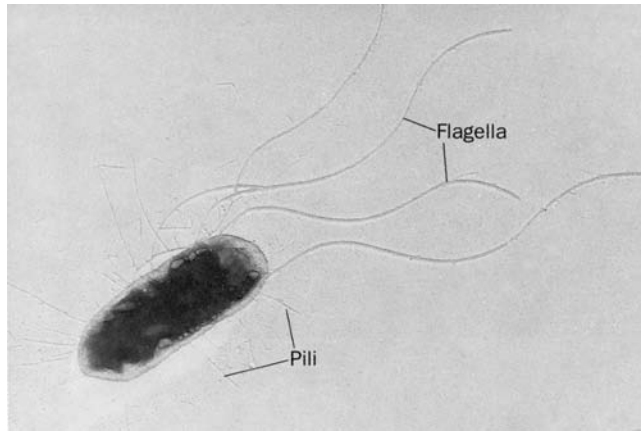


Figure 1-2 **Schematic diagram of a prokaryotic cell.**



(*a*)



(*b*)

Figure 1-3 **Electron micrographs of *E. coli* cells.** (*a*) Stained to show internal structure. (*b*) Stained to reveal flagella and pili. [*a*: CNRI/Photo Researchers; *b*: Courtesy of Howard Berg, Harvard University.]

biologically most well-characterized organism as a result of its intensive biochemical and genetic study over the past 70 years. Indeed, much of the subject matter of this text deals with the biochemistry of *E. coli*. Cells of this normal inhabitant of the higher mammalian colon (Fig. 1-3) are typically 2-μm-long rods that are 1 μm in diameter and weigh $\sim 2 \times 10^{-12}$ g. Its DNA, which has a molecular mass of 2.5×10^9 **daltons (D),*** encodes ~4300 proteins (of which only ~60 to 70% have been identified), although, typically, only ~2600 different proteins are present in a cell at any given time. Altogether an *E. coli* cell contains 3 to 6 thousand different types of molecules, including proteins, nucleic acids, polysaccharides, lipids, and various small molecules and ions (Table 1-1).

Table 1-1 **Molecular Composition of *E. coli***

Component	Percentage by Weight
H_2O	70
Protein	15
Nucleic acids:	
DNA	1
RNA	6
Polysaccharides and precursors	3
Lipids and precursors	2
Other small organic molecules	1
Inorganic ions	1

Source: Watson, J.D., *Molecular Biology of the Gene* (3rd ed.), *p.* 69, Benjamin (1976).

b. Prokaryotes Employ a Wide Variety of Metabolic Energy Sources

The nutritional requirements of the prokaryotes are enormously varied. **Autotrophs** (Greek*: autos,* self + *trophikos,* to feed) can synthesize all their cellular constituents from simple molecules such as H_2O, CO_2, NH_3, and H_2S. Of course they need an energy source to do so as well as to power their other functions. **Chemolithotrophs** (Greek: *lithos,* stone) obtain their energy through the oxidation of inorganic compounds such as NH_3, H_2S, or even Fe^{2+}:

$$2\,NH_3 + 4\,O_2 \longrightarrow 2\,HNO_3 + 2\,H_2O$$
$$H_2S + 2\,O_2 \longrightarrow H_2SO_4$$
$$4\,FeCO_3 + O_2 + 6\,H_2O \longrightarrow 4\,Fe(OH)_3 + 4\,CO_2$$

Indeed, studies have revealed the existence of extensive albeit extremely slow-growing colonies of chemolithotrophs that live as far as 5 kilometers underground and whose aggregate biomass appears to rival that of surface-dwelling organisms.

Photoautotrophs are autotrophs that obtain energy via **photosynthesis** (Chapter 24), a process in which light energy powers the transfer of electrons from inorganic donors to CO_2 yielding **carbohydrates** $[(CH_2O)_n]$. In the most widespread form of photosynthesis, the electron donor in the light-driven reaction sequence is H_2O.

$$n\,CO_2 + n\,H_2O \longrightarrow CH_2O_n + n\,O_2$$

This process is carried out by **cyanobacteria** (e.g., the green slimy organisms that grow on the walls of aquariums; cyanobacteria were formerly known as **blue-green algae**), as well as by plants. This form of photosynthesis is thought to have generated the O_2 in Earth's atmosphere. Some species of cyanobacteria have the ability to convert N_2 from the atmosphere to organic nitrogen compounds. This **nitrogen fixation** capacity gives them the simplest nutritional

*The **molecular mass** of a particle may be expressed in units of daltons, which are defined as 1/12th the mass of a ^{12}C atom [atomic mass units (amu)]. Alternatively, this quantity may be expressed in terms of **molecular weight,** a dimensionless quantity defined as the ratio of the particle mass to 1/12th the mass of a ^{12}C atom and symbolized M_r (for relative molecular mass). In this text, we shall refer to the molecular mass of a particle rather than to its molecular weight.

requirements of all organisms: With the exception of their need for small amounts of minerals, they can literally live on sunlight and air.

In a more primitive form of photosynthesis, substances such as H_2, H_2S, thiosulfate, or organic compounds are the electron donors in light-driven reactions such as

$$n\,CO_2 + 2n\,H_2S \longrightarrow CH_2O_n + n\,H_2O + 2n\,S$$

The **purple** and the **green photosynthetic bacteria** that carry out these processes occupy such oxygen-free habitats as shallow muddy ponds in which H_2S is generated by rotting organic matter.

Heterotrophs (Greek: *hetero,* other) obtain energy through the oxidation of organic compounds and hence are ultimately dependent on autotrophs for these substances. **Obligate aerobes** (which include animals) must utilize O_2, whereas **anaerobes** employ oxidizing agents such as sulfate **(sulfate-reducing bacteria)** or nitrate **(denitrifying bacteria).** Many organisms can partially metabolize various organic compounds in intramolecular oxidation–reduction processes known as **fermentation. Facultative anaerobes** such as *E. coli* can grow in either the presence or the absence of O_2. **Obligate anaerobes,** in contrast, are poisoned by the presence of O_2. Their metabolisms are thought to resemble those of the earliest life-forms (which arose over 3.8 billion years ago when Earth's atmosphere lacked O_2; Section 1-5B). At any rate, there are few organic compounds that cannot be metabolized by some prokaryotic organism.

B. *Prokaryotic Classification*

The traditional methods of **taxonomy** (the science of biological classification), which are based largely on the anatomical comparisons of both contemporary and fossil organisms, are essentially inapplicable to prokaryotes. This is because the relatively simple cell structures of prokaryotes, including those of ancient bacteria as revealed by their microfossil remnants, provide little indication of their phylogenetic relationships (**phylogenesis:** evolutionary development). Compounding this problem is the observation that prokaryotes exhibit little correlation between form and metabolic function. Moreover, the eukaryotic definition of a species as a population that can interbreed is meaningless for the asexually reproducing prokaryotes. Consequently, the conventional prokaryotic classification schemes are rather arbitrary and lack the implied evolutionary relationships of the eukaryotic classification scheme (Section 1-2B).

In the most widely used prokaryotic classification scheme, the **prokaryotae** (also known as **monera**) have two divisions: the cyanobacteria and the **bacteria.** The latter are further subdivided into 19 parts based on their various distinguishing characteristics, most notably cell structure, metabolic behavior, and staining properties.

A simpler classification scheme, which is based on cell wall properties, distinguishes three major types of prokaryotes: the **mycoplasmas,** the **gram-positive bacteria,** and the **gram-negative bacteria.** Mycoplasmas lack the rigid cell wall of other prokaryotes. They are the smallest of all living cells (as small as 0.12 μm in diameter, Fig. 1-1) and possess ~20% of the DNA of an *E. coli*. Presumably this quantity of genetic information approaches the minimum amount necessary to specify the essential metabolic machinery required for cellular life. Gram-positive and gram-negative bacteria are distinguished according to whether or not they take up **gram stain** (a procedure developed in 1884 by Christian Gram in which heat-fixed cells are successively treated with the dye crystal violet and iodine and then destained with either ethanol or acetone). Gram-negative bacteria possess a complex **outer membrane** that surrounds their cell wall and excludes gram stain, whereas gram-positive bacteria lack such a membrane (Section 11-3B).

The development, in recent decades, of techniques for determining amino acid sequences in proteins (Section 7-1) and base sequences in nucleic acids (Section 7-2A) has provided abundant indications as to the genealogical relationships between organisms. Indeed, these techniques make it possible to place these relationships on a quantitative basis, and thus to construct a phylogenetically based classification system for prokaryotes.

By the analysis of ribosomal RNA sequences, Carl Woese showed that a group of prokaryotes he named the **Archaea** (also known as the **archaebacteria**) are as distantly related to the other prokaryotes, the **Bacteria** (also called the **eubacteria**), as both of these groups are to the **Eukarya** (the eukaryotes). The Archaea initially appeared to constitute three different kinds of unusual organisms: the **methanogens,** obligate anaerobes that produce methane (marsh gas) by the reduction of CO_2 with H_2; the **halobacteria,** which can live only in concentrated brine solutions (>2*M* NaCl); and certain **thermoacidophiles,** organisms that inhabit acidic hot springs (~90°C and pH < 2). However, recent evidence indicates that ~40% of the microorganisms in the oceans are Archaea, and hence they may be the most common form of life on Earth.

On the basis of a number of fundamental biochemical traits that differ among the Archaea, the Bacteria, and the Eukarya, but that are common within each group, Woese proposed that these groups of organisms constitute the three primary **urkingdoms** or **domains** of evolutionary descent (rather than the traditional division into prokaryotes and eukaryotes). However, further sequence determinations have revealed that the Eukarya share sequence similarities with the Archaea that they do not share with the Bacteria. Evidently, the Archaea and the Bacteria diverged from some simple primordial life-form following which the Eukarya diverged from the Archaea, as the **phylogenetic tree** in Fig. 1-4 indicates.

2 EUKARYOTES

Eukaryotic cells are generally 10 to 100 μm in diameter and thus have a thousand to a million times the volume of typical prokaryotes. It is not size, however, but a profusion of membrane-enclosed organelles, each with a specialized

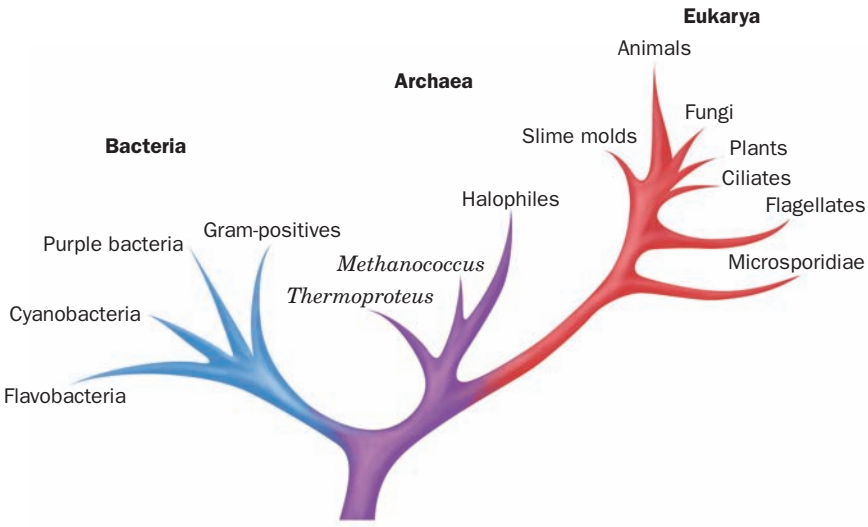


Figure 1-4 **Phylogenetic tree.** This "family tree" indicates the evolutionary relationships among the three domains of life. The root of the tree represents the last common ancestor of all life on Earth. [After Wheelis, M.L., Kandler, O., and Woese, C.R., *Proc. Natl. Acad. Sci.* **89,** 2931 (1992).]

function, that best characterizes eukaryotic cells (Fig. 1-5). In fact, *eukaryotic structure and function are more complex than those of prokaryotes at all levels of organization,* from the molecular level on up.

Eukaryotes and prokaryotes have developed according to fundamentally different evolutionary strategies. Prokaryotes have exploited the advantages of simplicity and miniaturization: Their rapid growth rates permit them to occupy ecological niches in which there may be drastic fluctuations of the available nutrients. In contrast, the complexity of eukaryotes, which renders them larger and more slowly growing than prokaryotes, gives them the competitive

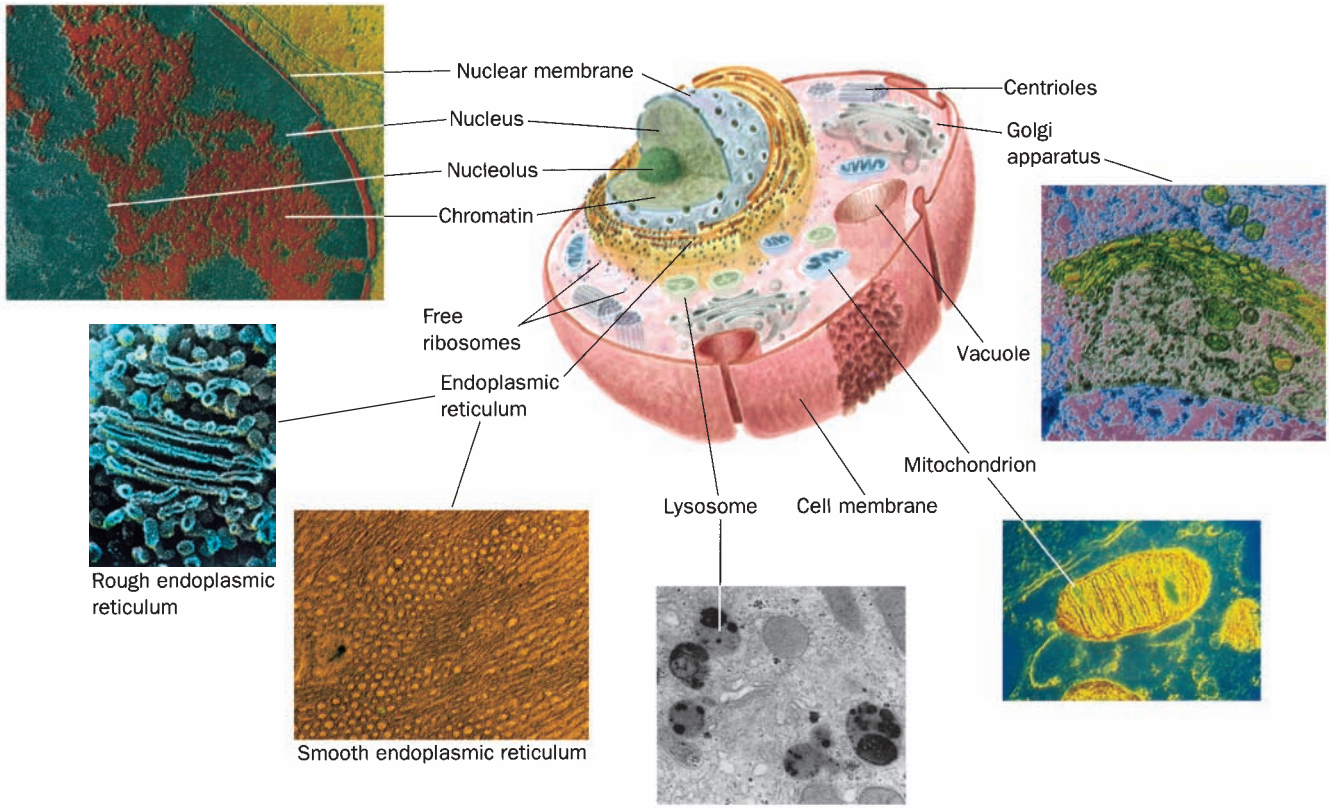


Figure 1-5 **Schematic diagram of an animal cell accompanied by electron micrographs of its organelles.** [Nucleus: Tektoff-RM, CNRI/Photo Researchers; rough endoplasmic reticulum: Pietro M. Motta & Tomonori Naguro/Photo Researchers, Inc. and Golgi apparatus: Secchi-Lecaque/Roussel-UCLAF/CNRI/Photo Researchers, Inc.; smooth endoplasmic reticulum: David M. Phillips/Visuals Unlimited; mitochondrion: CNRI/Photo Researchers; lysosome: Biophoto Associates/Photo Researchers.]

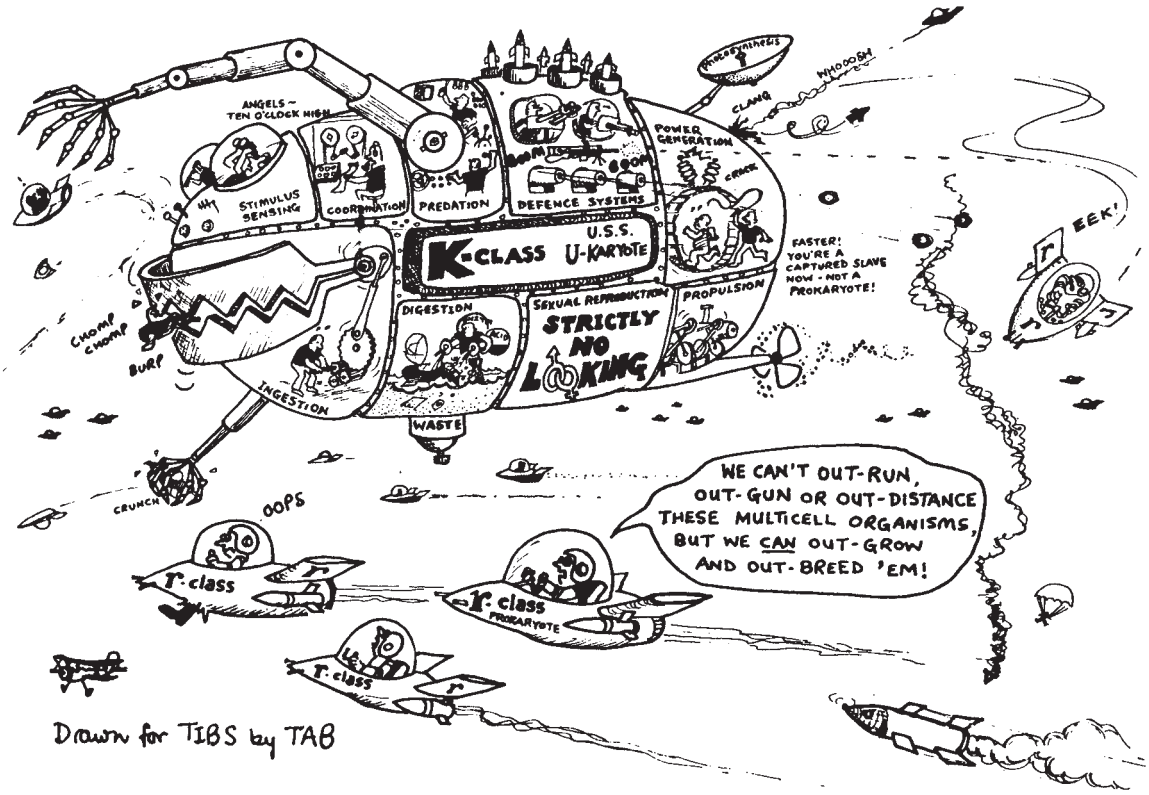


Figure 1-6 [Drawing by T.A. Bramley, in Carlile, M., *Trends Biochem. Sci.* **7,** 128 (1982). Copyright © Elsevier Biomedical Press, 1982. Used by permission.]

advantage in stable environments with limited resources (Fig. 1-6). It is therefore erroneous to consider prokaryotes as evolutionarily primitive with respect to eukaryotes. Both types of organisms are well adapted to their respective lifestyles.

The earliest known microfossils of eukaryotes date from ~1.4 billion years ago, some 2.4 billion years after life arose. This observation supports the classical notion that eukaryotes are descended from a highly developed prokaryote, possibly a mycoplasma. The differences between eukaryotes and modern prokaryotes, however, are so profound as to render this hypothesis improbable. Perhaps the early eukaryotes, which according to Woese's evidence evolved from a primordial life-form, were relatively unsuccessful and hence rare. Only after they had developed some of the complex organelles described in the following section did they become common enough to generate significant fossil remains.

A. *Cellular Architecture*

Eukaryotic cells, like prokaryotes, are bounded by a plasma membrane. The large size of eukaryotic cells results in their surface-to-volume ratios being much smaller than those of prokaryotes (the surface area of an object increases as the square of its radius, whereas volume does so as the cube). This geometrical constraint, coupled with the fact that many essential enzymes are membrane associated, partially rationalizes the large amounts of intracellular membranes in eukaryotes (the plasma membrane typically constitutes <10% of the membrane in a eukaryotic cell). Since all the matter that enters or leaves a cell must somehow pass through its plasma membrane, the surface areas of many eukaryotic cells are increased by numerous projections and/or invaginations (Fig. 1-7). Moreover, portions of the plasma membrane often bud inward, in a process known as **endocytosis,** so that the cell surrounds portions of the external medium. Thus eukaryotic cells can engulf and digest food particles such as bacteria, whereas prokaryotes are limited to the absorption of individual nutrient molecules. The reverse of endocytosis, a process termed **exocytosis,** is a common eukaryotic secretory mechanism.

a. The Nucleus Contains the Cell's DNA

The nucleus, the eukaryotic cell's most conspicuous organelle, is the repository of its genetic information. This information is encoded in the base sequences of DNA molecules that form the discrete number of chromosomes characteristic of each species. The chromosomes consist of **chromatin,** a complex of DNA and protein. The amount of genetic information carried by eukaryotes is enormous; for example, a human cell has over 700 times the DNA of *E. coli* [in the terms commonly associated with computer memories, the **genome** (genetic complement) in each human

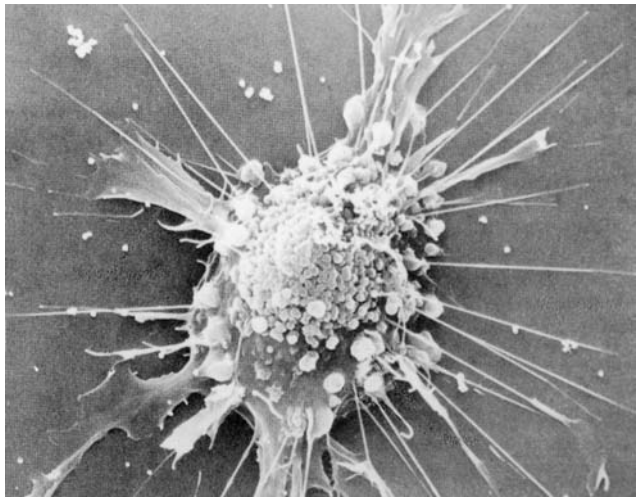


Figure 1-7 **Scanning electron micrograph of a fibroblast.** [Courtesy of Guenther Albrecht-Buehler, Northwestern University.]

cell specifies around 800 megabytes of information—about 200 times the information content of this text]. Within the nucleus, the genetic information encoded by the DNA is transcribed into molecules of RNA (Chapter 31), which, after extensive processing, are transported to the cytoplasm (in eukaryotes, the cell contents exclusive of the nucleus), where they direct the ribosomal synthesis of proteins (Chapter 32). The nuclear envelope consists of a double membrane that is perforated by numerous ~90-Å-wide pores that regulate the flow of proteins and RNA between the nucleus and the cytoplasm.

