MOLECULAR BIOLOGY OF
THE CELL

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"Long ago it became evident that the key to every biological problem must finally be sought in the cell, for every living organism is, or at sometime has been, a cell."

Edmund B. Wilson
The Cell in Development and Heredity
3rd edition, 1925, Macmillan, Inc.

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Cover photograph kindly provided by Michael Verderame and Robert Pollack of Columbia University. The fluorescein-phalloidin used to stain the actin cables was the generous gift of Drs. Theodor Wieland and A. Deboben of the Max Planck Institute, West Germany. The photograph is of a mouse fibroblast that had been transformed to anchorage-independent growth by the virus Simian Virus 40 (SV40) and subsequently selected for anchorage-dependent growth. This particular cell was stained for SV40 large T antigen (*red*) and fluorescein-phalloidin (*green*), which specifically stains F actin.

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1 The Evolution of the Cell

All living creatures are made of cells—small membrane-bounded compartments filled with a concentrated aqueous solution of chemicals. The simplest forms of life are solitary cells that propagate by dividing in two. Higher organisms, such as ourselves, are like cellular cities in which groups of cells perform specialized functions and are linked by intricate systems of communication. In a sense, cells are halfway between molecules and man. We study them to learn, on the one hand, how they are made from molecules and, on the other, how they cooperate to make an organism as complex as a human being.

All organisms, and all of the cells that constitute them, are believed to have descended from a common ancestor cell by *evolution*. Evolution involves two essential processes: (1) the occurrence of random *variation* in the genetic information passed from an individual to its descendants and (2) the *selection* of genetic information that helps its possessors to survive and propagate. Evolution is the central principle of biology, helping us to make sense of the bewildering variety in the living world.

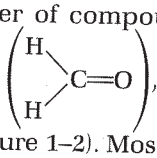
This chapter, like the book as a whole, is concerned with the progression from molecules to multicellular organisms. It discusses the evolution of the cell, first as a living unit constructed from smaller parts, and then as a building block for larger structures. Through evolution, we introduce the cell components and activities that are to be treated in detail, in broadly similar sequence, in the chapters that follow. Beginning with the origins of the first cell on earth, we consider how the properties of certain types of large molecules allow hereditary information to be transmitted and expressed, and permit evolution to occur. Enclosed in a membrane, these molecules provide the essentials of a self-replicating cell. Following this, we describe the major transition that occurred in the course of evolution, from small bacteriumlike cells to much larger and more complex cells such as are found in present-day plants and animals. Lastly, we suggest ways in which single free-living cells might have given rise to large multicellular organisms, becoming specialized and cooperating in the formation of such intricate organs as the brain.

Clearly, there are dangers in an evolutionary approach: the large gaps in our knowledge can be filled only by speculations that are likely to be wrong in many details. But there is enough evidence from fossils and from comparative studies of present-day organisms and molecules to allow us to make intelligent guesses about the major stages in the evolution of life.

From Molecules to the First Cell[1]

Simple Biological Molecules Can Form Under Prebiotic Conditions

The conditions that existed on the earth in its first billion years are still a matter of dispute. Was the surface initially molten? Did the atmosphere contain ammonia, or methane? Everyone seems to agree, however, that the earth was a violent place with volcanic eruptions, lightning, and torrential rains. There was little if any free oxygen and no layer of ozone to absorb the harsh ultraviolet radiation from the sun.

Simple organic molecules (that is, molecules containing carbon) are likely to have been produced under such conditions. The best evidence for this comes from laboratory experiments. If mixtures of gases such as CO_2, CH_4, NH_3, and H_2 are heated with water and energized by electrical discharge or by ultraviolet radiation, they react to form small organic molecules—usually a rather small selection, each made in large amounts (Figure 1–1). Among these products are a number of compounds, such as hydrogen cyanide (H—C≡N) and formaldehyde  , that readily undergo further reactions in aqueous solution (Figure 1–2). Most important, the four major classes of small organic molecules found in cells—*amino acids, nucleotides, sugars,* and *fatty acids*—are generated.

While such experiments cannot reproduce the early conditions on the earth exactly, they make it plain that the formation of organic molecules is surprisingly easy. And the developing earth had immense advantages over any human experimenter; it was very large and could produce a wide spectrum of conditions. But above all, it had much more time—hundreds of millions of years. In such circumstances it seems very likely that, at some time and place, many of the simple organic molecules found in present-day cells accumulated in high concentrations.