The nucleus of most eukaryotic cells contains at least one dark-staining body known as the **nucleolus,** which is the site of ribosomal assembly. It contains chromosomal segments bearing multiple copies of genes specifying ribosomal RNA. These genes are transcribed in the nucleolus, and the resulting RNA is combined with ribosomal proteins that have been imported from their site of synthesis in the **cytosol** (the cytoplasm exclusive of its membrane-bound organelles). The resulting immature ribosomes are then exported to the cytosol, where their assembly is completed. Thus protein synthesis occurs almost entirely in the cytosol.

b. The Endoplasmic Reticulum and the Golgi Apparatus Function to Modify Membrane-Bound and Secretory Proteins

The most extensive membrane in the cell, which was discovered in 1945 by Keith Porter, forms a labyrinthine compartment named the **endoplasmic reticulum.** A large portion of this organelle, called the **rough endoplasmic reticulum,** is studded with ribosomes that are engaged in the synthesis of proteins that are either membrane-bound or destined for secretion. The **smooth endoplasmic reticulum,** which is devoid of ribosomes, is the site of lipid synthesis. Many of the products synthesized in the endoplasmic reticulum are eventually transported to the **Golgi apparatus** (named after Camillo Golgi, who first described it in 1898), a stack of flattened membranous sacs in which these products are further processed (Section 23-3B).

c. Mitochondria Are the Site of Oxidative Metabolism

The **mitochondria** (Greek: *mitos,* thread + *chondros,* granule) are the site of cellular **respiration** (aerobic metabolism) in almost all eukaryotes. These cytoplasmic organelles, which are large enough to have been discovered by nineteenth century cytologists, vary in their size and shape but are often ellipsoidal with dimensions of around 1.0 × 2.0 μm—much like a bacterium. A eukaryotic cell typically contains on the order of 2000 mitochondria, which occupy roughly one-fifth of its total cell volume.

The mitochondrion, as the electron microscopic studies of George Palade and Fritjof Sjöstrand first revealed, has two membranes: a smooth outer membrane and a highly folded inner membrane whose invaginations are termed **cristae** (Latin: crests). Thus the mitochondrion contains two compartments, the **intermembrane space** and the internal **matrix space.** The enzymes that catalyze the reactions of respiration are components of either the gel-like **matrix** or the inner mitochondrial membrane. *These enzymes couple the energy-producing oxidation of nutrients to the energy-requiring synthesis of* ***adenosine triphosphate*** (**ATP;** Section 1-3B and Chapter 22). Adenosine triphosphate, after export to the rest of the cell, fuels its various energy-consuming processes.

Mitochondria are bacteria-like in more than size and shape. Their matrix space contains mitochondrion-specific DNA, RNA, and ribosomes that participate in the synthesis of several mitochondrial components. Moreover, they reproduce by binary fission, and the respiratory processes that they mediate bear a remarkable resemblance to those of modern aerobic bacteria. These observations led to the now widely accepted hypothesis championed by Lynn Margulis that mitochondria evolved from originally free-living gram-negative aerobic bacteria, which formed a symbiotic relationship with a primordial anaerobic eukaryote. The eukaryote-supplied nutrients consumed by the bacteria were presumably repaid severalfold by the highly efficient oxidative metabolism that the bacteria conferred on the eukaryote. This hypothesis is corroborated by the observation that the amoeba *Pelomyxa palustris,* one of the few eukaryotes that lack mitochondria, permanently harbors aerobic bacteria in such a symbiotic relationship.

d. Lysosomes and Peroxisomes Are Containers of Degradative Enzymes

Lysosomes, which were discovered in 1949 by Christian de Duve, are organelles bounded by a single membrane that are of variable size and morphology, although most have diameters in the range 0.1 to 0.8 μm. Lysosomes, which are essentially membranous bags containing a large variety of hydrolytic enzymes, function to digest materials ingested by endocytosis and to recycle cellular components (Section 32-6). Cytological investigations have revealed that lysosomes form by budding from the Golgi apparatus.

Peroxisomes (also known as **microbodies**) are membrane-enclosed organelles, typically 0.5 μm in diameter, that contain oxidative enzymes. They are so named because some peroxisomal reactions generate **hydrogen peroxide** (H_2O_2), a reactive substance that is either utilized in the enzymatic oxidation of other substances or degraded through a disproportionation reaction catalyzed by the enzyme **catalase:**

$$2\,H_2O_2 \longrightarrow 2\,H_2O + O_2$$

It is thought that peroxisomes function to protect sensitive cell components from oxidative attack by H_2O_2. Certain plants contain a specialized type of peroxisome, the **glyoxysome,** so named because it is the site of a series of reactions that are collectively termed the **glyoxylate pathway** (Section 23-2).

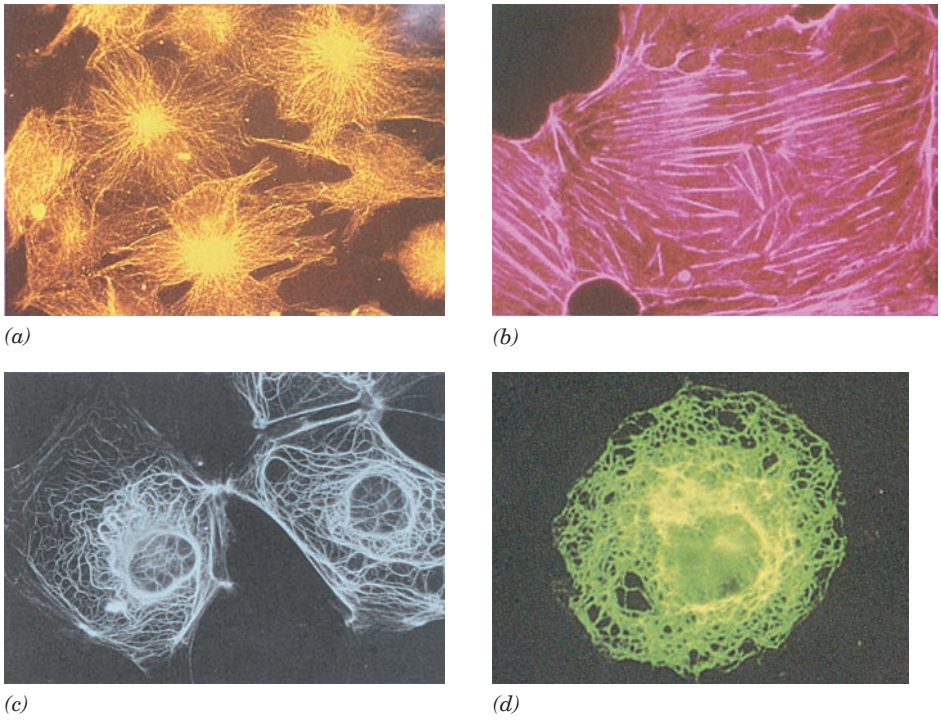
e. The Cytoskeleton Organizes the Cytosol

The cytosol, far from being a homogeneous solution, is a highly organized gel that can vary significantly in its composition throughout the cell. Much of its internal variability arises from the action of the **cytoskeleton,** an extensive array of filaments that gives the cell its shape and the ability to move and is responsible for the arrangement and internal motions of its organelles (Fig. 1-8).

The most conspicuous cytoskeletal components, the **microtubules,** are ~250-Å-diameter tubes that are composed of the protein **tubulin** (Section 35-3G). They form the supportive framework that guides the movements of organelles within a cell. For example, the **mitotic spindle** is an assembly of microtubules and associated proteins that participates in the separation of replicated chromosomes during cell division. Microtubules are also major constituents of **cilia,** the hairlike appendages extending from many cells, whose whiplike motions move the surrounding fluid past the cell or propel single cells through solution. Very long cilia, such as sperm tails, are termed **flagella** (prokaryotic flagella, which are composed of the protein **flagellin,** are quite different from and unrelated to those of eukaryotes).

The **microfilaments** are ~90-Å-diameter fibers that consist of the protein **actin.** Microfilaments, as do microtubules, have a mechanically supportive function. Furthermore, through their interactions with the protein **myosin,** microfilaments form contractile assemblies that are responsible for many types of intracellular movements such as cytoplasmic streaming and the formation of cellular protuberances or invaginations. More conspicuously, however, actin and myosin are the major protein components of muscle (Section 35-3A).

The third major cytoskeletal component, the **intermediate filaments,** are protein fibers that are 100 to 150 Å in diameter. Their prominence in parts of the cell that are subject to mechanical stress suggests that they have a load-bearing function. For example, skin in higher animals contains an extensive network of intermediate filaments made of the protein **keratin** (Section 8-2A), which is largely



(a) *(b)* *(c)* *(d)*

Figure 1-8 **Immunofluorescence micrographs showing cytoskeletal components.** Cells were treated with antibodies raised against (*a*) tubulin, (*b*) actin, (*c*) keratin, and (*d*) **vimentin** (a protein constituent of a type of intermediate filament) and then stained with fluorescently labeled antibodies that bound to the foregoing antibodies. [*a* and *d*: K.G. Murti/Visuals Unlimited; *b*: M. Schliwa/Visuals Unlimited; *c*: courtesy of Mary Osborn, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany.]

responsible for the toughness of this protective outer covering. In contrast to the case with microtubules and microfilaments, the proteins forming intermediate filaments vary greatly in size and composition, both among the different cell types within a given organism and among the corresponding cell types in different organisms.

f. Plant Cells Are Enclosed by Rigid Cell Walls

Plant cells (Fig. 1-9) contain all of the previously described organelles. They also have several additional features, the most conspicuous of which is a rigid cell wall that lies outside the plasma membrane. These cell walls, whose major component is the fibrous polysaccharide **cellulose** (Section 11-2C), account for the structural strength of plants.

A **vacuole** is a membrane-enclosed space filled with fluid. Although vacuoles occur in animal cells, they are most prominent in plant cells, where they typically occupy 90% of the volume of a mature cell. Vacuoles function as storage depots for nutrients, wastes, and specialized materials such as pigments. The relatively high concentration of solutes inside a plant vacuole causes it to take up water osmotically, thereby raising its internal pressure. This effect, combined with the cell walls' resistance to bursting, is largely responsible for the turgid rigidity of nonwoody plants.

g. Chloroplasts Are the Site of Photosynthesis in Plants

One of the definitive characteristics of plants is their ability to carry out photosynthesis. The site of photosynthesis is an organelle known as the **chloroplast,** which, although generally several times larger than a mitochondrion, resembles it in that both organelles have an inner and an outer membrane. Furthermore, the chloroplast's inner membrane space, the **stroma,** is similar to the mitochondrial matrix in that it contains many soluble enzymes. However, the inner chloroplast membrane is not folded

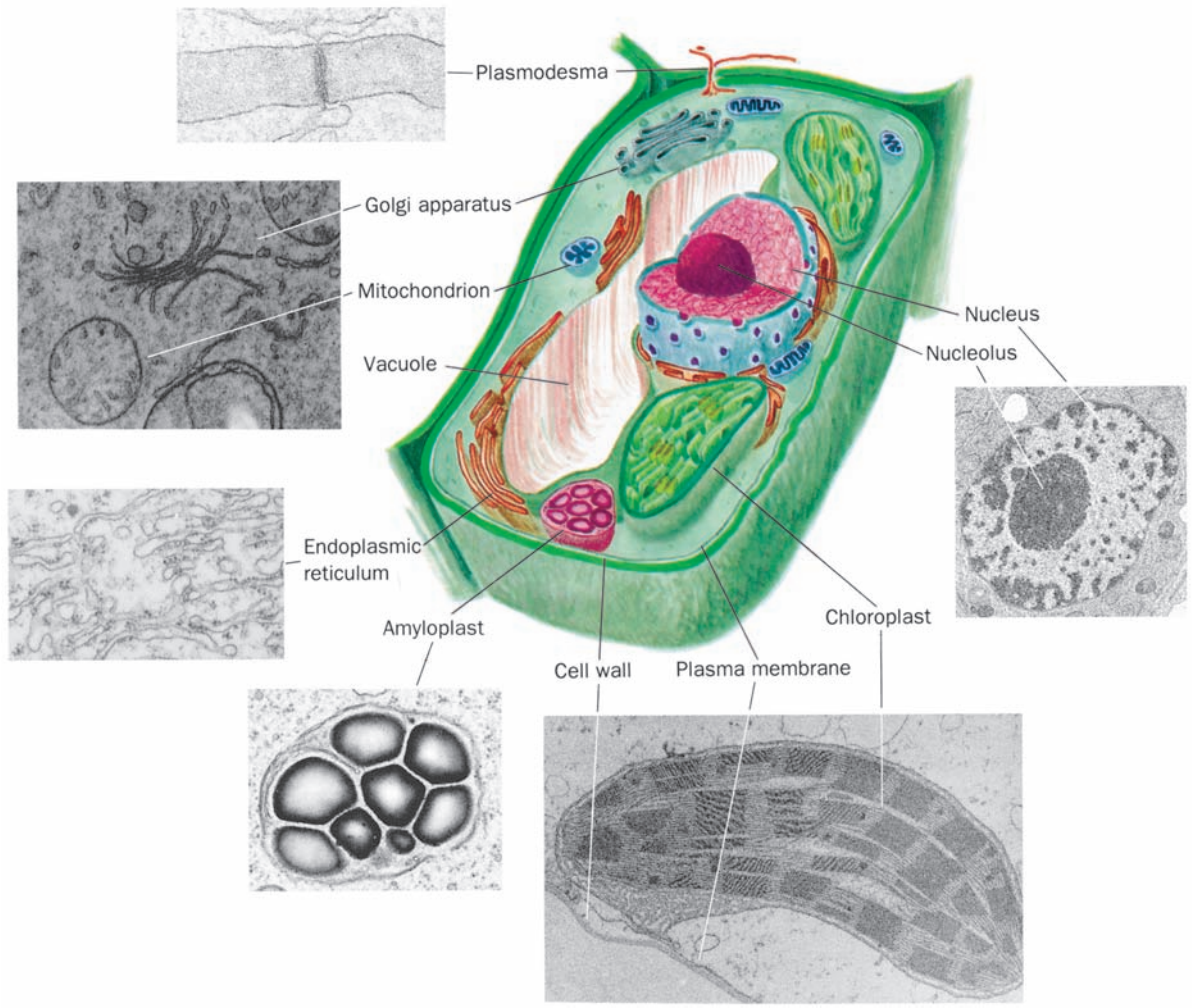


Figure 1-9 **Drawing of a plant cell accompanied by electron micrographs of its organelles.** [Plasmodesma: Courtesy of Hilton Mollenhauer, USDA; nucleus: Courtesy of Myron Ledbetter, Brookhaven National Laboratory; Golgi apparatus: Courtesy of W. Gordon Whaley, University of Texas; chloroplast: Courtesy of Lewis Shumway, College of Eastern Utah; amyloplast: Biophoto Associates; endoplasmic reticulum: Biophoto Associates/Photo Researchers.]

into cristae. Rather, the stroma encloses a third membrane system that forms interconnected stacks of disklike sacs called **thylakoids,** which contain the photosynthetic pigment **chlorophyll.** The thylakoid uses chlorophyll-trapped light energy to generate ATP, which is used in the stroma to drive biosynthetic reactions forming carbohydrates and other products (Chapter 24).

Chloroplasts, as do mitochondria, contain their own DNA, RNA, and ribosomes, and they reproduce by fission. Apparently chloroplasts, much like mitochondria, evolved from an ancient cyanobacterium that took up symbiotic residence in an ancestral nonphotosynthetic eukaryote. In fact, several modern nonphotosynthetic eukaryotes have just such a symbiotic relationship with authentic cyanobacteria. Hence *most modern eukaryotes are genetic "mongrels" in that they simultaneously have nuclear, mitochondrial, and in the case of plants, chloroplast lines of descent.*

B. *Phylogeny and Differentiation*

One of the most remarkable characteristics of eukaryotes is their enormous morphological diversity, on both the cellular and organismal levels. Compare, for example, the architectures of the various human cells drawn in Fig. 1-10. Similarly, recall the great anatomical differences among, say, an amoeba, an oak tree, and a human being.

Taxonometric schemes based on gross morphology as well as on protein and nucleic acid sequences (Sections 7-1 and 7-2) indicate that eukaryotes may be classified into three kingdoms: **Fungi, Plantae** (plants), and **Animalia** (animals). The relative structural simplicity of many unicellular eukaryotes, however, makes their classification under this scheme rather arbitrary. Consequently, these organisms are usually assigned a fourth eukaryotic kingdom, the **Protista.** (Note that biological classification schemes are for the convenience of biologists; nature is rarely neatly categorized.) Figure 1-11 is a phylogenetic tree for eukaryotes.

Anatomical comparisons among living and fossil organisms indicate that the various kingdoms of multicellular organisms independently evolved from Protista (Fig. 1-11). The programs of growth, differentiation, and development followed by multicellular animals (the **metazoa**) in their transformation from fertilized ova to adult organisms provide a remarkable indication of this evolutionary history. For example, all vertebrates exhibit gill-like pouches in their early embryonic stages, which presumably reflect their common fish ancestry (Fig. 1-12). Indeed, these early embryos are similar in size and anatomy even though their respective adult forms are vastly different in these characteristics. Such observations led Ernst Haeckel to formulate his famous (although overstated) dictum: *Ontogeny recapitulates phylogeny* (ontogeny: biological development).

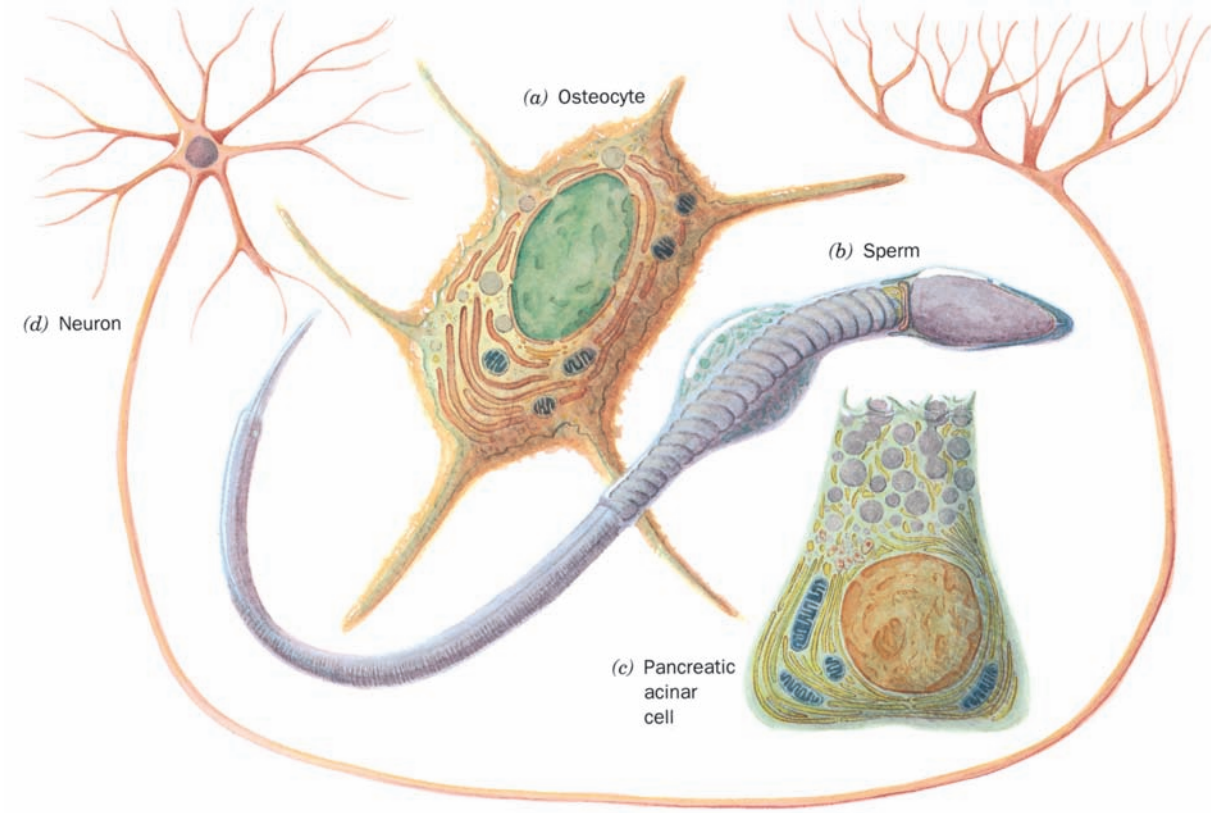


Figure 1-10 **Drawings of some human cells.** (*a*) An osteocyte (bone cell), (*b*) a sperm, (*c*) a pancreatic acinar cell (which secretes digestive enzymes), and (*d*) a neuron (nerve cell).

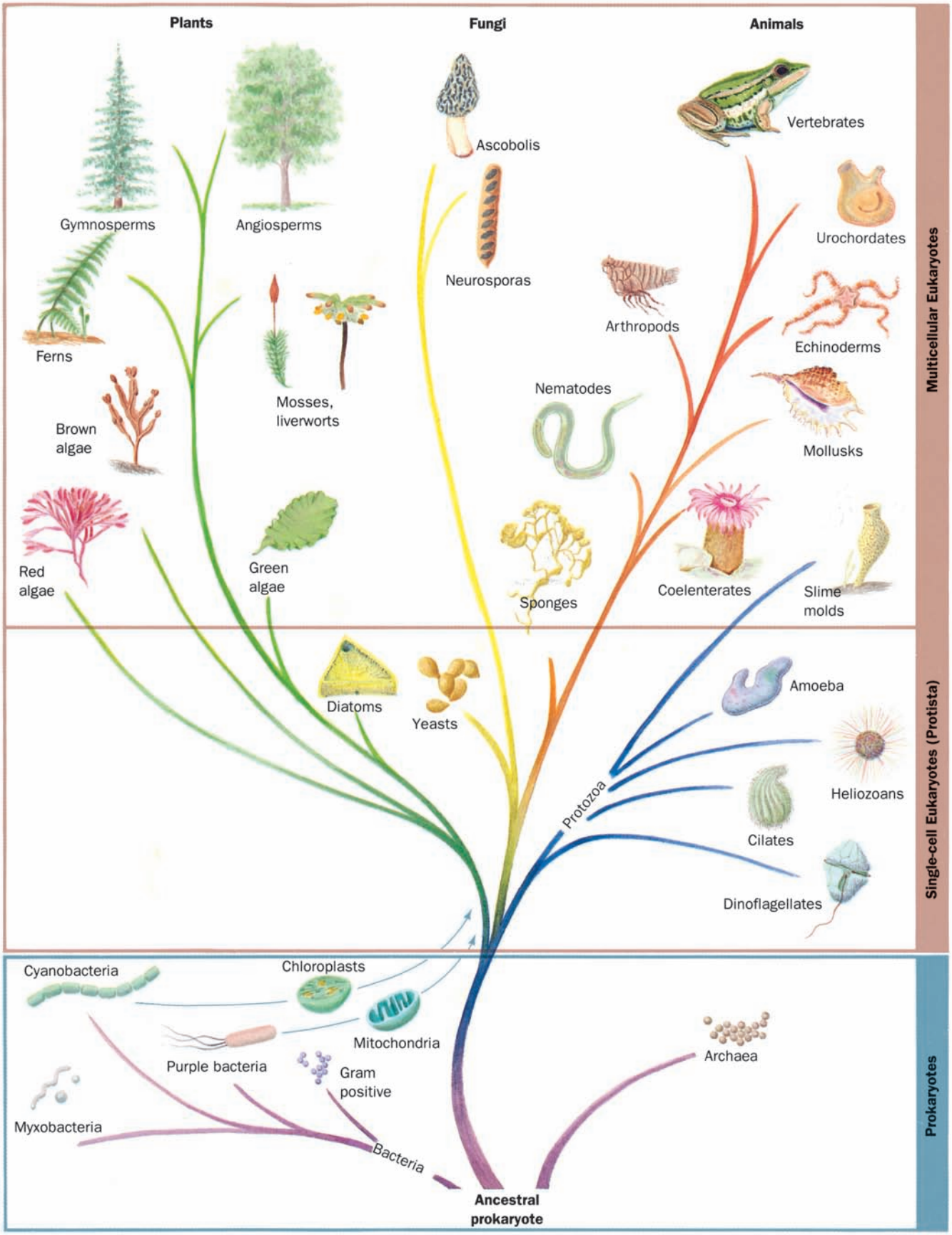


Figure 1-11 **Evolutionary tree indicating the lines of descent of cellular life on Earth.**

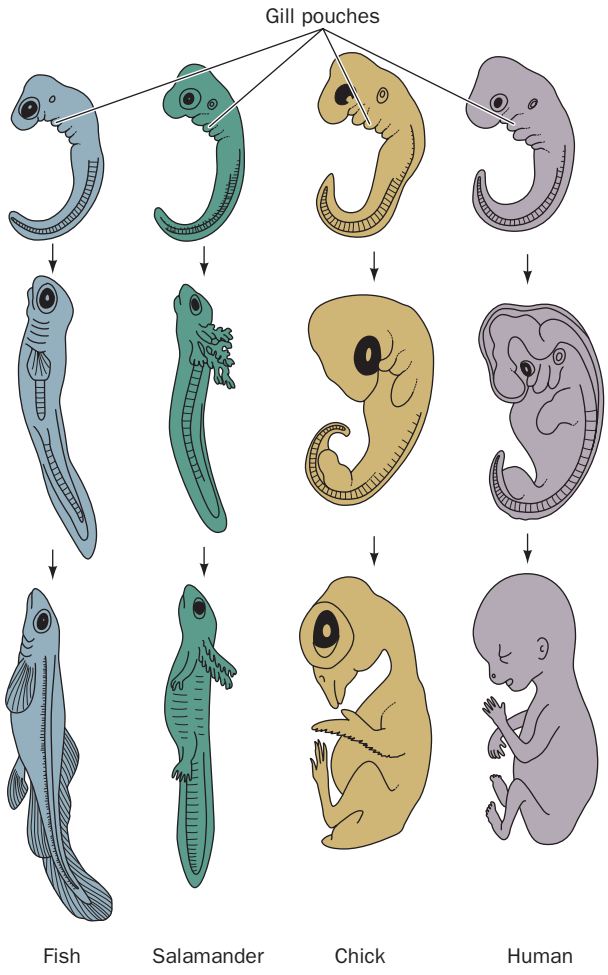


Figure 1-12 **Embryonic development of a fish, an amphibian (salamander), a bird (chick), and a mammal (human).** At early stages they are similar in both size and anatomy (the top drawings have around the same scale), although it is now known that their similarites are not as great as these classic drawings indicate. Later they diverge in both of these properties. [After Haeckel, *E., Anthropogenie oder Entwickelungsgeschichte des Menschen,* Engelmann (1874).]

The elucidation of the mechanism of cellular differentiation in eukaryotes is one of the major long-range goals of modern biochemistry.

3 BIOCHEMISTRY: A PROLOGUE

Biochemistry, as the name implies, is the chemistry of life. It therefore bridges the gap between chemistry, the study of the structures and interactions of atoms and molecules, and biology, the study of the structures and interactions of cells and organisms. Since living things are composed of inanimate molecules, *life, at its most basic level, is a biochemical phenomenon.*

Although living organisms, as we have seen, are enormously diverse in their macroscopic properties, there is a remarkable similarity in their biochemistry that provides a unifying theme with which to study them. For example, hereditary information is encoded and expressed in an almost identical manner in all cellular life. Moreover, the series of biochemical reactions, which are termed **metabolic pathways,** as well as the structures of the enzymes that catalyze them are, for many basic processes, nearly identical from organism to organism. This strongly suggests that all known life-forms are descended from a single primordial ancestor in which these biochemical features first developed.

Although biochemistry is a highly diverse field, it is largely concerned with a limited number of interrelated issues. These are

1. What are the chemical and three-dimensional structures of biological molecules and assemblies, how do they form these structures, and how do their properties vary with them?

2. How do proteins work; that is, what are the molecular mechanisms of enzymatic catalysis, how do receptors recognize and bind specific molecules, and what are the intramolecular and intermolecular mechanisms by which receptors transmit information concerning their binding states?

3. How is genetic information expressed and how is it transmitted to future cell generations?

4. How are biological molecules and assemblies synthesized?

5. What are the control mechanisms that coordinate the myriad biochemical reactions that take place in cells and in organisms?

6. How do cells and organisms grow, differentiate, and reproduce?

These issues are previewed in this section and further illuminated in later chapters. However, as will become obvious as you read further, in all cases, our knowledge, extensive as it is, is dwarfed by our ignorance.

A. *Biological Structures*

Living things are enormously complex. As indicated in Section 1-1A, even the relatively simple *E. coli* cell contains some 3 to 6 thousand different compounds, most of which are unique to *E. coli* (Fig. 1-13). Higher organisms have a correspondingly greater complexity. ***Homo sapiens*** (human beings), for example, may contain 100,000 different types of molecules, although only a small fraction of them have been characterized. One might therefore suppose that to obtain a coherent biochemical understanding of any organism would be a hopelessly difficult task. This, however, is not the case. *Living things have an underlying regularity that derives from their being constructed in a hierarchical manner.* Anatomical and cytological studies have shown that multicellular organisms are organizations of organs, which are made of tissues consisting of cells, composed of

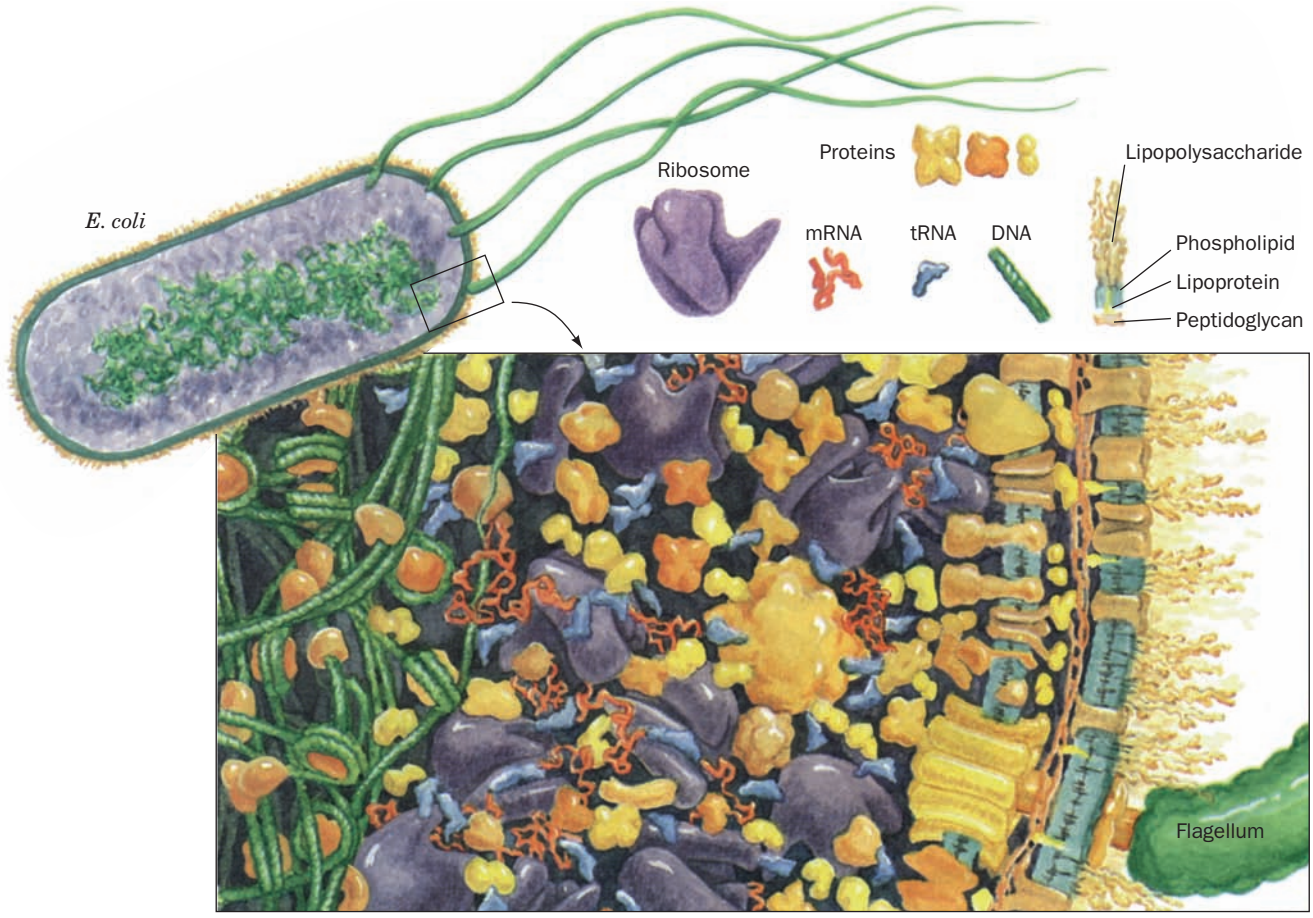


Figure 1-13 **Simulated cross section of an *E. coli* cell magnified around one millionfold.** The right side of the drawing shows the multilayered cell wall and membrane, decorated on its exterior surface with lipopolysaccharides (Section 11-3Bc). A flagellum *(lower right)* is driven by a motor anchored in the inner membrane (Section 35-3I). The cytoplasm, which occupies the middle region of the drawing, is predominantly filled with ribosomes engaged in protein synthesis (Section 32-3). The left side of the drawing contains a dense tangle of DNA in complex with specific proteins. Only the largest macromolecules and molecular assemblies are shown. In a living cell, the remaining space in the cytoplasm would be crowded with smaller molecules and water (a water molecule would be about the size of the period at the end of this sentence). [After a drawing by David Goodsell, UCLA.]

subcellular organelles (e.g., Fig. 1-14). At this point in our hierarchical descent, we enter the biochemical realm since organelles consist of **supramolecular assemblies,** such as membranes or fibers, that are organized clusters of **macromolecules** (polymeric molecules with molecular masses from thousands of daltons on up).

As Table 1-1 indicates, *E. coli,* and living things in general, contain only a few different types of macromolecules: **proteins** (Greek: *proteios,* of first importance; a term coined in 1838 by Jacob Berzelius), **nucleic acids,** and **polysaccharides** (Greek: *sakcharon,* sugar). *All of these substances have a modular construction; they consist of linked monomeric units that occupy the lowest level of our structural hierarchy.* Thus, as Fig. 1-15 indicates, proteins are polymers of amino acids (Section 4-1B), nucleic acids are polymers of nucleotides (Section 5-1), and polysaccharides are polymers of sugars (Section 11-2). **Lipids** (Greek: *lipos,* fat), the fourth major class of biological molecules, are too small to be classified as macromolecules but also have a modular construction (Section 12-1).

The task of the biochemist has been vastly simplified by the finding that *there are relatively few species of monomeric units that occur in each class of biological macromolecule.* Proteins are all synthesized from the same 20 species of **amino acids,** nucleic acids are made from 8 types of **nucleotides** (4 each in DNA and RNA), and there are ~8 commonly occurring types of **sugars** in polysaccharides. The great variation in properties observed among macromolecules of each type largely arises from the enormous number of ways its monomeric units can be arranged and, in many cases, derivatized.

One of the central questions in biochemistry is how biological structures are formed. As is explained in later chapters, the monomeric units of macromolecules are either

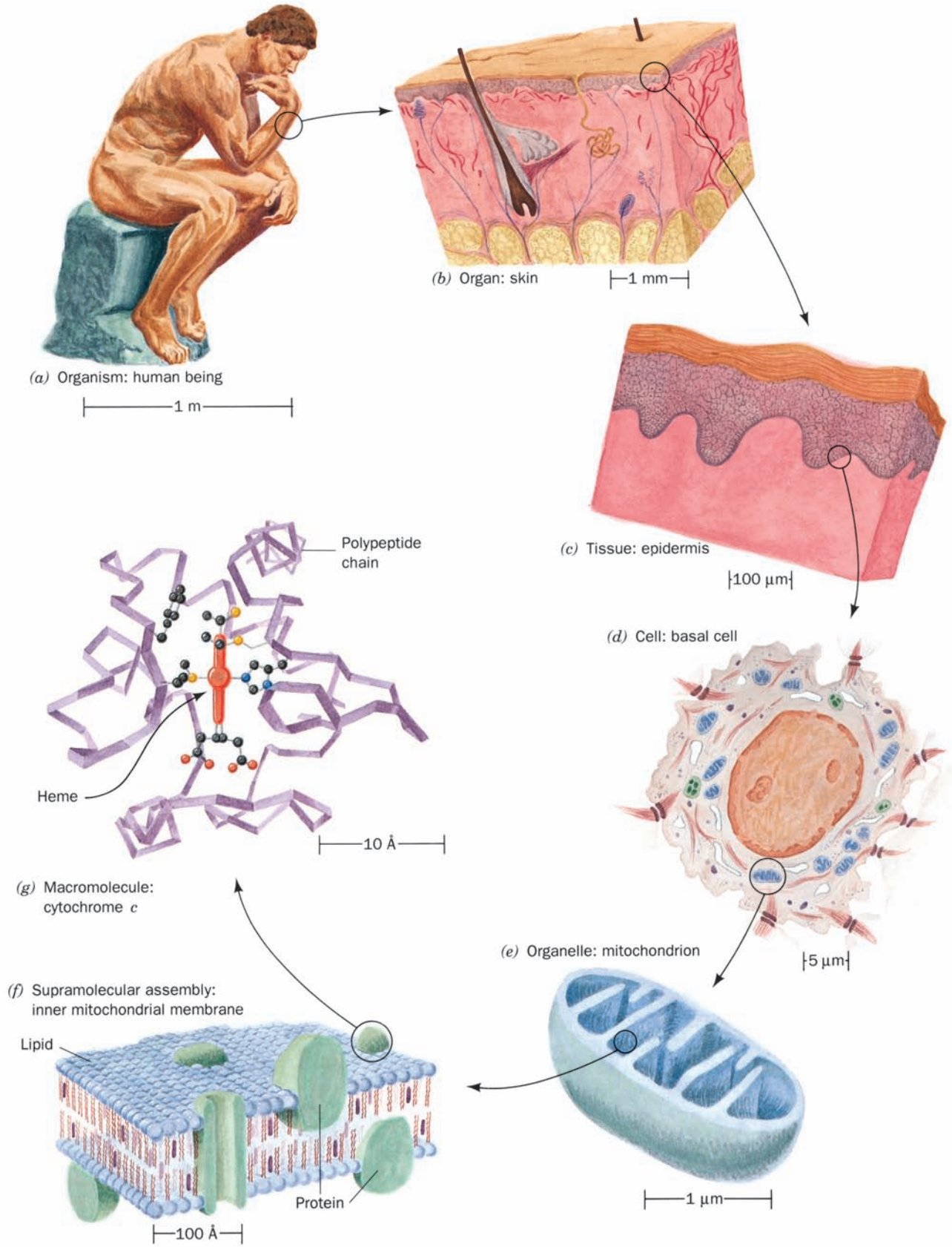


Figure 1-14 **Example of the hierarchical organization of biological structures.**

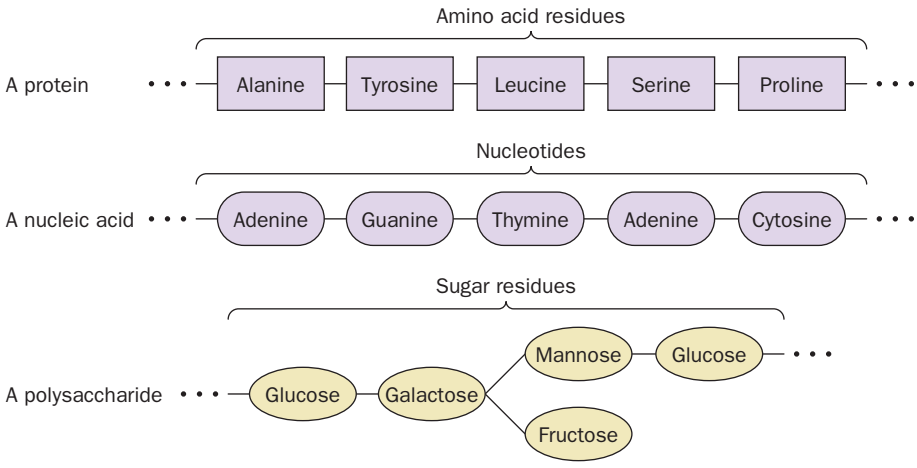


Figure 1-15 **Polymeric organization of proteins, nucleic acids, and polysaccharides.**

directly acquired by the cell as nutrients or enzymatically synthesized from simpler substances. Macromolecules are synthesized from their monomeric precursors in complex enzymatically mediated processes.

Newly synthesized proteins spontaneously fold to assume their native conformations (Section 9-1A); that is, they undergo **self-assembly.** Apparently their amino acid sequences specify their three-dimensional structures. Likewise, the structures of other types of macromolecules are specified by the sequences of their monomeric units. The principle of self-assembly extends at least to the level of supramolecular assemblies. However, the way in which higher levels of biological structures are generated is largely unknown. The elucidation of the mechanisms of cellular and organismal growth and differentiation is a major area of biological research.

B. *Metabolic Processes*

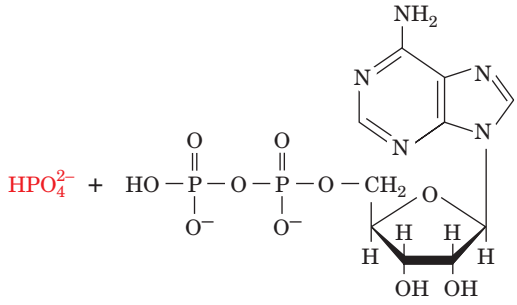
There is a bewildering array of chemical reactions that simultaneously occur in any living cell. Yet these reactions follow a pattern that organizes them into the coherent process we refer to as life. For instance, most biological reactions are members of a metabolic pathway; that is, they function as one of a sequence of reactions that produce one or more specific products. Moreover, one of the hallmarks of life is that the rates of its reactions are so tightly regulated that there is rarely an unsatisfied need for a reactant in a metabolic pathway or an unnecessary buildup of some product.

Metabolism has been traditionally (although not necessarily logically) divided into two major categories:

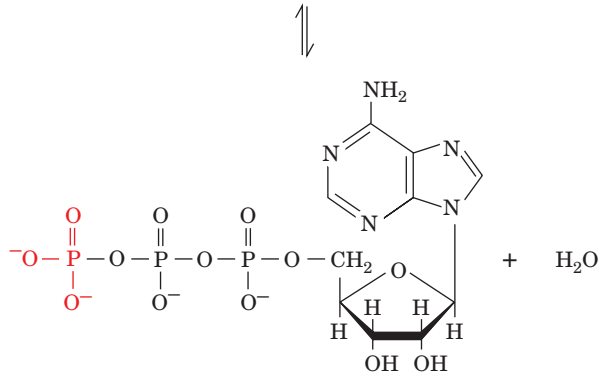
1. Catabolism or degradation, in which nutrients and cell constituents are broken down so as to salvage their components and/or to generate energy.

2. Anabolism or biosynthesis, in which biomolecules are synthesized from simpler components.

The energy required by anabolic processes is provided by catabolic processes largely in the form of **adenosine triphosphate (ATP).** For instance, such energy-generating processes as photosynthesis and the biological oxidation of nutrients produce ATP from **adenosine diphosphate (ADP)** and a phosphate ion.