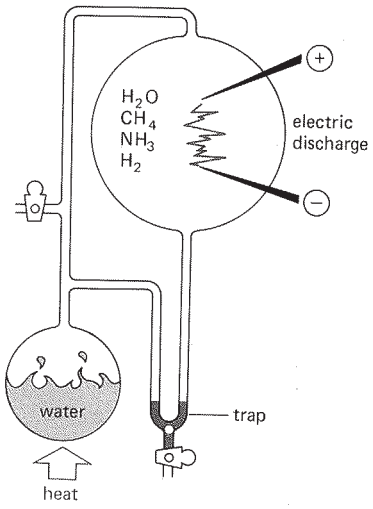


Figure 1–1 A typical experiment simulating conditions on the primitive earth. Water is heated in a closed apparatus containing CH_4, NH_3, and H_2, and an electric discharge is passed through the vaporized mixture. Organic compounds accumulate in the U-tube trap.

HCHO	formaldehyde
CH_3COOH	acetic acid
NH_2CH_2COOH	glycine
HCOOH	formic acid
$CH_3CH(OH)COOH$	lactic acid
$NH_2CH(CH_3)COOH$	alanine
$NH(CH_3)-CH_2COOH$	sarcosine
H − C ≡ N	hydrogen cyanide
$NH_2-C(=O)-NH_2$	urea
$NH_2CH(CH_2COOH)COOH$	aspartic acid

Figure 1–2 A few of the compounds that might be formed in the experiment described in Figure 1–1. Compounds shown in color are important components of present-day living cells.

Polynucleotides Are Capable of Directing Their Own Synthesis

Simple organic molecules such as amino acids and nucleotides can associate to form large *polymers.* One amino acid can join with another by forming a peptide bond, while two nucleotides can join together by a phosphodiester bond. The repetition of these reactions leads to linear polymers known as **polypeptides** and **polynucleotides,** respectively. In present-day living organisms, polypeptides—known as *proteins*—and polynucleotides—in the form of both *ribonucleic acids* (*RNA*) and *deoxyribonucleic acids* (*DNA*)—are commonly viewed as the most important constituents. A restricted set of 20 amino acids constitute the universal building blocks of the proteins, while RNA and DNA molecules are constructed from four types of nucleotides each. One can only speculate as to why these particular sets of monomers should have been selected for biosynthesis in preference to others that are chemically similar.

The earliest polymers may have formed in several ways—for example, by the heating of dry organic compounds or by the catalytic activity of high concentrations of inorganic polyphosphates. The products of similar reactions in the test tube are polymers of variable length and random sequence in which the amino acid or nucleotide added at any point depends mainly on chance (Figure 1–3). However, once a polymer has formed, it is able to influence the formation of other polymers. Polynucleotides, in particular, have the ability to specify the sequence of nucleotides in new polynucleotides by acting as *templates* for the polymerization reactions. For example, a polymer composed of one nucleotide (polyuridylic acid, or poly U) can serve as a template for the synthesis of a second polymer composed of another type of nucleotide (polyadenylic acid, or poly A). Such templating depends on the fact that one polymer preferentially binds the other. By lining up the subunits required to make poly A along its surface, poly U promotes the formation of poly A (Figure 1–4).

Specific pairing between complementary nucleotides probably played a crucial part in the origin of life. Consider, for example, a polynucleotide such as RNA, made of a string of four nucleotides, containing the bases uracil (U), adenine (A), cytosine (C), and guanine (G). Because of complementary pairing between the bases A and U and between the bases G and C, when RNA is added to a mixture of activated nucleotides under conditions that favor polymerization, new RNA molecules are produced in which nucleotides are joined in a sequence that is complementary to the first. That is, the new molecules are rather like a mold of the original, with each A in the original corresponding to a U in the copy, and so on. The sequence of nucleotides in the original RNA strand contains information that is, in essence, preserved in the newly formed complementary strands. A second round of copying, with the complementary strand as a template, restores the original sequence (Figure 1–5).

Such *complementary templating* mechanisms are elegantly simple, and they lie at the heart of information-transfer processes in biological systems. Genetic information contained in every cell is encoded in the sequences of nucleotides in its polynucleotide molecules, and this information is passed on (inherited) from generation to generation by means of complementary base-pairing interactions.