Adenosine diphosphate (ADP)



Adenosine triphosphate (ATP)

Conversely, such energy-consuming processes as biosynthesis, the transport of molecules against a concentration gradient, and muscle contraction are driven by the reverse of this reaction, the hydrolysis of ATP:

$$ATP + H_2O \rightleftharpoons ADP + HPO_4^{2-}$$

Thus, *anabolic and catabolic processes are coupled together through the mediation of the universal biological energy "currency," ATP.*

C. *Expression and Transmission of Genetic Information*

Deoxyribonucleic acid (DNA) is the cell's master repository of genetic information. This macromolecule, as is diagrammed in Fig. 1-16, consists of two strands of linked **nucleotides,** each of which is composed of a **deoxyribose** sugar residue, a phosphoryl group, and one of four bases: **adenine (A), thymine (T), guanine (G), or cytosine (C).** Genetic information is encoded in the sequence of these bases. Each DNA base is hydrogen bonded to a base on the opposite strand to form an entity known as a **base pair.** However, A can only hydrogen bond with T, and G with C,

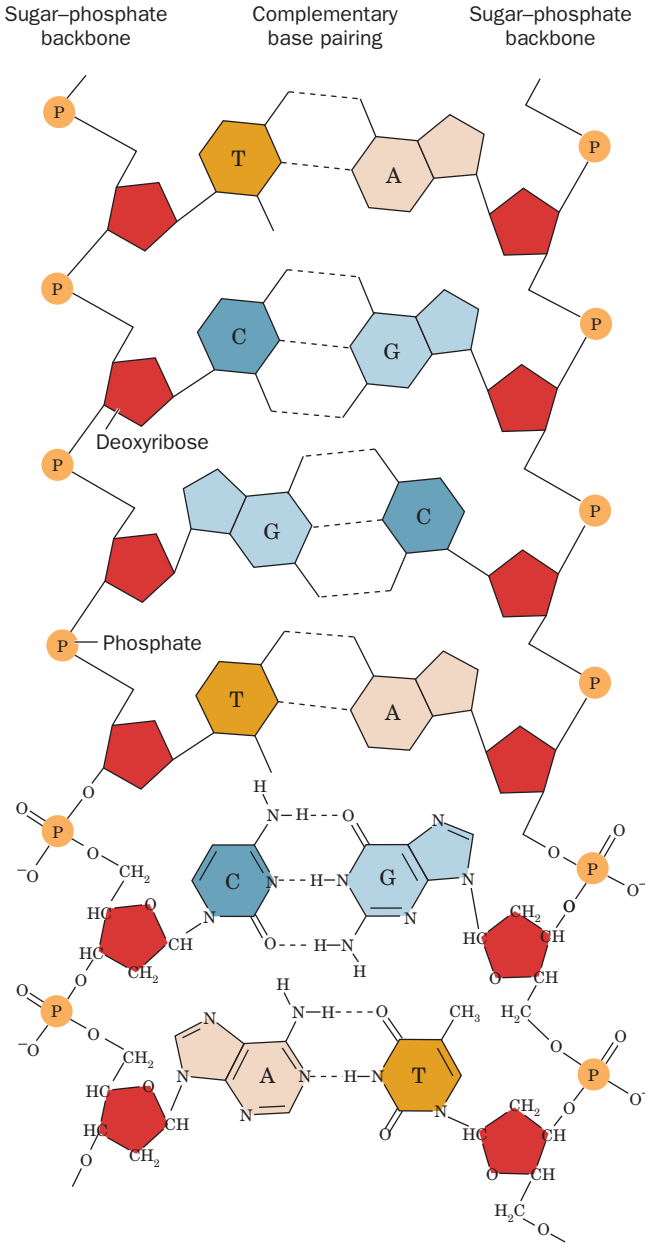


Figure 1-16 **Double-stranded DNA.** The two polynucleotide chains associate through complementary base pairing. A pairs with T, and G pairs with C by forming specific hydrogen bonds.

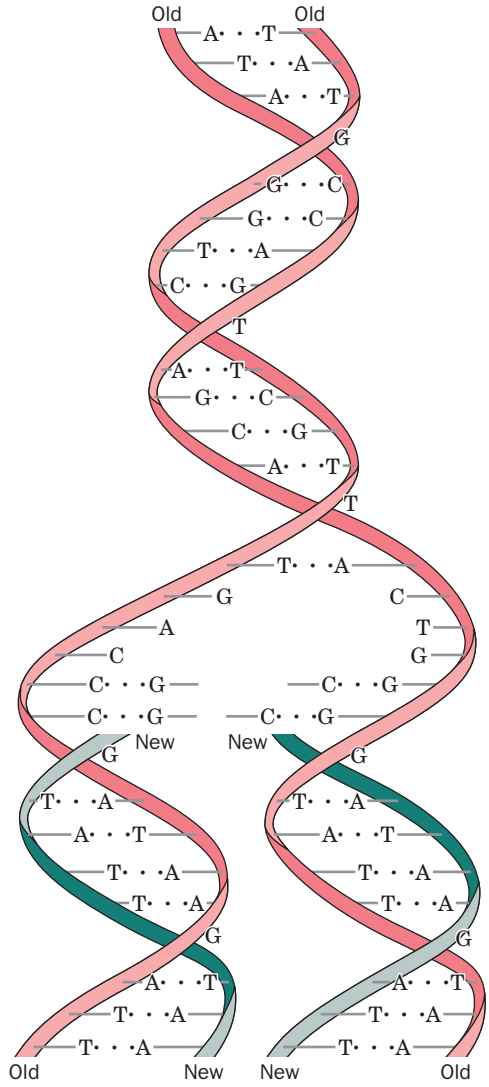


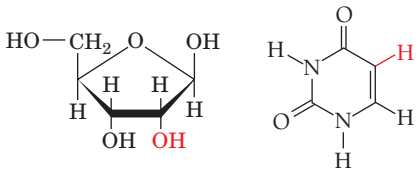
Figure 1-17 **Schematic diagram of DNA replication.** Each strand of parental DNA (*red*) acts as a template for the synthesis of a complementary daughter strand (*green*). Consequently, the resulting double-stranded molecules are identical.

so that the two strands are **complementary;** that is, the sequence of one strand implies the sequence of the other.

The division of a cell must be accompanied by the replication of its DNA. In this enzymatically mediated process, each DNA strand acts as a template for the formation of its complementary strand (Fig. 1-17; Section 5-4C). Consequently, every progeny cell contains a complete DNA molecule (or set of DNA molecules), each of which consists of one parental strand and one daughter strand. Mutations arise when, through rare copying errors or damage to a parental strand, one or more wrong bases are incorporated into a daughter strand. Most mutations are either innocuous or deleterious. Occasionally, however, one results in a new characteristic that confers some sort of selective advantage on its recipient. Individuals with such mutations, according to the tenets of the Darwinian theory of evolution, have an increased probability of

reproducing. New species arise through a progression of such mutations.

The expression of genetic information is a two-stage process. In the first stage, which is termed **transcription,** a DNA strand serves as a template for the synthesis of a complementary strand of ribonucleic acid (RNA; Section 31-2). This nucleic acid, which is generally single stranded, differs chemically from DNA (Fig. 1-16) only in that it has **ribose** sugar residues in place of DNA's deoxyribose and **uracil (U)** replacing DNA's thymine base.



Ribose **Uracil**

In the second stage of genetic expression, which is known as **translation,** ribosomes enzymatically link together amino acids to form proteins (Section 32-3). The order in which the amino acids are linked together is prescribed by the RNA's sequence of bases. Consequently, since proteins are self-assembling, the genetic information encoded by DNA serves, through the intermediacy of RNA, to specify protein structure and function. Just which genes are expressed in a given cell under a particular set of circumstances is controlled by complex regulatory systems whose workings are understood only in outline.

4 GENETICS: A REVIEW

One has only to note the resemblance between parent and child to realize that physical traits are inherited. Yet the mechanism of inheritance was unknown until the mid-twentieth century. The theory of **pangenesis,** which originated with the ancient Greeks, held that semen, which clearly has something to do with procreation, consists of representative particles from all over the body **(pangenes).** This idea was extended in the late eighteenth century by Jean Baptiste de Lamarck, who, in a theory known as **Lamarckism,** hypothesized that an individual's acquired characteristics, such as large muscles resulting from exercise, would be transmitted to his/her offspring. Pangenesis and at least some aspects of Lamarckism were accepted by most nineteenth century biologists, including Charles Darwin.

The realization, in the mid-nineteenth century, that all organisms are derived from single cells set the stage for the development of modern biology. In his **germ plasm theory,** August Weismann pointed out that sperm and ova, the **germ cells** (whose primordia are set aside early in embryonic development), are directly descended from the germ cells of the previous generation and that other cells of the body, the **somatic cells,** although derived from germ cells, do not give rise to them. He refuted the ideas of pangenesis and Lamarckism by demonstrating that the progeny of many successive generations of mice whose tails had been cut off had tails of normal length.

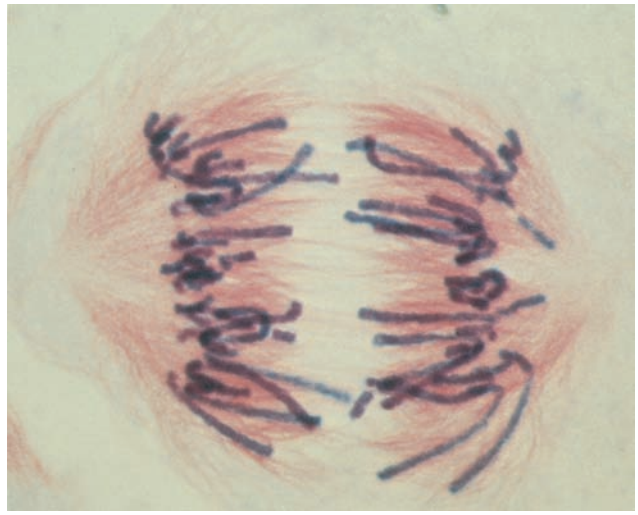


Figure 1-18 **Chromosomes.** A photomicrograph of a plant cell (*Scadoxus katherinae* Bak.) during anaphase of mitosis showing its chromosomes being pulled to opposite poles of the cell by the mitotic spindle. The microtubules forming the mitotic spindle are stained red and the chromosomes are blue. [Courtesy of Andrew S. Bajer, University of Oregon.]

A. *Chromosomes*

In the 1860s, eukaryotic cell nuclei were observed to contain linear bodies that were named chromosomes (Greek: *chromos,* color + *soma,* body) because they are strongly stained by certain basic dyes (Fig. 1-18). There are normally two copies of each chromosome **(homologous pairs)** present in every somatic cell. The number of unique chromosomes (N) in such a cell is known as its **haploid number,** and the total number of chromosomes ($2N$) is its **diploid number.** Different species differ in their haploid number of chromosomes (Table 1-2).

Table 1-2 **Number of Chromosomes ($2N$) in Some Eukaryotes**

Organism	Chromosomes
Human	46
Dog	78
Rat	42
Turkey	82
Frog	26
Fruit fly	8
Hermit crab	~254
Garden pea	14
Potato	48
Yeast	34
Green alga	~20

Source: Ayala, F.J. and Kiger, J.A., Jr., *Modern Genetics* (2nd ed.), *p.* 9, Benjamin/Cummings (1984).

a. Somatic Cells Divide by Mitosis

The division of somatic cells, a process known as **mitosis** (Fig. 1-19), is preceded by the duplication of each chromosome to form a cell with 4*N* chromosomes. During cell division, each chromosome attaches by its **centromere** to the **mitotic spindle** such that the members of each duplicate pair line up across the equatorial plane of the cell. The members of each duplicate pair are then pulled to opposite poles of the dividing cell by the action of the spindle to yield diploid daughter cells that each have the same 2*N* chromosomes as the parent cell.

b. Germ Cells Are Formed by Meiosis

The formation of germ cells, a process known as **meiosis** (Fig. 1-20), requires two consecutive cell divisions. Before the first meiotic division each chromosome replicates, but the resulting sister **chromatids** remain attached at their centromere. The homologous pairs of the doubled chromosomes then line up across the equatorial plane of the cell in zipperlike fashion, which permits an exchange of the corresponding sections of homologous chromosomes in a process known as **crossing-over.** The spindle then moves the members of each homologous pair to opposite poles of the cell so that, after the first meiotic division, each daughter cell contains *N* doubled chromosomes. In the second meiotic division, the sister chromatids separate to form chromosomes and move to opposite poles of the dividing cell to yield a total of four haploid cells that are known as **gametes.** Fertilization consists of the fusion of a male gamete (sperm) with a female gamete (ovum) to yield a diploid cell known as a **zygote** that has received *N* chromosomes from each of its parents.

B. *Mendelian Inheritance*

The basic laws of inheritance were reported in 1866 by Gregor Mendel. They were elucidated by the analysis of a series of **genetic crosses** between true-breeding strains (producing progeny that have the same characteristics as the parents) of garden peas, *Pisum sativum,* that differ in certain well-defined traits such as seed shape (round vs wrinkled), seed color (yellow vs green), or flower color (purple vs white). Mendel found that in crossing parents (*P*) that differ in a single trait, say seed shape, the progeny (F_1; first filial generation) all have the trait of only one of the parents, in this case round seeds (Fig. 1-21). The trait appearing in F_1 is said to be **dominant,** whereas the alternative trait is called **recessive.** In F_2, the progeny of F_1, three-quarters have the dominant trait and one-quarter have the recessive trait. Those peas with the recessive trait breed true; that is, self-crossing recessive F_2's results in progeny (F_3) that also have the recessive trait. The F_2's exhibiting the dominant trait, however, fall into two categories: One-third of them breed true, whereas the remainder have progeny with the same 3:1 ratio of dominant to recessive traits as do the members of F_2.

Mendel accounted for his observations by hypothesizing that *the various pairs of contrasting traits each result from a factor (now called a* ***gene****) that has alternative forms*

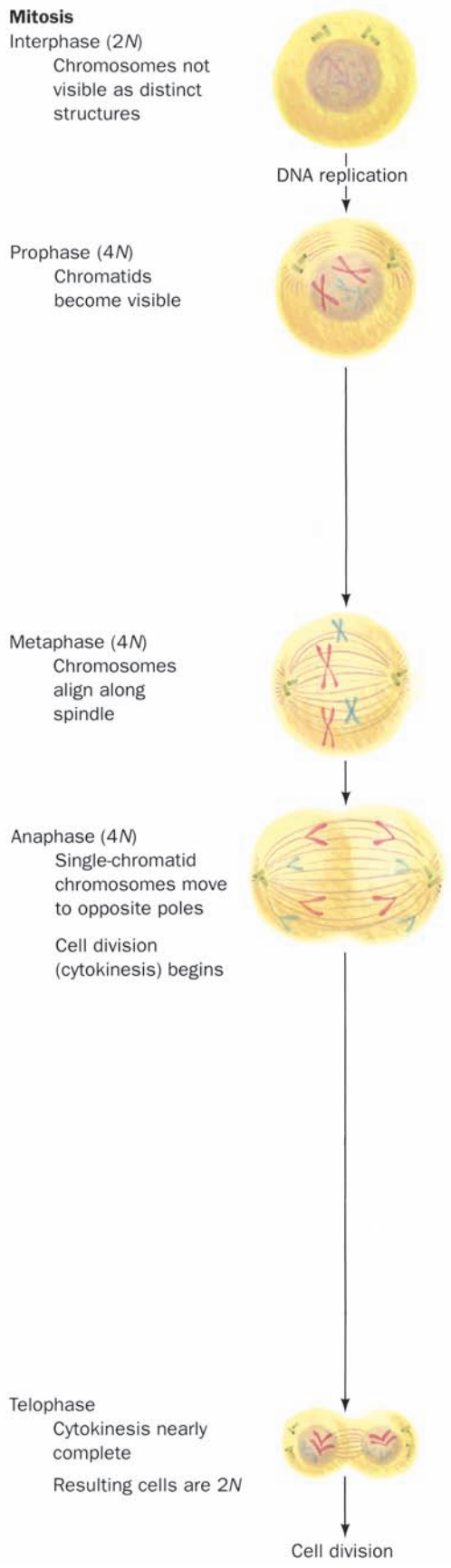


Figure 1-19 **Mitosis, the usual form of cell division in eukaryotes.** Mitosis yields two daughter cells, each with the same chromosomal complement as the parental cell.

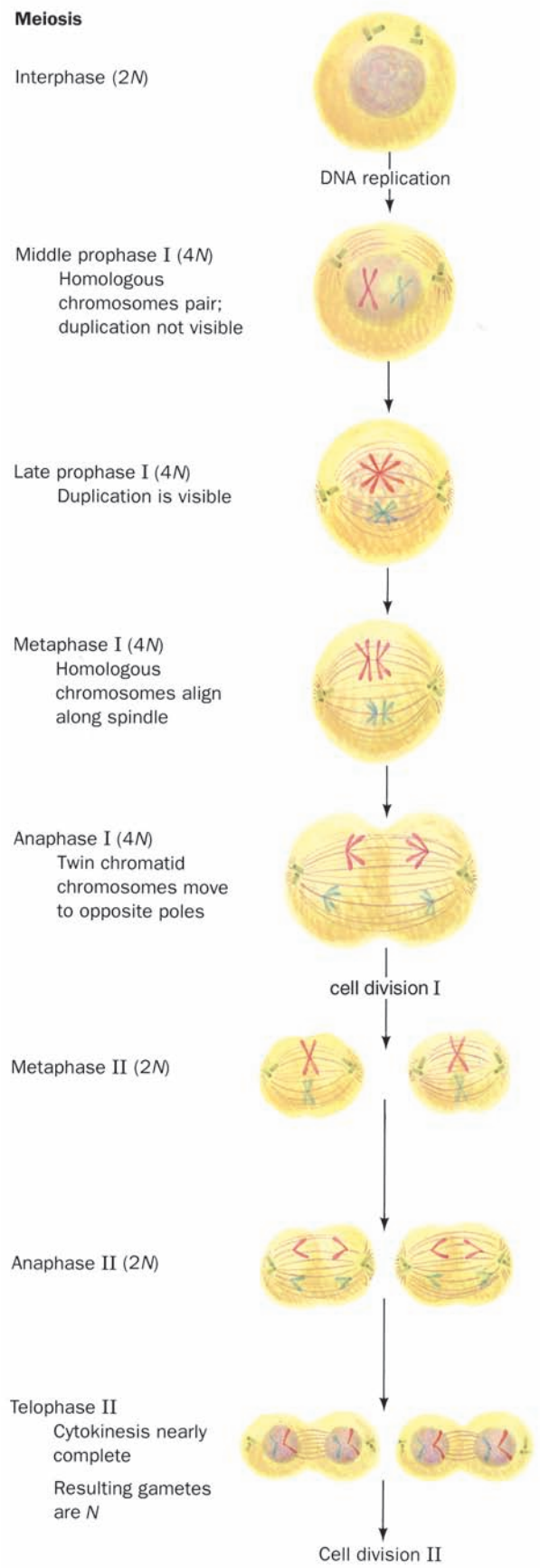


Figure 1-20 **Meiosis, which leads to the formation of gametes (sex cells).** Meiosis comprises two consecutive cell divisions to yield four daughter cells, each with half of the chromosomal complement of its parental cell.

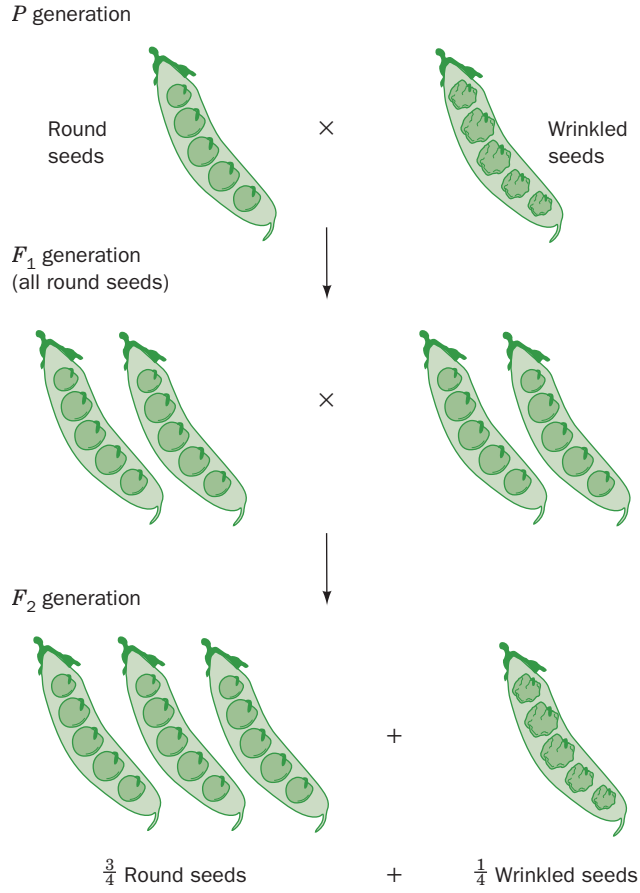


Figure 1-21 **Genetic crosses.** Crossing a pea plant that has round seeds with one that has wrinkled seeds yields F_1 progeny that all have round seeds. Crossing these F_1 peas yields an F_2 generation, of which three-quarters have round seeds and one-quarter have wrinkled seeds.

(alleles). *Every plant contains a pair of genes governing a particular trait, one inherited from each of its parents.* The alleles for seed shape are symbolized *R* for round seeds and *r* for wrinkled seeds (gene symbols are generally given in italics). The pure-breeding plants with round and wrinkled seeds, respectively, have *RR* and *rr* **genotypes** (genetic composition) and are both said to be **homozygous** in seed shape. Plants with the *Rr* genotype are **heterozygous** in seed shape and have the round seed **phenotype** (appearance or character) because *R* is dominant over *r*. *The two alleles do not blend or mix in any way in the plant and are independently transmitted through gametes to progeny (Fig. 1-22).*

Mendel also found that *different traits are independently inherited.* For example, crossing peas that have round yellow seeds (*RRYY*) with peas that have wrinkled green seeds (*rryy*) results in F_1 progeny (*RrYy*) that have round yellow seeds (yellow seeds are dominant over green seeds). The F_2 phenotypes appear in the ratio 9 round yellow : 3 round green : 3 wrinkled yellow : 1 wrinkled green. This result indicates that there is no tendency for the genes from

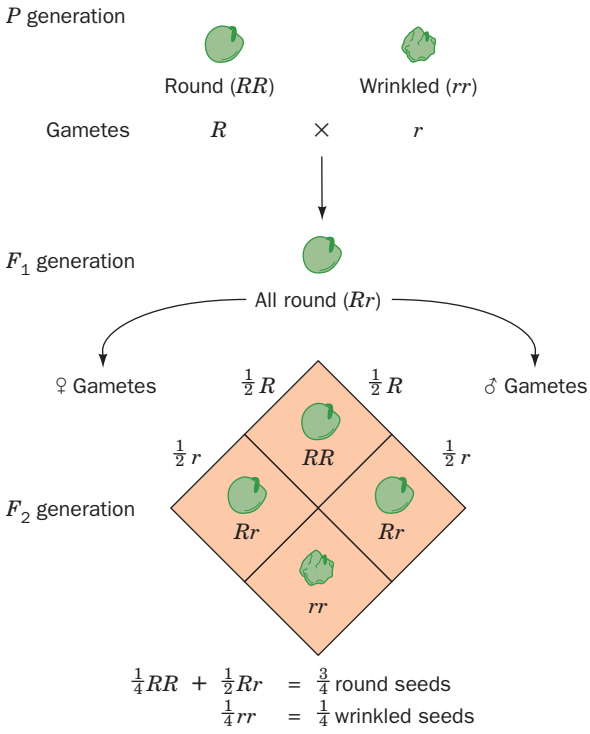


Figure 1-22 **Genotypes and phenotypes.** In a genetic cross between peas with round seeds and peas with wrinkled seeds, the F_1 generation has the round seed phenotype because the round seed genotype is dominant over the wrinkled seed genotype. In the F_2 generation, three-fourths of the seeds are round and one-fourth are wrinkled because the genes for these alleles are independently transmitted by haploid gametes.

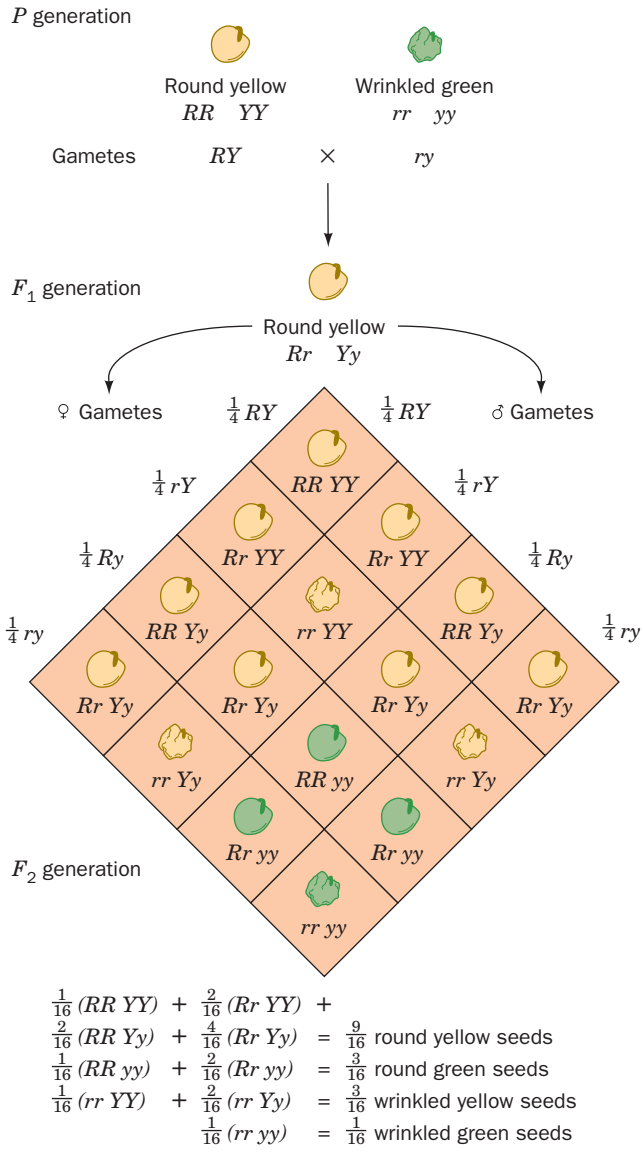


Figure 1-23 **Independent assortment.** The genes for round (R) versus wrinkled (r) and yellow (Y) versus green (y) pea seeds assort independently. The F_2 progeny consist of nine genotypes comprising the four possible phenotypes.

any parent to assort together (Fig. 1-23). It was later shown, however, *that only genes that occur on different chromosomes exhibit such independence.*

The dominance of one trait over another is a common but not universal phenomenon. For example, crossing a pure-breeding red variety of the snapdragon *Antirrhinum* with a pure-breeding white variety results in pink-colored F_1 progeny. The F_2 progeny have red, pink, and white flowers in a 1:2:1 ratio because the flowers of homozygotes for the red color (AA) contain more red pigment than do the heterozygotes (Aa; Fig. 1-24). The red and white traits are therefore said to be **codominant.** In the case of codominance, the phenotype reveals the genotype.

A given gene may have multiple alleles. A familiar example is the human **ABO blood group system** (Section 12-3E). A person may have type A, type B, type AB, or type O blood depending on whether his/her red blood cells bear A antigens, B antigens, both, or neither. The A and B antigens are specified by the codominant I^A and I^B alleles, respectively, and the O phenotype is homozygous for the recessive i allele.

C. *Chromosomal Theory of Inheritance*

Mendel's theory of inheritance was almost universally ignored by his contemporaries. This was partially because in analyzing his data he used probability theory, an alien subject to most biologists of the time. The major reason his theory was ignored, however, is that it was ahead of its time: Contemporary knowledge of anatomy and physiology provided no basis for its understanding. For instance, mitosis and meiosis had yet to be discovered. Yet, after Mendel's work was rediscovered in 1900, it was shown that his principles explained inheritance in animals as well as in plants. In 1903, as a result of the realization that chromosomes and genes behave in a parallel fashion, Walter Sutton formulated the **chromosomal theory of inheritance** in which he hypothesized that genes are parts of chromosomes.

The first trait to be assigned a chromosomal location was that of sex. *In most eukaryotes, the cells of females each contain two copies of the* ***X chromosome*** *(XX), whereas*

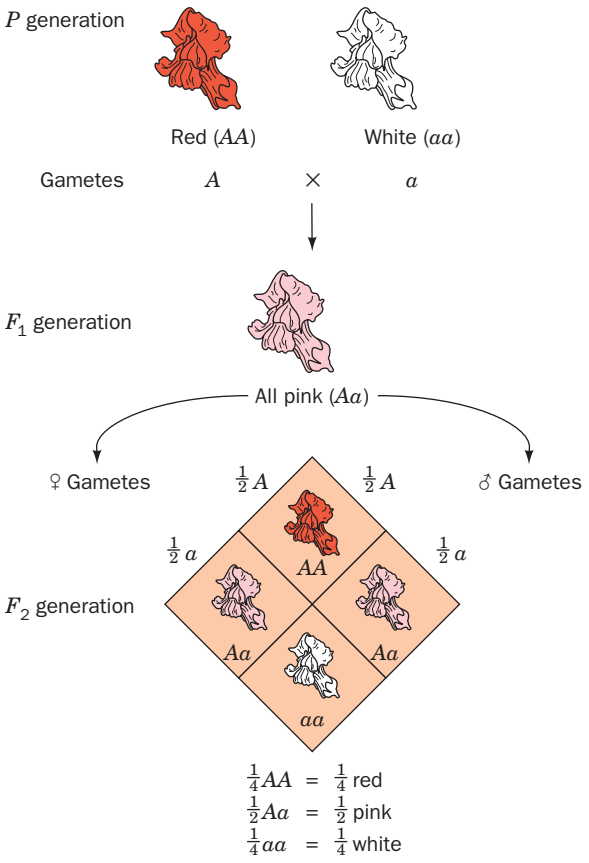


Figure 1-24 **Codominance.** In a cross between snapdragons with red (*AA*) and white (*aa*) flowers, the F_1 generation is pink (*Aa*), which demonstrates that the two alleles, *A* and *a*, are codominant. The F_2 flowers are red, pink, and white in a 1:2:1 ratio.

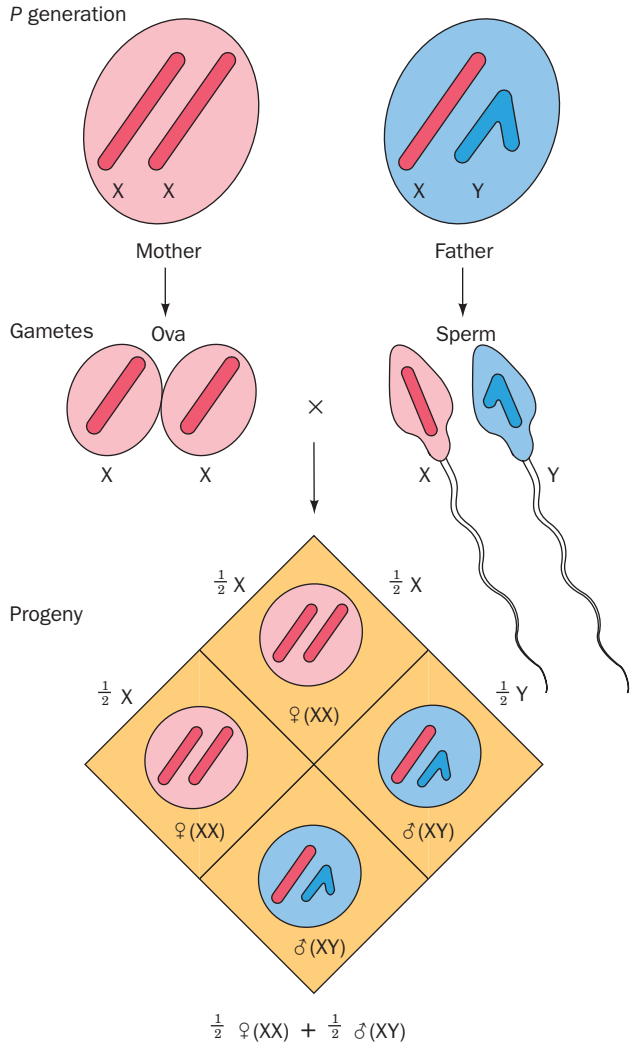


Figure 1-25 **Independent segregation.** The independent segregation of the sex chromosomes, X and Y, results in a 1:1 ratio of males to females.

male cells contain one copy of X and a morphologically distinct ***Y chromosome*** *(XY; Fig. 1-25).* Ova must therefore contain a single X chromosome, and sperm contain either an X or a Y chromosome (Fig. 1-25). Fertilization by an X-bearing sperm therefore results in a female zygote and fertilization by a Y-bearing sperm yields a male zygote. This explains the observed 1:1 ratio of males to females in most species. The X and Y chromosomes are referred to as **sex chromosomes;** the others are known as **autosomes.**

a. Fruit Flies Are Favorite Genetic Subjects

The pace of genetic research greatly accelerated after Thomas Hunt Morgan began using the fruit fly *Drosophila melanogaster* as an experimental subject. This small prolific insect (Fig. 1-26), which is often seen hovering around ripe fruit in summer and fall, is easily maintained in the laboratory, where it produces a new generation every 14 days. With *Drosophila,* the results of genetic crosses can be determined some 25 times faster than they can with peas. *Drosophila* is presently the genetically best characterized higher organism.

The first known mutant strain of *Drosophila* had white eyes rather than the red eyes of the **wild type** (occurring in nature). Through genetic crosses of the white eye strain

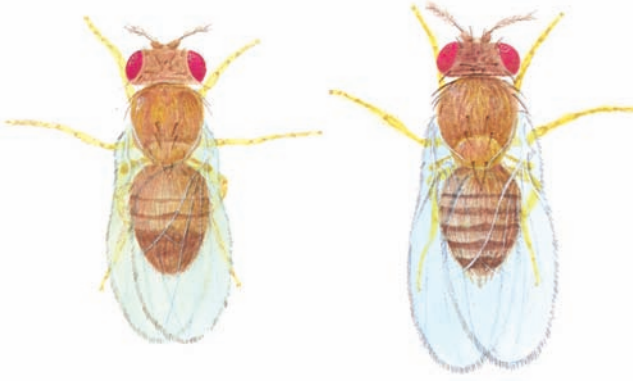


Figure 1-26 **The fruit fly *Drosophila melanogaster.*** The male (*left*) and the female (*right*) are shown in their relative sizes; they are actually ~2 mm long and weigh ~1 mg.

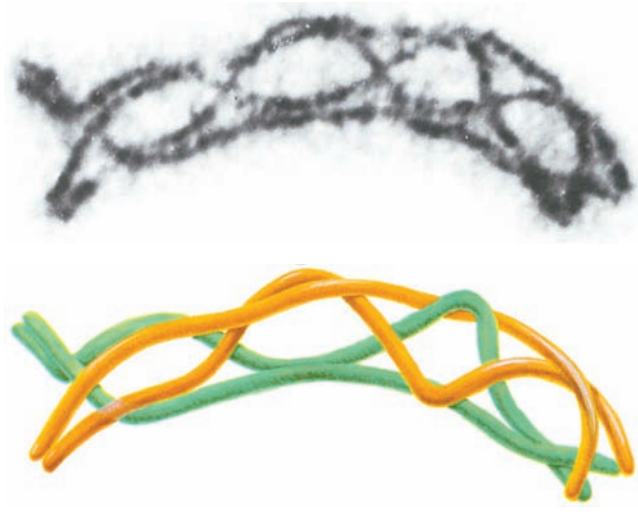
with the wild type, Morgan showed that the distribution of the white eye gene (*wh*) parallels that of the X chromosome. This indicates that the *wh* gene is located on the X chromosome and that the Y chromosome does not contain it. The *wh* gene is therefore said to be **sex linked.**

b. Genetic Maps Can Be Constructed from an Analysis of Crossover Rates

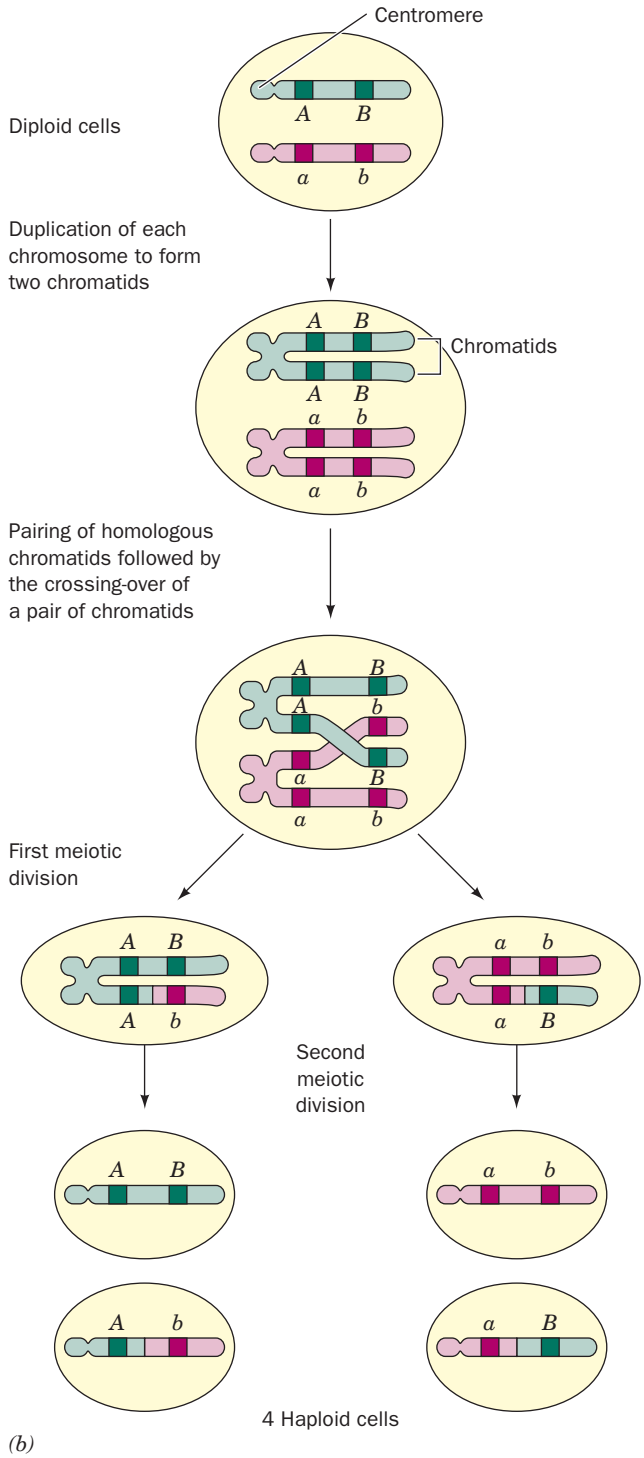
In succeeding years, the chromosomal locations of many *Drosophila* genes were determined. Those genes that reside on the same chromosome do not assort independently. However, any pair of such **linked** genes **recombine** (exchange relative positions with their allelic counterparts on the homologous chromosome) with a characteristic frequency. The cytological basis of this phenomenon was found to occur at the start of meiosis when the homologous doubled chromosomes line up in parallel (metaphase I; Fig. 1-20). Homologous chromatids then exchange equivalent sections by crossing-over (Fig. 1-27). The chromosomal location of the crossover point varies nearly randomly from event to event. Consequently, *the crossover frequency of a pair of linked genes varies directly with their physical separation along the chromosome.* Morgan and Alfred Sturtevant made use of this phenomenon to **map** (locate) the relative positions of genes on *Drosophila*'s four unique chromosomes. Such studies have demonstrated that *chromosomes are linear unbranched structures.* We now know that such **genetic maps** (Fig. 1-28) parallel the corresponding base sequences of the DNA within the chromosomes.

c. Nonallelic Genes Complement One Another

Whether or not two recessive traits that affect similar functions are allelic (different forms of the same gene) can be determined by a **complementation test.** In this test, a homozygote for one of the traits is crossed with a homozygote for the other. If the two traits are nonallelic, the progeny will have the wild-type phenotype because each of the homologous chromosomes supplies the wild-type function that the other lacks; that is, they complement each other. For example, crossing a *Drosophila* that is homozygous for



(a)



(b)

Figure 1-27 **Crossing-over.** (*a*) An electron micrograph, together with an interpretive drawing, of two homologous pairs of chromatids during meiosis in the grasshopper *Chorthippus parallelus.* Nonsister chromatids (*different colors*) may recombine at any of the points where they cross over. [Courtesy of Bernard John, The Australian National University.] (*b*) A diagram showing the recombination of pairs of allelic genes (*A, B*) and (*a, b*) during crossover.

an eye color mutation known as purple (*pr*) with a homozygote for another eye color mutation known as brown (*bw*) yields progeny with wild-type eye color, thereby demonstrating that these two genes are not allelic (Fig. 1-29*a*).

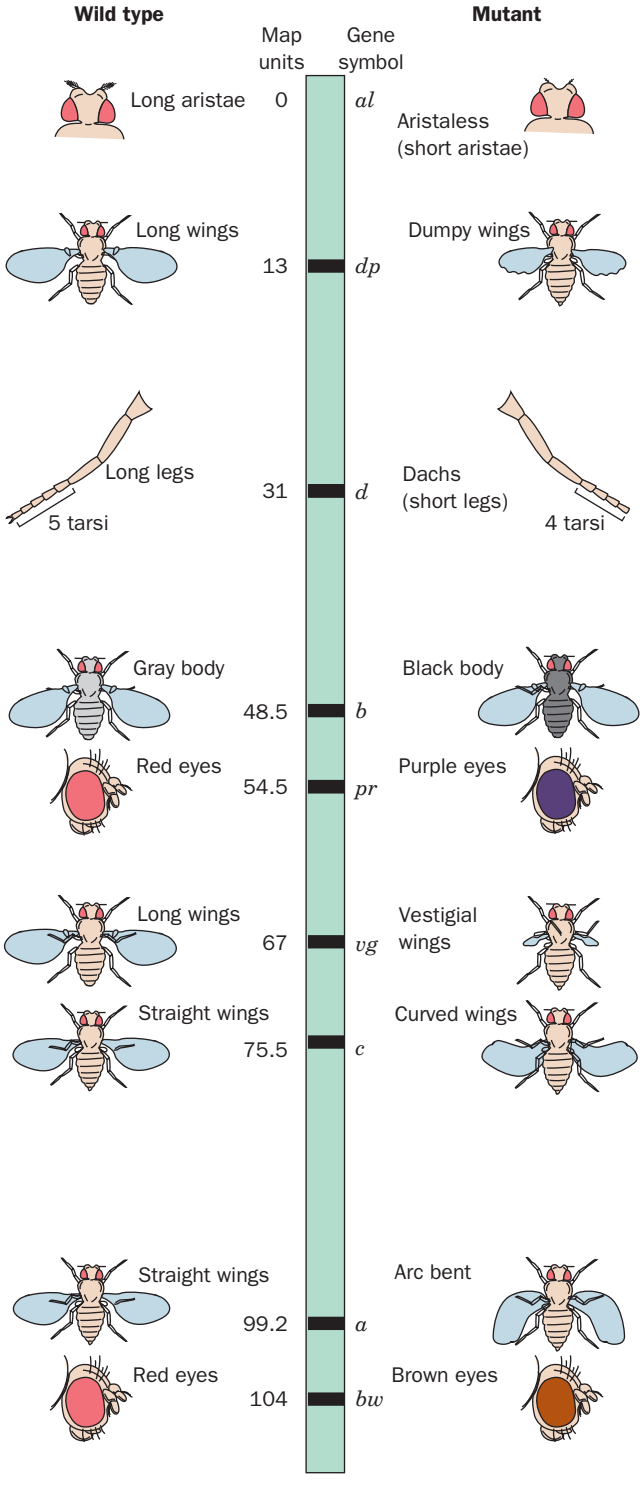


Figure 1-28 **Portion of the genetic map of chromosome 2 of *Drosophila*.** The positions of the genes are given in map units. Two genes separated by *m* map units recombine with a frequency of *m*%.

In contrast, in crossing a female *Drosophila* that is homozygous for the sex-linked white eye color allele (*wh*) with a male carrying the sex-linked coffee eye color allele (*cf*), the female progeny do not have wild-type eye color (Fig. 1-29*b*). The *wh* and *cf* genes must therefore be allelic.

d. Genes Direct Protein Expression

The question of how genes control the characteristics of organisms took some time to be answered. Archibald Garrod was the first to suggest a specific connection between genes and enzymes. Individuals with **alkaptonuria** produce urine that darkens alarmingly on exposure to air, a consequence of the oxidation of the **homogentisic acid** they excrete (Section 16-3Ab). In 1902, Garrod showed that this

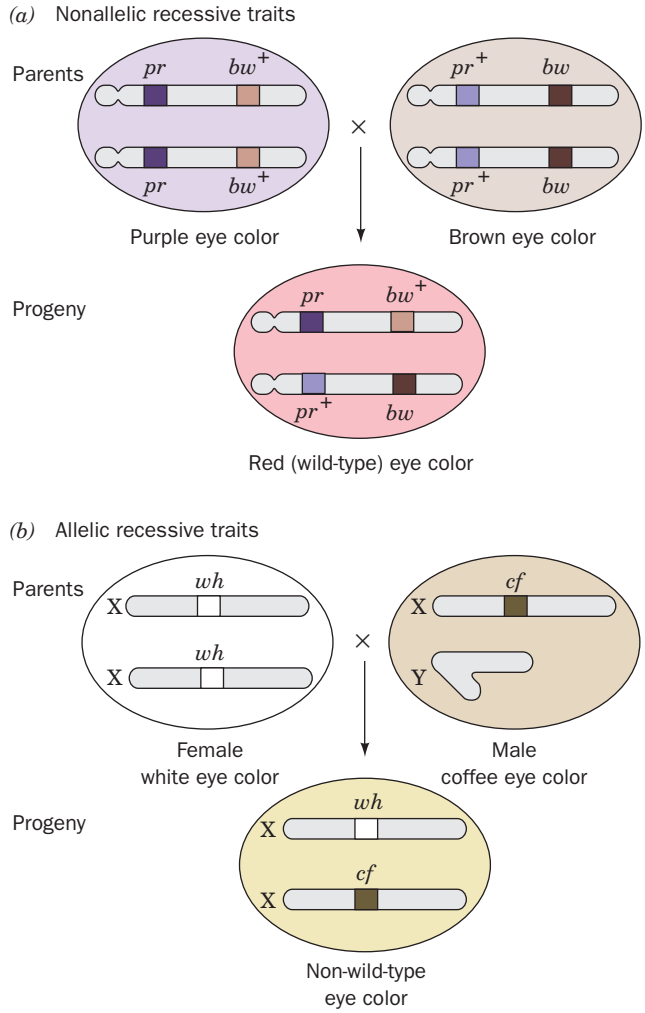


Figure 1-29 **The complementation test indicates whether two recessive traits are allelic.** Two examples in *Drosophila* are shown. (*a*) Crossing a homozygote for purple eye color (*pr*) with a homozygote for brown eye color (*bw*) yields progeny with wild-type eye color. This indicates that *pr* and *bw* are nonallelic. Here the superscript "+" indicates the wild-type allele. (*b*) In crossing a female that is homozygous for the sex-linked white eye color gene *wh* with a male bearing the sex-linked coffee eye color gene *cf*, the female progeny do not have the wild-type eye color. The *wh* and *cf* genes must therefore be allelic.

rather benign metabolic disorder (its only adverse effect is arthritis in later life) results from a recessive trait that is inherited in a Mendelian fashion. He further demonstrated that alkaptonurics are unable to metabolize the homogentisic acid fed to them and therefore concluded that *they lack an enzyme that metabolizes this substance.* Garrod described alkaptonuria and several other inherited human diseases he had studied as **inborn errors of metabolism.**

Beginning in 1940, George Beadle and Edward Tatum, in a series of investigations that mark the beginning of biochemical genetics, showed that *there is a one-to-one correspondence between a mutation and the lack of a specific enzyme.* The wild-type mold *Neurospora* grows on a "minimal medium" in which the only sources of carbon and nitrogen are glucose and NH_3. Certain mutant varieties of *Neurospora* that were generated by means of irradiation with X-rays, however, require an additional substance in order to grow. Beadle and Tatum demonstrated, in several cases, that the mutants lack a normally present enzyme that participates in the biosynthesis of the required substance (Section 16-3Ac). This resulted in their famous maxim **one gene–one enzyme.** Today we know this principle to be only partially true since many genes specify proteins that are not enzymes and many proteins consist of several independently specified subunits (Section 8-5). A more accurate dictum might be **one gene–one polypeptide.** Yet even that is not completely correct because RNAs with structural and functional roles are also genetically specified.

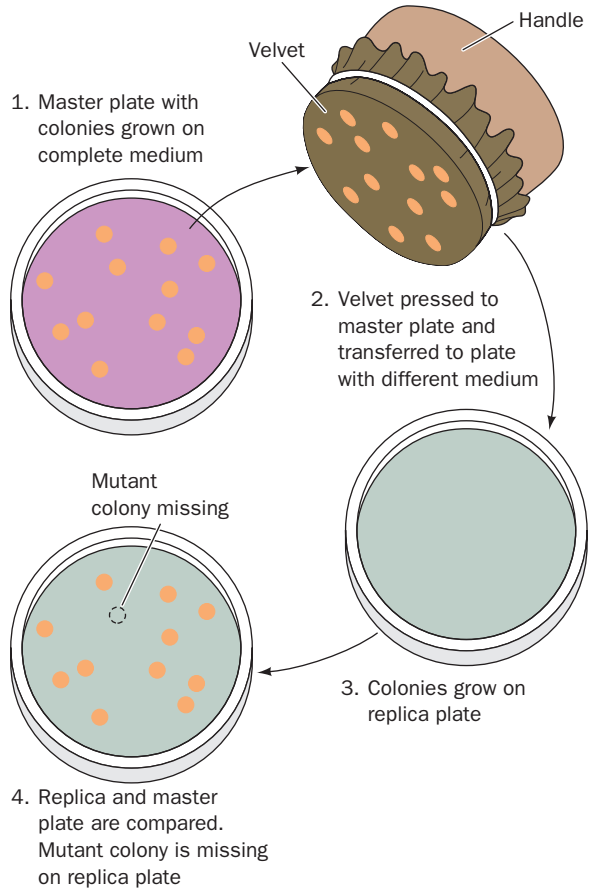


Figure 1-30 **Replica plating.** A technique for rapidly and conveniently transferring colonies from a "master" culture plate (Petri dish) to a different medium on another culture plate. Since the colonies on the master plate and on the replicas should have the same spatial distribution, it is easy to identify the desired mutants.

D. *Bacterial Genetics*

Bacteria offer several advantages for genetic study. Foremost of these is that *under favorable conditions, many have generation times of under 20 min. Consequently, the results of a genetic experiment with bacteria can be ascertained in a matter of hours rather than the weeks or years required for an analogous study with higher organisms. The tremendous number of bacteria that can be quickly grown ($\sim 10^{10}$ mL^{-1}) permits the observation of extremely rare biological events.* For example, an event that occurs with a frequency of 1 per million can be readily detected in bacteria with only a few minutes' work. To do so in *Drosophila* would be an enormous and probably futile effort. Moreover, bacteria are usually haploid, so their phenotype indicates their genotype. Nevertheless, the basic principles of genetics were elucidated from the study of higher plants and animals. This is because bacteria do not reproduce sexually in the manner of higher organisms, so the basic technique of classical genetics, the genetic cross, is not normally applicable to bacteria. In fact, before it was shown that DNA is the carrier of hereditary information, it was not altogether clear that bacteria had chromosomes.

The study of bacterial genetics effectively began in the 1940s when procedures were developed for isolating bacterial mutants. Since bacteria have few easily recognized morphological features, *their mutants are usually detected (selected for) by their ability or inability to grow under certain conditions.* For example, wild-type *E. coli* can grow on a medium in which glucose is the only carbon source. Mutants that are unable to synthesize the amino acid **leucine,** for instance, require the presence of leucine in their growth media. Mutants that are resistant to an antibiotic, say **ampicillin,** can grow in the presence of that antibiotic, whereas the wild type cannot. Mutants in which an essential protein has become temperature sensitive grow at 30°C but not at 42°C, whereas the wild type grows at either temperature. By using a suitable screening protocol, a bacterial colony containing a particular mutation or combination of mutations can be selected. This is conveniently done by the method of **replica plating** (Fig. 1-30).

E. *Viral Genetics*

Viruses are infectious particles consisting of a nucleic acid molecule enclosed by a protective ***capsid*** *(coat) that consists largely or entirely of protein.* A virus specifically adsorbs to a susceptible cell into which it insinuates its nucleic acid. Over the course of the infection (Fig. 1-31), the viral chromosome redirects the cell's metabolism so as to

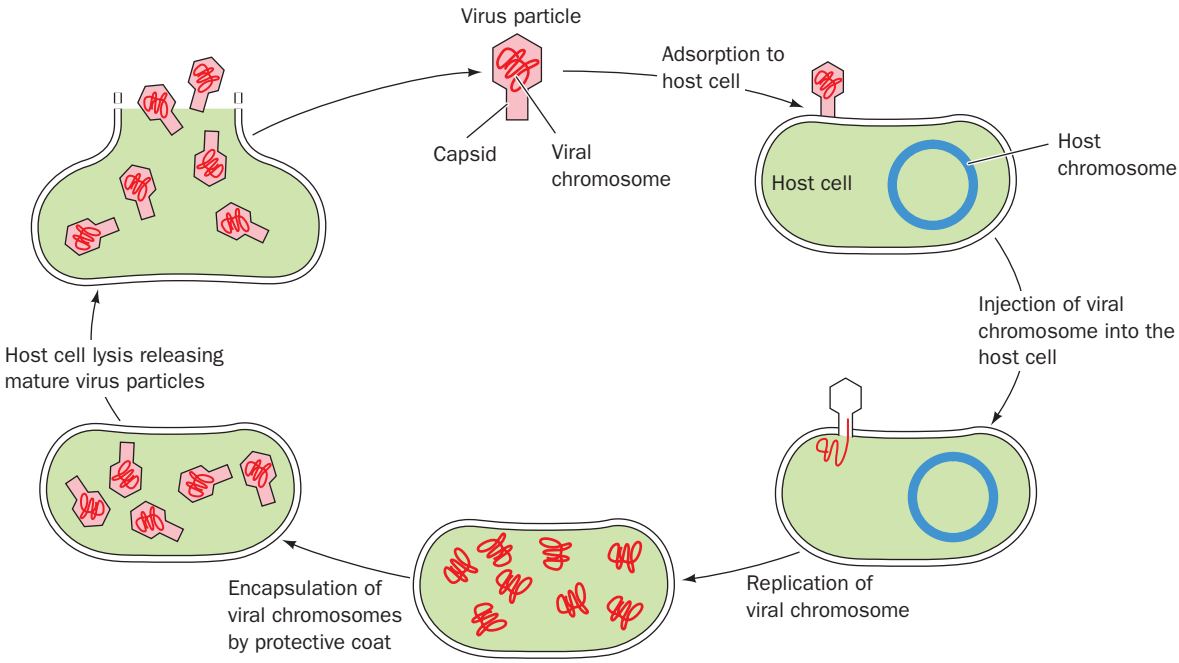


Figure 1-31 **The life cycle of a virus.**

produce new viruses. A viral infection usually culminates in the **lysis** (breaking open) of the host cell, thereby releasing large numbers (tens to thousands) of mature virus particles that can each initiate a new round of infection. Viruses, having no metabolism of their own, are the ultimate parasites. They are not living organisms since, in the absence of their host, they are as biologically inert as any other large molecule.

a. Viruses Are Subject to Complementation and Recombination

The genetics of viruses can be studied in much the same way as that of cellular organisms. Since viruses have no metabolism, however, their presence is usually detected by their ability to kill their host. The presence of viable **bacteriophages** (viruses infecting bacteria, **phages** for short; Greek: *phagein,* to eat) is conveniently indicated by **plaques** (clear spots) on a "lawn" of bacteria on a culture plate (Fig. 1-32). Plaques mark the spots where single phage particles had multiplied with the resulting lysis of the bacteria in the area. A mutant phage, which can produce progeny under certain **permissive conditions,** is detected by its inability to do so under other **restrictive conditions** in which the wild-type phage is viable. These conditions usually involve differences in the strain of the bacterial host employed or in the temperature.

Viruses are subject to complementation. Simultaneous infection of a bacterium by two different mutant varieties of a phage may yield progeny under conditions in which neither variety by itself can reproduce. If this occurs, then each mutant phage must have supplied a function that could not be supplied by the other. Each such mutation is said to belong to a different **complementation group,** a term synonymous for gene.

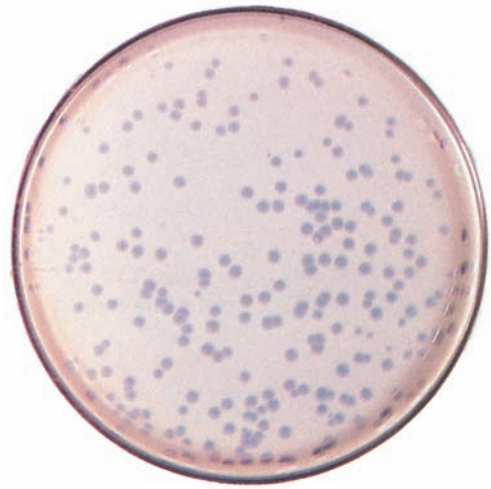


Figure 1-32 **Screening for viral mutants.** A culture plate covered with a lawn of bacteria on which bacteriophage have formed plaques. [Jack Bostrack/Visuals Unlimited.]

Viral chromosomes are also subject to recombination. This occurs when a single cell is simultaneously infected by two mutant strains of a virus (Fig. 1-33). The dynamics of viral recombination differ from those in eukaryotes or bacteria because the viral chromosome undergoes recombination throughout the several rounds of DNA replication that occur during the viral life cycle. Recombinant viral

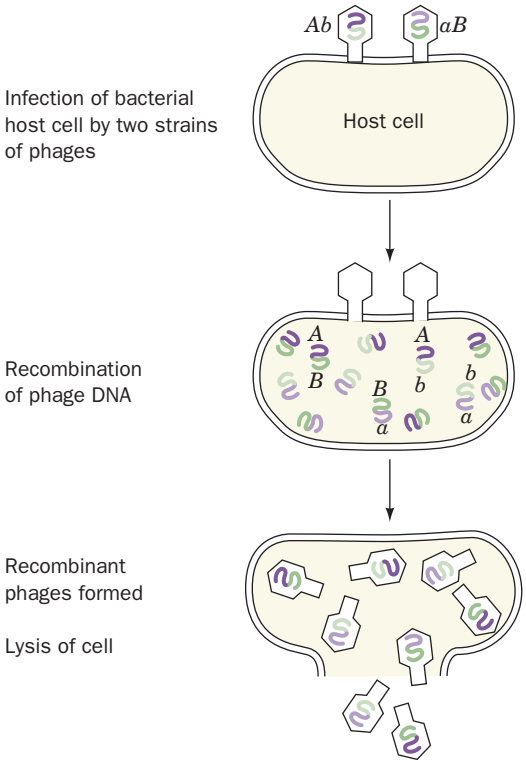


Figure 1-33 **Viral recombination.** Recombination of bacteriophage chromosomes occurs on simultaneous infection of a bacterial host by two phage strains carrying the genes *Ab* and *aB*.

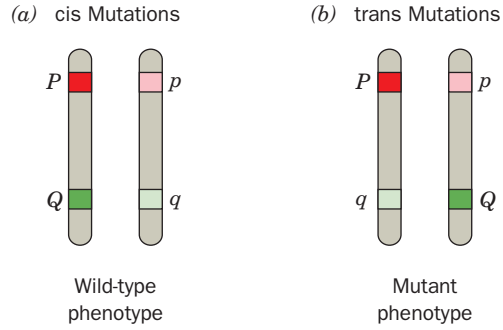


Figure 1-34 **The cis–trans test.** Consider a chromosome that is present in two copies in which two positions on the same gene, *P* and *Q*, have defective (recessive) mutants, *p* and *q*, respectively. (*a*) If the two mutations are cis (physically on the same chromosome), one gene will be wild type, so the organism will have a wild-type phenotype. (*b*) If the mutations are trans (on physically different chromosomes), both genes will be defective and the organism will have a mutant phenotype.

progeny therefore consist of many if not all of the possible recombinant types.

b. The Recombinational Unit Is a Base Pair

The enormous rate at which bacteriophages reproduce permits the detection of recombinational events that occur with a frequency of as little as 1 in 10^8. In the 1950s, Seymour Benzer carried out high-resolution genetic studies of the *rII* region of the **bacteriophage T4** chromosome. This ~4000-base pair **(bp)** region, which represents ~2% of the T4 chromosome, consists of two adjacent complementation groups designated *rIIA* and *rIIB*. In a permissive host, *E. coli* B, a mutation that inactivates the product of either gene causes the formation of plaques that are easily identified because they are much larger than those of the wild-type phage (the designation *r* stands for rapid lysis). However, only the wild-type phage will lyse the restrictive host, *E. coli* K12(λ). The presence of plaques in an *E. coli* K12(λ) culture plate that had been simultaneously infected with two different *rII* mutants in the same complementation group demonstrated that *recombination can take place within a gene.* This refuted a then widely held model of the chromosome in which genes were thought to be discrete entities, rather like beads on a string, such that recombination could take place only between intact genes. The genetic mapping of mutations at over 300 distinguishable sites in the *rIIA* and *rIIB* regions indicated that *genes, as are chromosomes, are linear unbranched structures.*

Benzer also demonstrated that a complementation test between two mutations in the same complementation group yields progeny in the restrictive host when the two mutations are in the **cis** configuration (on the same chromosome; Fig. 1-34*a*), but fails to do so when they are in the **trans** configuration (on physically different chromosomes; Fig. 1-34*b*). This is because only when both mutations physically occur in the same gene will the other gene be functionally intact. The term **cistron** was coined to mean a functional genetic unit defined according to this **cis–trans test.** This word has since become synonymous with gene or complementation group.

The recombination of pairs of *rII* mutants was observed to occur at frequencies as low as 0.01% (although frequencies as low as 0.0001% could, in principle, have been detected). Since a recombination frequency in T4 of 1% corresponds to a 240-bp separation of mutation sites, the unit of recombination can be no larger than $0.01 \times 240 = 2.4$ bp. For reasons having to do with the mechanism of recombination, this is an upper-limit estimate. On the basis of high-resolution genetic mapping, it was therefore concluded that *the unit of recombination is about the size of a single base pair.*

5 THE ORIGIN OF LIFE

People have always pondered the riddle of their existence. Indeed, all known cultures, past and present, primitive and sophisticated, have some sort of a creation myth that rationalizes how life arose. Only in the modern era, however, has it been possible to consider the origin of life in terms of a scientific framework, that is, in a manner subject to experimental verification. One of the first to do so was Charles

Darwin, the originator of the theory of evolution. In 1871, he wrote in a letter to a colleague:

> *It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh what a big if) we could conceive in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured, or absorbed, which would not have been the case before living creatures were formed.*

Radioactive dating studies indicate that Earth formed ~4.6 billion years ago but, due to the impacts of numerous large objects, its surface remained too hot to support life for several hundred million years thereafter. The earliest evidence of cellular life, microfossils of what appear to be organisms resembling modern cyanobacteria (Fig. 1-35), is ~3.5 billion years old. However, the oldest known sedimentary rocks on Earth, which are ~3.8 billion years old, have been subject to such extensive metamorphic forces (500ºC and 5000 atm) that any microfossils they contained would have been obliterated. Nevertheless, geochemical analysis indicates (although not without dispute) that these rocks contain carbonaceous inclusions that are likely to be of biological origin and hence that life must have existed at the time these sedimentary rocks were laid down. If so, life on Earth must have arisen within a window of as little as a hundred million years that opened up ~4 billion years ago.

Since the prebiotic era left no direct record, *we cannot hope to determine exactly how life arose. Through laboratory experimentation, however, we can at least demonstrate what sorts of abiotic chemical reactions may have led to the formation of a living system.* Moreover, we are not entirely without traces of prebiotic development. The underlying biochemical and genetic unity of modern organisms suggests that life as we know it arose but once (if life arose more than once, the other forms must have rapidly died out, possibly because they were "eaten" by the present form). Thus, by comparing the corresponding genetic messages of a wide variety of modern organisms it may be possible to derive reasonable models of the primordial messages from which they have descended.

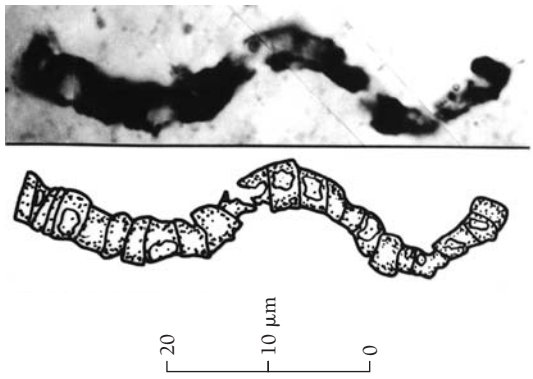


Figure 1-35 **Microfossil of what appears to be a cyanobacterium.** This fossil, shown with its interpretive drawing, is from ~3.5-billion-year-old rock from western Australia. [Courtesy of J. William Schopf, UCLA.]

It is generally accepted that the development of life occupied three stages (Fig. 1-36):

1. Chemical evolution, in which simple geologically occurring molecules reacted to form complex organic polymers.

2. The self-organization of collections of these polymers to form replicating entities. At some point in this process, the transition from a lifeless collection of reacting molecules to a living system occurred.

3. Biological evolution to ultimately form the complex web of modern life.

In this section, we outline what has been surmised about these processes. We precede this discussion by a consideration of why only carbon, of all the elements, is suitable as the basis of the complex chemistry required for life.

A. *The Unique Properties of Carbon*

Living matter, as Table 1-3 indicates, consists of a relatively small number of elements. C, H, O, N, P, and S, all of which readily form covalent bonds, comprise 92% of the dry weight of living things (most organisms are ~70% water). The balance consists of elements that are mainly present as ions and for the most part occur only in trace quantities (they usually carry out their functions at the active sites of enzymes). Note, however, that there is no known biological requirement for 64 of the 90 naturally occurring elements

Table 1-3 **Elemental Composition of the Human Body**

Element	Dry Weight (%)[a]	Elements Present in Trace Amounts
C	61.7	B
N	11.0	F
O	9.3	Si
H	5.7	V
Ca	5.0	Cr
P	3.3	Mn
K	1.3	Fe
S	1.0	Co
Cl	0.7	Ni
Na	0.7	Cu
Mg	0.3	Zn
		Se
		Mo
		Sn
		I

[a]Calculated from Frieden, E., *Sci. Am.* **227**(1), 54–55 (1972).

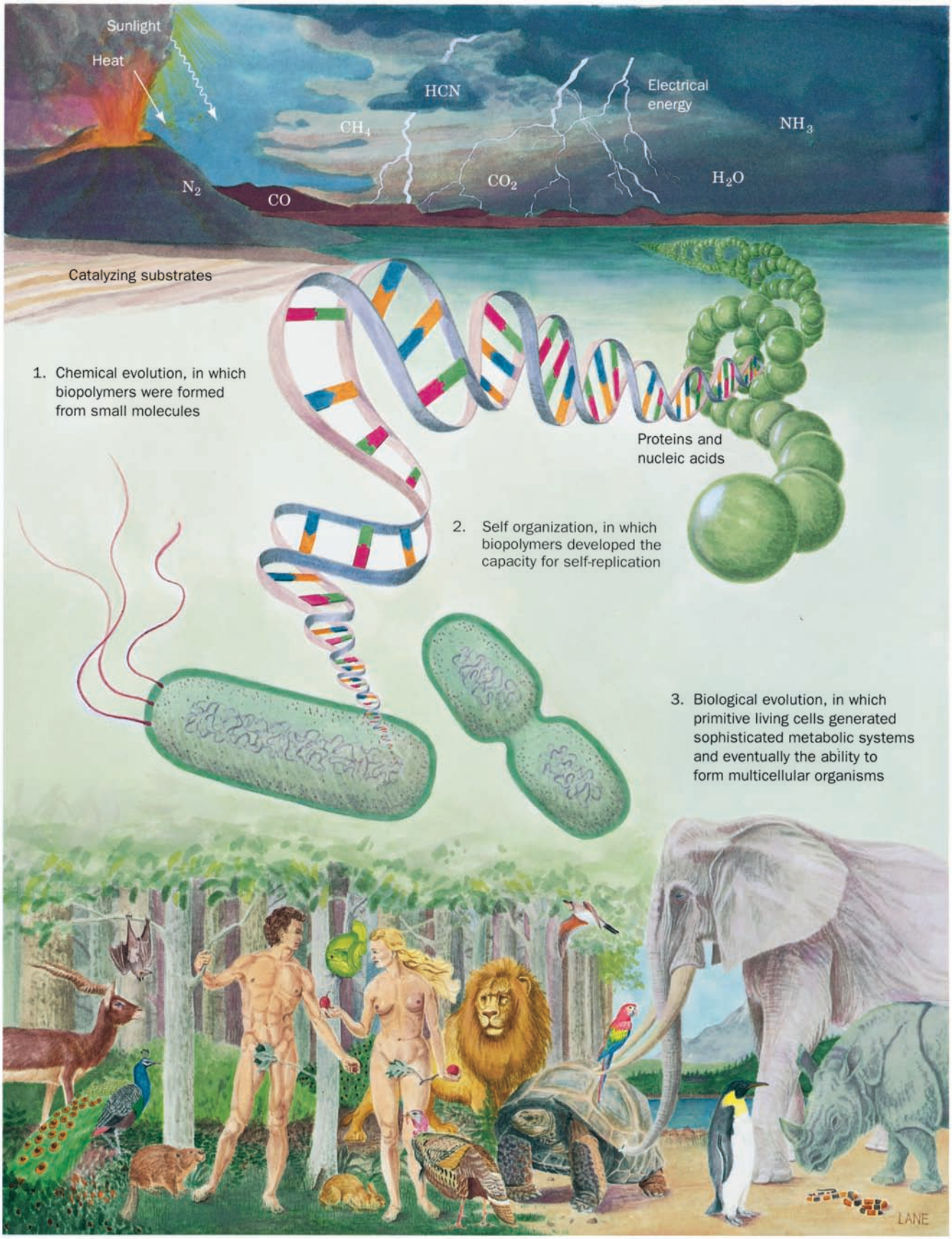


Figure 1-36 **The three stages in the evolution of life.**

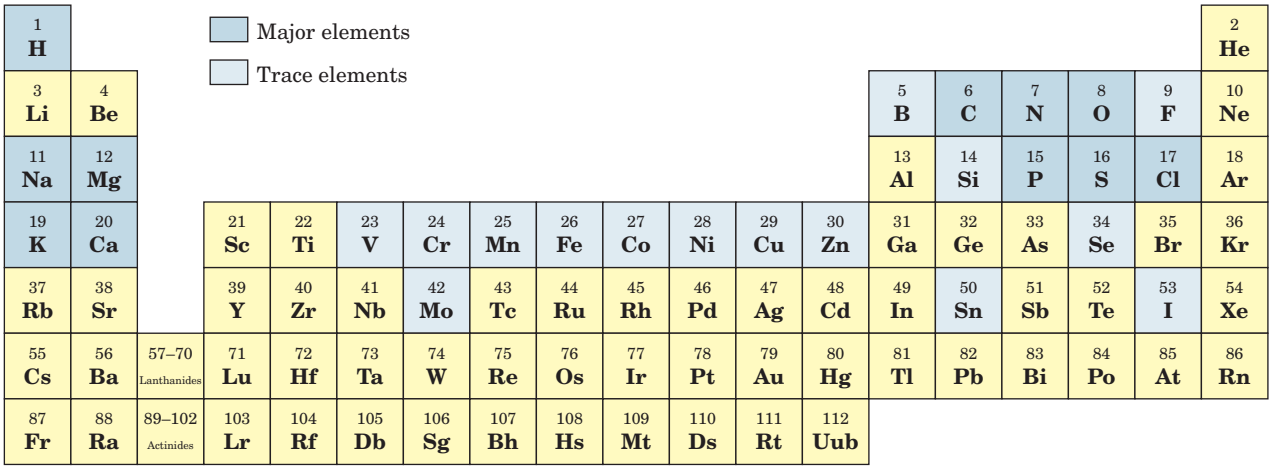


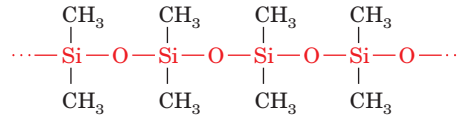
Figure 1-37 **Periodic table in which the 26 elements utilized by living systems are highlighted in blue.**

(Fig. 1-37). Conversely, with the exceptions of oxygen and calcium, the biologically most abundant elements are but minor constituents of Earth's crust (the most abundant components of which are O, 47%; Si, 28%; Al, 7.9%; Fe, 4.5%; and Ca, 3.5%).

The predominance of carbon in living matter is no doubt a result of its tremendous chemical versatility compared with all the other elements. Carbon has the unique ability to form a virtually infinite number of compounds as a result of its capacity to make as many as four highly stable covalent bonds (including single, double, and triple bonds) combined with its ability to form covalently linked C—C *chains of unlimited extent.* Thus, of the nearly 40 million chemical compounds that are presently known, ~90% are organic (carbon-containing) substances. Let us examine the other elements in the periodic table to ascertain why they lack these combined properties.

Only five elements, B, C, N, Si, and P, have the capacity to make three or more bonds each and thus to form chains of covalently linked atoms that can also have pendant side chains. The other elements are either metals, which tend to form ions rather than covalent bonds; noble gases, which are essentially chemically inert; or atoms such as H or O that can each make only one or two covalent bonds. However, although B, N, Si, and P can each participate in at least three covalent bonds, they are, for reasons indicated below, unsuitable as the basis of a complex chemistry.

Boron, having fewer valence electrons (3) than valence orbitals (4), is electron deficient. This severely limits the types and stabilities of compounds that B can form. Nitrogen has the opposite problem; its 5 valence electrons make it electron rich. The repulsions between the lone pairs of electrons on covalently bonded N atoms serve to greatly reduce the bond energy of an N—N bond (171 kJ · mol^{-1} vs 348 kJ · mol^{-1} for a C—C single bond) relative to the unusually stable triple bond of the N_2 molecule (946 kJ · mol^{-1}). Even short chains of covalently bonded N atoms therefore tend to decompose, usually violently, to N_2. Silicon and carbon, being in the same column of the periodic table, might be expected to have similar chemistries. Silicon's large atomic radius, however, prevents two Si atoms from approaching each other closely enough to gain much orbital overlap. Consequently Si—Si bonds are weak (177 kJ · mol^{-1}) and the corresponding multiple bonds are rarely stable. Si—O bonds, in contrast, are so stable (369 kJ · mol^{-1}) that chains of alternating Si and O atoms are essentially inert (silicate minerals, whose frameworks consist of such bonds, form Earth's crust). Science fiction writers have speculated that **silicones,** which are oily or rubbery organosilicon compounds with backbones of linked Si—O units, for example, **methyl silicones,**



could form the chemical basis of extraterrestrial life-forms. Yet the very inertness of the Si—O bond makes this seem unlikely. Phosphorus, being below N in the periodic table, forms even less stable chains of covalently bonded atoms.

The foregoing does not imply that heteronuclear bonds are unstable. On the contrary, proteins contain C—N—C linkages, carbohydrates have C—O—C linkages, and nucleic acids possess C—O—P—O—C linkages. However, *these heteronuclear linkages are less stable than are* C—C *bonds. Indeed, they usually form the sites of chemical cleavage in the degradation of macromolecules and, conversely, are the bonds formed when monomer units are linked together to form macromolecules.* In the same vein, homonuclear linkages other than C—C bonds are so reactive that they are, with the exception of S—S bonds in proteins, extremely rare in biological systems.

B. *Chemical Evolution*

In the remainder of this section, we describe the most widely favored scenario for the origin of life. *Keep in mind, however, that there are valid scientific objections to this scenario as well as to the several others that have been seriously*

entertained, so that we are far from certain as to how life arose.

The solar system is thought to have formed by the gravitationally induced collapse of a large interstellar cloud of dust and gas. The major portion of this cloud, which was composed mostly of hydrogen and helium, condensed to form the sun. The rising temperature and pressure at the center of the protosun eventually ignited the self-sustaining thermonuclear reaction that has since served as the sun's energy source. The planets, which formed from smaller clumps of dust, were not massive enough to support such a process. In fact the smaller planets, including Earth, consist of mostly heavier elements because their masses are too small to gravitationally retain much H_2 and He.

The primordial Earth's atmosphere was quite different from what it is today. It could not have contained significant quantities of O_2, a highly reactive substance. Rather, in addition to the H_2O, N_2, and CO_2 that it presently has, the atmosphere probably contained smaller amounts of CO, CH_4, NH_3, SO_2, and possibly H_2, all molecules that have been spectroscopically detected in interstellar space. The chemical properties of such a gas mixture make it a **reducing atmosphere** in contrast to Earth's present atmosphere, which is an **oxidizing atmosphere.**

In the 1920s, Alexander Oparin and J.B.S. Haldane independently suggested that *ultraviolet (UV) radiation from the sun [which is presently largely absorbed by an ozone (O_3) layer high in the atmosphere] or lightning discharges caused the molecules of the primordial reducing atmosphere to react to form simple organic compounds such as amino acids, nucleic acid bases, and sugars*. That this process is possible was first experimentally demonstrated in 1953 by Stanley Miller and Harold Urey, who, in the apparatus diagrammed in Fig. 1-38, simulated effects of lightning storms in the primordial atmosphere by subjecting a refluxing mixture of H_2O, CH_4, NH_3, and H_2 to an electric discharge for about a week. (Although it now appears that Earth's primordial atmosphere did not have the strongly reducing composition assumed by Miller and Urey, localized reducing environments may have existed, particularly near volcanic plumes.) The resulting solution contained significant amounts of water-soluble organic compounds, the most abundant of which are listed in Table 1-4, together with a

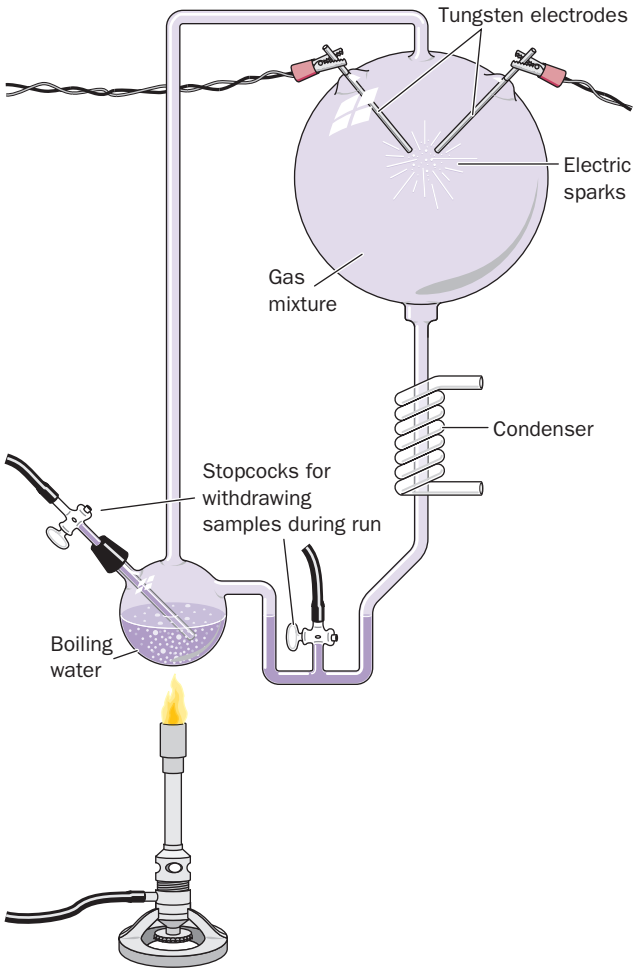


Figure 1-38 **Apparatus for emulating the synthesis of organic compounds on the prebiotic Earth.** A mixture of gases thought to resemble the primitive Earth's reducing atmosphere is subjected to an electric discharge, to simulate the effects of lightning, while the water in the flask is refluxed so that the newly formed compounds dissolve in the water and accumulate in the flask. [After Miller, S.L. and Orgel, L.E., *The Origins of Life on Earth, p.* 84, Prentice-Hall (1974).]

Table 1-4 **Yields from Sparking a Mixture of CH_4, NH_3, H_2O, and H_2**

Compound	Yield (%)
Glycine[a]	2.1
Glycolic acid	1.9
Sarcosine	0.25
Alanine[a]	1.7
Lactic acid	1.6
N-Methylalanine	0.07
α-Amino-*n*-butyric acid	0.34
α-Aminoisobutyric acid	0.007
α-Hydroxybutyric acid	0.34
β-Alanine	0.76
Succinic acid	0.27
Aspartic acid[a]	0.024
Glutamic acid[a]	0.051
Iminodiacetic acid	0.37
Iminoaceticpropionic acid	0.13
Formic acid	4.0
Acetic acid	0.51
Propionic acid	0.66
Urea	0.034
N-Methylurea	0.051

[a]Amino acid constituent of proteins.

Source: Miller, S.J. and Orgel, L.E., *The Origins of Life on Earth, p.* 85, Prentice-Hall (1974).

substantial quantity of insoluble tar (polymerized material). Several of the soluble compounds are amino acid components of proteins, and many of the others, as we shall see, are also of biochemical significance. Similar experiments in which the reaction conditions, the gas mixture, and/or the energy source were varied have resulted in the synthesis of many other amino acids. This, together with the observation that carbonaceous meteorites contain many of the same amino acids, strongly suggests that these substances were present in significant quantities on the primordial Earth. Indeed, it seems likely that large quantities of organic molecules were delivered to the primordial Earth by the meteorites and dust that so heavily bombarded it.

Nucleic acid bases can also be synthesized under supposed prebiotic conditions. In particular, adenine is formed by the condensation of HCN, a plentiful component of the prebiotic atmosphere, in a reaction catalyzed by NH_3 [note that the chemical formula of adenine is $(HCN)_5$]. The other bases have been synthesized in similar reactions involving HCN and H_2O. Sugars have been synthesized by the polymerization of formaldehyde (CH_2O) in reactions catalyzed by divalent cations, alumina, or clays. It is probably no accident that these compounds are the basic components of biological molecules. *They were apparently the most common organic substances in prebiotic times.*

The above described prebiotic reactions probably occurred over a period of hundreds of millions of years. Ultimately, it has been estimated, the oceans attained the organic consistency of a thin bouillon soup. Of course there must have been numerous places, such as tidal pools and shallow lakes, where the prebiotic soup became much more concentrated. In such environments its component organic molecules could have condensed to form, for example, polypeptides and polynucleotides (nucleic acids). Quite possibly these reactions were catalyzed by the adsorption of the reactants on minerals such as clays. If, however, life were to have formed, the rates of synthesis of these complex polymers would have had to be greater than their rates of hydrolysis. Therefore, the "pond" in which life arose may have been cold rather than warm, possibly even below 0°C (seawater freezes solidly only below −21°C), since hydrolysis reactions are greatly retarded at such low temperatures.

C. *The Rise of Living Systems*

Living systems have the ability to replicate themselves. The inherent complexity of such a process is such that no man-made device has even approached having this capacity. Clearly there is but an infinitesimal probability that a collection of molecules can simply gather at random to form a living entity (the likelihood of a living cell forming spontaneously from simple organic molecules has been said to be comparable to that of a modern jet aircraft being assembled by a tornado passing through a junkyard). How then did life arise? The answer, most probably, is that it was guided according to the Darwinian principle of the survival of the fittest as it applies at the molecular level.

a. Life Probably Arose Through the Development of Self-Replicating RNA Molecules

The primordial self-replicating system is widely believed to have been a collection of nucleic acid molecules because such molecules, as we have seen in Section 1-3C, can direct the synthesis of molecules complementary to themselves. RNA, as does DNA, can direct the synthesis of a complementary strand. In fact, RNA serves as the hereditary material of many viruses (Chapter 33). The polymerization of the progeny molecules would, at first, have been a simple chemical process and hence could hardly be expected to be accurate. The early progeny molecules would therefore have been only approximately complementary to their parents. Nevertheless, repeated cycles of nucleic acid synthesis would eventually exhaust the supply of free nucleotides so that the synthesis rate of new nucleic acid molecules would be ultimately limited by the hydrolytic degradation rate of old ones. Suppose, in this process, a nucleic acid molecule randomly arose that, through folding, was more resistant to degradation than its cousins. The progeny of this molecule, or at least its more faithful copies, could then propagate at the expense of the nonresistant molecules; that is, the resistant molecules would have a Darwinian advantage over their fellows. Theoretical studies suggest that such a system of molecules would evolve so as to optimize its replication efficiency under its inherent physical and chemical limitations.

In the next stage of the evolution of life, it is thought the dominant nucleic acids evolved the capacity to influence the efficiency and accuracy of their own replication. This process occurs in living systems through the nucleic acid–directed ribosomal synthesis of enzymes that catalyze nucleic acid synthesis. How nucleic acid–directed protein synthesis could have occurred before ribosomes arose is unknown because nucleic acids are not known to interact selectively with particular amino acids. This difficulty exemplifies the major problem in tracing the pathway of prebiotic evolution. Suppose some sort of rudimentary nucleic acid–influenced system arose that increased the efficiency of nucleic acid replication. This system must have eventually been replaced, presumably with almost no trace of its existence, by the much more efficient ribosomal system. Our hypothetical nucleic acid synthesis system is therefore analogous to the scaffolding used in the construction of a building. After the building has been erected the scaffolding is removed, leaving no physical evidence that it ever was there. *Most of the statements in this section must therefore be taken as educated guesses.* Without our having witnessed the event, it seems unlikely that we shall ever be certain of how life arose.

A plausible hypothesis for the evolution of self-replicating systems is that they initially consisted entirely of RNA, a scenario known as the ***"RNA world."*** This idea is based, in part, on the observation that certain species of RNA exhibit enzymelike catalytic properties (Section 31-4A). Moreover, since ribosomes are approximately two-thirds RNA and only one-third protein, it is plausible that the primordial ribosomes were entirely RNA. A cooperative relationship between RNA and protein might have arisen

when these self-replicating protoribosomes evolved the ability to influence the synthesis of proteins that increased the efficiency and/or the accuracy of RNA synthesis. *From this point of view, RNA is the primary substance of life; the participation of DNA and proteins were later refinements that increased the Darwinian fitness of an already established self-replicating system.*

The types of systems that we have so far described were bounded only by the primordial "pond." A self-replicating system that developed a more efficient component would therefore have to share its benefits with all the "inhabitants" of the "pond," a situation that minimizes the improvement's selective advantage. Only through compartmentalization, that is, the generation of cells, could developing biological systems reap the benefits of any improvements that they might have acquired. Of course, cell formation would also hold together and protect any self-replicating system and therefore help it spread beyond its "pond" of origin. Indeed, the importance of compartmentalization is such that it may have preceded the development of self-replicating systems. The erection of cell boundaries is not without its price, however. Cells, as we shall see in later chapters, must expend much of their metabolic effort in selectively transporting substances across their cell membranes. How cell boundaries first arose, or even what they were made from, is presently unknown. However, one plausible theory holds that membranes first arose as empty vesicles whose exteriors could serve as attachment sites for such entities as enzymes and chromosomes in ways that facilitated their function. Evolution then flattened and folded these vesicles so that they enclosed their associated molecular assemblies, thereby defining the primordial cells.

b. Competition for Energy Resources Led to the Development of Metabolic Pathways, Photosynthesis, and Respiration

At this stage in their development, the entities we have been describing already fit Horowitz's criteria for life (exhibiting replication, catalysis, and mutability). The polymerization reactions through which these primitive organisms replicated were entirely dependent on the environment to supply the necessary monomeric units and the energy-rich compounds such as ATP or, more likely, just polyphosphates, that powered these reactions. As some of the essential components in the prebiotic soup became scarce, organisms developed the enzymatic systems that could synthesize these substances from simpler but more abundant precursors. As a consequence, energy-producing metabolic pathways arose. This latter development only postponed an "energy crisis," however, because these pathways consumed other preexisting energy-rich substances. The increasing scarcity of all such substances ultimately stimulated the development of photosynthesis to take advantage of a practically inexhaustible energy supply, the sun. Yet this process, as we saw in Section 1-1Ab, consumes reducing agents such as H_2S. The eventual exhaustion of these substances led to the refinement of the photosynthetic process so that it used the ubiquitous H_2O as its reducing agent, thereby yielding O_2 as a by-product. The discovery, in ~3.5-billion-year-old rocks, of what appears to be fossilized cyanobacteria-like microorganisms (Fig. 1-35) suggests that oxygen-producing photosynthesis developed very early in the history of life.

The development of oxygen-producing photosynthesis led to yet another problem. The accumulation of the highly reactive O_2, which over the eons converted the reducing atmosphere of the prebiotic Earth to the modern oxidizing atmosphere (21% O_2), eventually interfered with the existing metabolic apparatus, which had evolved to operate under reducing conditions. The O_2 accumulation therefore stimulated the development of metabolic refinements that protected organisms from oxidative damage. More importantly, it led to the evolution of a much more efficient form of energy metabolism than had previously been possible, **respiration** (oxidative metabolism), which used the newly available O_2 as an oxidizing agent. [The availability of atmospheric O_2 is also responsible for the generation of the stratospheric ozone (O_3) layer that absorbs most of the biologically harmful ultraviolet radiation that strikes Earth.]

As previously outlined, the basic replicative and metabolic apparatus of modern organisms evolved quite early in the history of life on Earth. Indeed, many modern prokaryotes appear to resemble their very ancient ancestors. The rise of eukaryotes, as Section 1-2 indicates, occurred perhaps 2 billion years after prokaryotes had become firmly established. Multicellular organisms are a relatively recent evolutionary innovation, having not appeared, according to the fossil record, until ~700 million years ago.

6 THE BIOCHEMICAL LITERATURE

The biochemical literature contains the results of the work of tens of thousands of scientists extending well over a century. Consequently a biochemistry textbook can report only selected highlights of this vast amount of information. Moreover, the tremendous rate at which biochemical knowledge is presently being acquired, which is perhaps greater than that of any other intellectual endeavor, guarantees that there will have been significant biochemical advances even in the year or so that it took to produce this text from its final draft. A serious student of biochemistry must therefore regularly read the biochemical literature to flesh out the details of subjects covered in (or omitted from) this text, as well as to keep abreast of new developments. This section provides a few suggestions on how to do so.

A. *Conducting a Literature Search*

The primary literature of biochemistry, those publications that report the results of biochemical research, is presently being generated at a rate of tens of thousands of papers per year appearing in over 200 periodicals. An individual can therefore only read this voluminous literature in a highly selective fashion. Indeed, most biochemists tend to "read"

only those publications that are likely to contain reports pertaining to their interests. By "read" it is meant that they scan the tables of contents of these journals for the titles of articles that seem of sufficient interest to warrant further perusal.

It is difficult to learn about a new subject by beginning with its primary literature. Instead, to obtain a general overview of a particular biochemical subject it is best to first peruse appropriate reviews and monographs. These usually present a synopsis of recent (at the time of their writing) developments in the area, often from the authors' particular point of view. There are more or less two types of reviews: those that are essentially a compilation of facts and those that critically evaluate the data and attempt to place them in some larger context. The latter type of review is of course more valuable, particularly for a novice in the field. Most reviews are published in specialized books and journals, although many journals that publish research reports also occasionally print reviews. Table 1-5 provides a list of many of the important biochemical review publications.

Monographs and reviews relevant to a subject of interest are usually easy to find through the use of a library catalog and the subject indexes of the major review publications (the chapter-end references of this text may also be helpful in this respect). An important part of any review is its reference list. It usually has previous reviews in the same or allied fields as well as indicating the most significant research reports in the area. Note the authors of these articles and the journals in which they tend to publish. When the most current reviews and research articles you have found tend to refer to the same group of earlier articles, you can be reasonably confident that your search for these earlier articles is largely complete. Finally, to familiarize yourself with the latest developments in the field, search the recent primary literature for the work of its most active research groups and visit the websites of these groups.

Academic libraries subscribe to Web-based reference search services such as MedLine, SciFinder Scholar, BIOSIS Previews, and Web of Science. MedLine can also be accessed free of charge through the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/PubMed). Google Scholar (http://scholar.google.com/) is a freely available search engine that indexes the scholarly literature across many disciplines. When used properly, these bibliographic search services are highly efficient tools for locating specific information. Wikipedia (http://wikipedia.org/) is also a valuable and easily available resource.

Table 1-5 **Some Biochemical Review Publications**

Accounts of Chemical Research
Advances in Protein Chemistry and Structural Biology
Annual Review of Biochemistry
Annual Review of Biophysics
Annual Review of Cell and Developmental Biology
Annual Review of Genetics
Annual Review of Genomics and Human Genetics
Annual Review of Immunology
Annual Review of Medicine
Annual Review of Microbiology
Annual Review of Physiology
Annual Review of Plant Biology
Biochemical Journal[a]
Biochemistry and Molecular Biology Education[a]
Biochimica et Biophysica Acta[a]
BioEssays
Cell[a]
Chemistry and Biology
Critical Reviews in Biochemistry and Molecular Biology
Current Biology
Current Opinion in Biotechnology
Current Opinion in Cell Biology
Current Opinion in Chemical Biology
Current Opinion in Genetics and Development
Current Opinion in Structural Biology
FASEB Journal[a]
Journal of Biological Chemistry[a]
Methods in Enzymology
Molecular Cell[a]
Nature[a]
Nature Reviews Molecular Cell Biology
Nature Structural & Molecular Biology[a]
Proceedings of the National Academy of Sciences USA[a]
Progress in Biophysics and Molecular Biology
Progress in Nucleic Acid Research and Molecular Biology
Protein Science[a]
Quarterly Reviews of Biophysics
Science[a]
Scientific American
Structure[a]
Trends in Biochemical Sciences
Trends in Cell Biology
Trends in Genetics

[a]Periodicals that mainly publish research reports.

B. *Reading a Research Article*

Research reports more or less all have the same six-part format. They usually have a short abstract or summary located before the main body of the paper. The paper then continues with an introduction, which often contains a short synopsis of the field, the motivation for the research reported, and a preview of its conclusions. The next section contains a description of the methods used to obtain the experimental data. This is followed by a presentation of the results of the investigation and then by a discussion section wherein the conclusions of the investigation are set forth and placed in the context of other work in the field. Finally, there is a list of references. Most articles are "full papers," which may be tens of pages long. However, many journals also contain "communications" or "letters," which are usually only a few

pages in length and are often published more quickly than are full papers. Many papers have accompanying supplementary material that is available on the journal's website.

It is by no means obvious how to read a scientific paper. Perhaps the worst way to do so is to read it from beginning to end as if it were some kind of a short story. In fact, most practicing scientists only occasionally read a research article in its entirety. It simply takes too long and is rarely productive. Rather, they scan selected parts of a paper and only dig deeper if it appears that to do so will be profitable. The following paragraph describes a reasonably efficient scheme for reading scientific papers. *This should be an active process in which the reader is constantly evaluating what is being read and relating it to his/her previous knowledge.* Moreover, the reader should maintain a healthy skepticism since there is a reasonable probability that any paper, particularly in its interpretation of experimental data and in its speculations, may be erroneous.

If the title of a paper indicates that it may be of interest, then this should be confirmed by a reading of its abstract. For many papers, even those containing useful information, it is unnecessary to read further. If you choose to continue, it is probably best to do so by scanning the introduction so as to obtain an overview of the work reported. At this point most experienced scientists scan the conclusions section of the paper to gain a better understanding of what was found. If further effort seems warranted, they scan the results section to ascertain whether the experimental data support the conclusions. The methods section (which in many journals is largely relegated to the supplementary materials) is usually not read in detail because it is often written in a condensed form that is only fully interpretable by an expert in the field. However, for such experts, the methods section may be the most valuable part of the paper. At this point, what to read next, if anything, is largely dictated by the remaining points of confusion. In many cases this confusion can only be eliminated by reading some of the references given in the paper. At any rate, unless you plan to repeat or extend some of the work described, it is rarely necessary to read an article in detail. To do so in a critical manner, you will find, takes several hours for a paper of even moderate size.

CHAPTER SUMMARY

1 Prokaryotes Prokaryotes are single-celled organisms that lack a membrane-enclosed nucleus. Most prokaryotes have similar anatomies: a rigid cell wall surrounding a cell membrane that encloses the cytoplasm. The cell's single chromosome is condensed to form a nucleoid. *Escherichia coli,* the biochemically most well-characterized organism, is a typical prokaryote. Prokaryotes have quite varied nutritional requirements. The chemolithotrophs metabolize inorganic substances. Photolithotrophs, such as cyanobacteria, carry out photosynthesis. Heterotrophs, which live by oxidizing organic substances, are classified as aerobes if they use oxygen in this process and as anaerobes if some other oxidizing agent serves as their terminal electron acceptor. Traditional prokaryotic classification schemes are rather arbitrary because of poor correlation between bacterial form and metabolism. Sequence comparisons of nucleic acids and proteins, however, have established that all life-forms can be classified into three domains of evolutionary descent: the Archaea (archaebacteria), the Bacteria (eubacteria), and the Eukarya (eukaryotes).

2 Eukaryotes Eukaryotic cells, which are far more complex than those of prokaryotes, are characterized by having numerous membrane-enclosed organelles. The most conspicuous of these is the nucleus, which contains the cell's chromosomes, and the nucleolus, where ribosomes are assembled. The endoplasmic reticulum is the site of synthesis of lipids and of proteins that are destined for secretion. Further processing of these products occurs in the Golgi apparatus. The mitochondria, wherein oxidative metabolism occurs, are thought to have evolved from a symbiotic relationship between an aerobic bacterium and a primitive eukaryote. The chloroplast, the site of photosynthesis in plants, similarly evolved from a cyanobacterium. Other eukaryotic organelles include the lysosome, which functions as an intracellular digestive chamber, and the peroxisome, which contains a variety of oxidative enzymes including some that generate H_2O_2. The eukaryotic cytoplasm is pervaded by a cytoskeleton whose components include microtubules, which consist of tubulin; microfilaments, which are composed of actin; and intermediate filaments, which are made of different proteins in different types of cells. Eukaryotes have enormous morphological diversity on the cellular as well as on the organismal level. They have been classified into four kingdoms: Protista, Plantae, Fungi, and Animalia. The pattern of embryonic development in multicellular organisms partially mirrors their evolutionary history.

3 Biochemistry: A Prologue Organisms have a hierarchical structure that extends down to the submolecular level. They contain but three basic types of macromolecules: proteins, nucleic acids, and polysaccharides, as well as lipids, each of which are constructed from only a few different species of monomeric units. Macromolecules and supramolecular assemblies form their native biological structures through a process of self-assembly. The assembly mechanisms of higher biological structures are largely unknown. Metabolic processes are organized into a series of tightly regulated pathways. These are classified as catabolic or anabolic depending on whether they participate in degradative or biosynthetic processes. The common energy "currency" in all these processes is ATP, whose synthesis is the product of many catabolic pathways and whose hydrolysis drives most anabolic pathways. DNA, the cell's hereditary molecule, encodes genetic information in its sequence of bases. The complementary base sequences of its two strands permit them to act as templates for their own replication and for the synthesis of complementary strands of RNA. Ribosomes synthesize proteins by linking amino acids together in the order specified by the base sequences of RNAs.

4 Genetics: A Review Eukaryotic cells contain a characteristic number of homologous pairs of chromosomes. In mito-

sis each daughter cell receives a copy of each of these chromosomes, but in meiosis each resulting gamete receives only one member of each homologous pair. Fertilization is the fusion of two haploid gametes to form a diploid zygote. The Mendelian laws of inheritance state that alternative forms of true-breeding traits are specified by different alleles of the same gene. Alleles may be dominant, codominant, or recessive depending on the phenotype of the heterozygote. Different genes assort independently unless they are on the same chromosome. The linkage between genes on the same chromosome, however, is never complete because of crossing-over among homologous chromosomes during meiosis. The rate at which genes recombine varies with their physical separation because crossing-over occurs essentially at random. This permits the construction of genetic maps. Whether two recessive traits are allelic may be determined by the complementation test. The nature of genes is largely defined by the dictum "one gene–one polypeptide." Mutant varieties of bacteriophages are detected by their ability to kill their host under various restrictive conditions. The fine structure analysis of the *rII* region of the bacteriophage T4 chromosome has revealed that recombination may take place within a gene, that genes are linear unbranched structures, and that the unit of mutation is ~1 bp.

5 The Origin of Life Life is carbon based because only carbon, among all the elements in the periodic table, has a sufficiently complex chemistry together with the ability to form virtually infinite stable chains of covalently bonded atoms. Reactions among the molecules in the reducing atmosphere of the prebiotic Earth are thought to have formed the simple organic precursors from which biological molecules developed. Eventually, in reactions that may have been catalyzed by minerals such as clays, polypeptides and polynucleotides formed. These evolved under the pressure of competition for the available monomeric units. Ultimately, a nucleic acid, most probably RNA, developed the capability of influencing its own replication by directing the synthesis of proteins that catalyze polynucleotide synthesis. This was followed by the development of cell membranes so as to form living entities. Subsequently, metabolic processes evolved to synthesize necessary intermediates from available precursors as well as the high-energy compounds required to power these reactions. Likewise, photosynthesis and respiration arose in response to environmental pressures brought about by the action of living organisms.

6 The Biochemical Literature The sheer size and rate of increase of the biochemical literature requires that it be read to attain a thorough understanding of any aspect of biochemistry. The review literature provides an entrée into a given subspeciality. To remain current in any field, however, requires a regular perusal of its primary literature. This should be read in a critical and highly selective fashion.

REFERENCES

Prokaryotes and Eukaryotes

Becker, W.M., Kleinsmith, L.J., Hardin, J., and Bertoni, G.P., *The World of the Cell* (7th ed.), Benjamin Cummings (2009). [A highly readable cell biology text.]

Boone, D.R. and Castenholz, R.W. (Eds.), *Bergey's Manual of Systematic Bacteriology* (2nd ed.), Vol. I; *and* Brenner, D.J., Kreig, N.R., and Staley, J.T. (Eds.), *Bergey's Manual of Systematic Bacteriology* (2nd ed.), Vols. IIA, B, & C, Springer (2001 and 2005).

Campbell, N.A. and Reece, J.B., *Biology* (8th ed.) Benjamin Cummings (2008). [A comprehensive general biology text. There are several others available with similar content.]

Frieden, E., The chemical elements of life, *Sci. Am.* **227**(1), 52–60 (1972).

Goodsell, D.S., *The Machinery of Life,* Springer-Verlag (1998).

Jørgensen, B.B. and D'Hondt, S., A starving majority beneath the sea floor, *Science* **314,** 932–934 (2006). [Discusses the prokaryotes that live in the rocks deep below Earth's surface.]

Madigan, M.T., Martinko, J.M., Dunlap, P.V., and Clark, D.P., *Brock Biology of Microorganisms* (12th ed.), Pearson Benjamin Cummings (2009).

Margulis, L. and Schwartz, K.V., *Five Kingdoms. An Illustrated Guide to the Phyla of Life on Earth* (3rd ed.), Freeman (1998).

Pace, N.R., A molecular view of microbial diversity and the biosphere, *Science* **276,** 734–740 (1997).

Whitman, W.B., Coleman, D.C., and Wiebe, W.J., Prokaryotes: The unseen majority, *Proc. Natl. Acad. Sci.* **95,** 6578–6583 (1998). [Estimates the number of prokaryotes on Earth ($4–6 \times 10^{30}$ cells) and the aggregate mass of their cellular carbon ($3.5–5.5 \times 10^{14}$ kg, which therefore comprises 66–100% of the carbon in plants).]

Genetics

Benzer, S., The fine structure of the gene, *Sci. Am.* **206**(1), 70–84 (1962).

Cairns, J., Stent, G.S., and Watson, J. (Eds.), *Phage and the Origins of Molecular Biology, The Centennial Edition*, Cold Spring Harbor Laboratory (2007). [A series of scientific memoirs by many of the pioneers of molecular biology.]

Hartwell, L.H., Hood, L., Goldberg, M.L., Reynolds, A.E., Silver, L.M., and Veres, R.C., *Genetics. From Genes to Genomes* (3rd ed.), Chapters 1–5, McGraw-Hill (2008).

Snustad, D.P. and Simmons, M.J., *Principles of Genetics* (5th ed.), Wiley (2009).

Origin of Life

Berstein, M.P., Sandford, S.A., and Allamandola, S.A., Life's far-flung raw materials, *Sci. Am.* **281**(1), 42–49 (1999). [A discussion of the possibility that the complex organic molecules which provided the starting materials for life were delivered to the primordial Earth by meteorites and dust.]

Brack, A. (Ed.), *The Molecular Origins of Life,* Cambridge University Press (1998).

Doolittle, F.W., Phylogenetic classification and the universal tree, *Science* **284,** 2124–2128 (1999). [A discussion of how lateral gene transfer among the various forms of life may have confounded the ability to elucidate the "universal tree of life" if, in fact, such a tree is a reasonable model of the history of life.]

Dyson, F., *Origins of Life,* Cambridge University Press (1985). [A fascinating philosophical discourse on theories of life's origins by a respected theoretical physicist.]

Fraústo da Silva, J.R. and Williams, R.J.P., *The Biological Chemistry of the Elements,* Oxford (1991).

Gesteland, R.F., Cech, T.R., and Atkins, J.F. (Eds.), *The RNA World* (3rd ed.), Chapters 1–3, Cold Spring Harbor Laboratory Press (2006).

Herdewijn, P. and Kisakürek, M.V. (Eds.), *Origin of Life. Chemical Approach,* Wiley-VCH (2008).

Knoll, A.H., The early evolution of eukaryotes: A geological perspective, *Science* **256,** 622–627 (1992).

Lahav, N., *Biogenesis. Theories of Life's Origins,* Oxford University Press (1999).

Lazcano, A. and Miller, S.L., The origin and early evolution of life: Prebiotic chemistry, the pre-RNA world, and time, *Cell* **85,** 793–798 (1996); Bada, J.L. and Lazcano, A., Prebiotic soup—Revisiting the Miller experiment, *Science* **300,** 745–746 (2003); *and* Johnson, A.P., Cleaves, H.J., Dworkin, J.P., Glavin, D.P., Lazcano, A., and Bada, J.L., The Miller volcanic spark discharge experiment, *Science* **322,** 404 (2008).

Lifson, S., On the crucial stages in the origin of animate matter, *J. Mol. Evol.* **44,** 1–8 (1997).

Lurquin, P.F., *The Origins of Life and the Universe,* Columbia University Press (2003).

McNichol, J., Primordial soup, fool's gold, and spontaneous generation, *Biochem. Mol. Biol. Ed.* **36,** 255–261 (2008). [A brief introduction to the theory, history, and philosophy of the search for the origin of life.]

Mojzsis, S.J., Arrhenius, G., McKeegan, K.D., Harrison, T.M., Nutman, A.P., and Friend, C.R.L., Evidence for life on Earth before 3,800 million years ago, *Nature* **384,** 55–57 (1996).

Orgel, L.E., The origin of life—a review of facts and speculations, *Trends Biochem. Sci.* **23,** 491–495 (1998). [Reviews the most widely accepted hypotheses on the origin of life and discusses the evidence supporting them and their difficulties.]

Schopf, J.W., Fossil evidence of Archean life, *Philos. Trans. R. Soc. B* **361,** 869–885 (2006).

Shapiro, R., *Origins. A Skeptic's Guide to the Creation of Life on Earth,* Summit Books (1986). [An incisive and entertaining critique of the reigning theories of the origin of life.]

PROBLEMS

It is very difficult to learn something well without somehow participating in it. The chapter-end problems are therefore an important part of this book. They contain few problems of the regurgitation type. Rather they are designed to make you think and to offer insights not discussed in the text. Their difficulties range from those that require only a few moments' reflection to those that might take an hour or more of concentrated effort to work out. The more difficult problems are indicated by a leading asterisk (*). The answers to the problems are worked out in detail in the *Solutions Manual to Accompany Biochemistry* (4th ed.) by Donald Voet and Judith G. Voet. You should, of course, make every effort to work out a problem before consulting the *Solutions Manual.*

1. Under optimal conditions for growth, an *E. coli* cell will divide around every 20 min. If no cells died, how long would it take a single *E. coli* cell, under optimal conditions in a 10-L culture flask, to reach its maximum cell density of 10^{10} cells · mL^{-1} (a "saturated" culture)? Assuming that optimum conditions could be maintained, how long would it take for the total volume of the cells alone to reach 1 km^3? (Assume an *E. coli* cell to be a cylinder 2 μm long and 1 μm in diameter.)

2. Without looking them up, draw schematic diagrams of a bacterial cell and an animal cell. What are the functions of their various organelles? How many lines of descent might a typical animal cell have?

3. Compare the surface-to-volume ratios of a typical *E. coli* cell (its dimensions are given in Problem 1) and a spherical eukaryotic cell that is 20 μm in diameter. How does this difference affect the lifestyles of these two cell types? In order to improve their ability to absorb nutrients, the **brush border cells** of the intestinal epithelium have velvetlike patches of **microvilli** facing into the intestine. How does the surface-to-volume ratio of this eukaryotic cell change if 20% of its surface area is covered with cylindrical microvilli that are 0.1 μm in diameter, 1 μm in length, and occur on a square grid with 0.2-μm center-to-center spacing?

4. Many proteins in *E. coli* are normally present at concentrations of two molecules per cell. What is the molar concentration of such a protein? (The dimensions of *E. coli* are given in Problem 1.) Conversely, how many glucose molecules does an *E. coli* cell contain if it has an internal glucose concentration of 1.0 m*M*?

5. The DNA of an *E. coli* chromosome measures 1.6 mm in length, when extended, and 20 Å in diameter. What fraction of an *E. coli* cell is occupied by its DNA? (The dimensions of *E. coli* are given in Problem 1.) A human cell has some 700 times the DNA of an *E. coli* cell and is typically spherical with a diameter of 20 μm. What fraction of such a human cell is occupied by its DNA?

***6.** A new planet has been discovered that has approximately the same orbit about the sun as Earth but is invisible from Earth because it is always on the opposite side of the sun. Interplanetary probes have already established that this planet has a significant atmosphere. The National Aeronautics and Space Administration is preparing to launch a new unmanned probe that will land on the surface of the planet. Outline a simple experiment for this lander that will test for the presence of life on the surface of this planet (assume that the life-forms, if any, on the planet are likely to be microorganisms and therefore unable to walk up to the lander's video cameras and say "Hello").

7. It has been suggested that an all-out nuclear war would so enshroud Earth with clouds of dust and smoke that the entire surface of the planet would be quite dark and therefore intensely cold (well below 0°C) for several years (the so-called nuclear winter). In that case, it is thought, eukaryotic life would die out and bacteria would inherit Earth. Why?

8. One method that Mendel used to test his laws is known as a **testcross.** In it, F_1 hybrids are crossed with their recessive parent. What is the expected distribution of progeny and what are their phenotypes in a testcross involving peas with different-colored seeds? What is it for snapdragons with different flower colors (use the white parent in this testcross)?

9. The disputed paternity of a child can often be decided on the basis of blood tests. The M, N, and MN blood groups (Section 12-3E) result from two alleles, L^M and L^N; the Rh^+ blood group arises from a dominant allele, *R*. Both sets of alleles occur on a different chromosome from each other and from the alleles responsible for the ABO blood groups. The following table gives the

blood types of three children, their mother, and the two possible fathers. Indicate, where possible, each child's paternity and justify your answer.

Child 1	B	M	Rh^-
Child 2	B	MN	Rh^+
Child 3	AB	MN	Rh^+
Mother	B	M	Rh^+
Male 1	B	MN	Rh^+
Male 2	AB	N	Rh^+

10. The most common form of color blindness, red–green color blindness, afflicts almost only males. What are the genotypes and phenotypes of the children and grandchildren of a red–green color-blind man and a woman with no genetic history of color blindness? Assume the children mate with individuals who also have no history of color blindness.

11. Green and purple photosynthetic bacteria are thought to resemble the first organisms that could carry out photosynthesis. Speculate on the composition of Earth's atmosphere when these organisms first arose.

12. Explore your local biochemistry library (it may be disguised as a biology, chemistry, or medical library). Locate where the current periodicals, the bound periodicals, and the books are kept. Browse through the contents of a current major biochemistry journal, such as *Biochemistry, Cell,* or *Proceedings of the National Academy of Sciences,* and pick a title that interests you. Scan the corresponding paper and note its organization. Likewise, peruse one of the articles in the latest volume of *Annual Review of Biochemistry.*

13. Using MedLine, look up the publications over the past 5 years of your favorite biomedical scientist. This person might be a recent Nobel prize winner or someone at your college/university. Note that even if the person you choose has an unusual name, it is likely that publications by other individuals with the same name will be included in your initial list.