Rapid formation of polynucleotides in a test tube requires the presence of specific protein catalysts, or *enzymes*, which would not have been present in the "prebiotic soup." However, less efficient catalysts in the form of minerals or metal ions would have been present; and, in any case, catalysts only speed up reactions that would occur anyway given sufficient time. Since both time and a supply of chemically reactive nucleotide precursors were available in abundance, it is likely that slowly replicating systems of polynucleotides became established in the prebiotic conditions on earth.

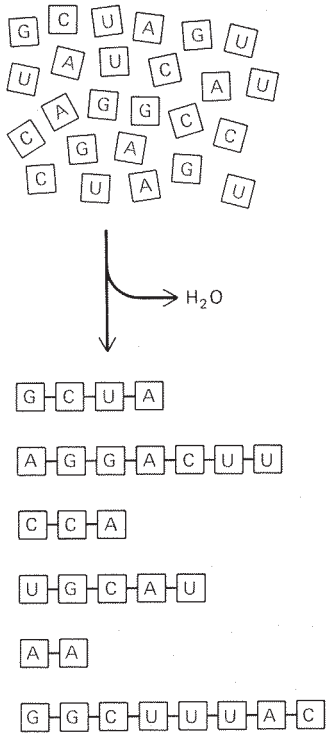
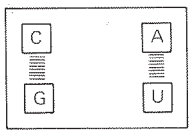


Figure 1–3 Nucleotides of four kinds (here represented by the single letters A, U, G, and C) can undergo spontaneous polymerization with the loss of water. The product is a mixture of polynucleotides that are random in length and sequence.



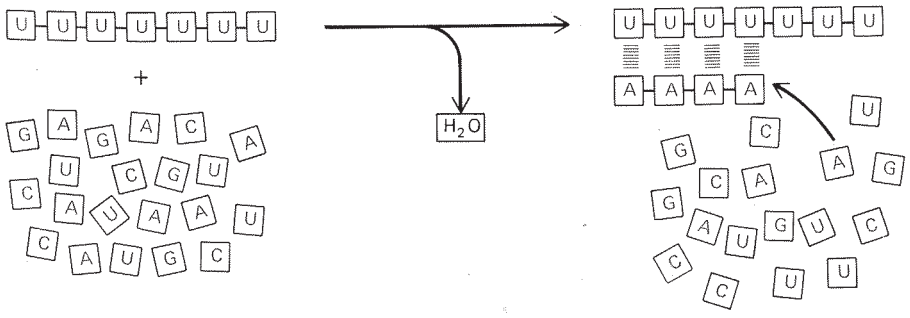


Figure 1–4 Preferential binding occurs between pairs of nucleotides (C with G and A with U) by relatively weak chemical bonds (*above*). This pairing enables one polynucleotide to act as a template for the synthesis of another (*left*).

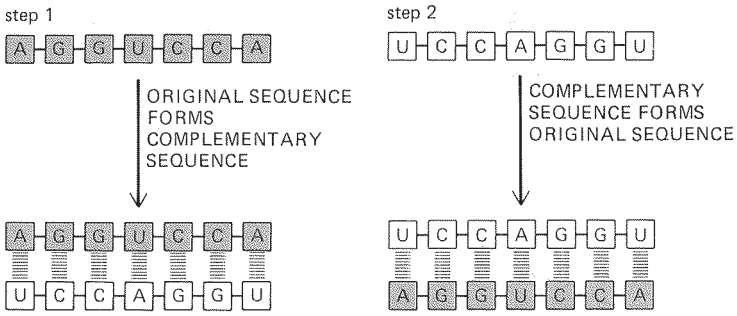


Figure 1–5 Replication of a polynucleotide sequence (here an RNA molecule). In step 1, the original RNA molecule acts as a template to form an RNA molecule of complementary sequence. In step 2, this complementary RNA molecule itself acts as a template, forming RNA molecules of the original sequence. Since each templating molecule can produce many copies of the complementary strand, these reactions can result in the "multiplication" of the original sequence.

Self-replicating Molecules Undergo Natural Selection

Under favorable conditions, a polynucleotide molecule in a rich soup of nucleotides is able to multiply, with each copy of the original serving as the parent for new copies. However, many errors will inevitably occur in the copying process, especially under primordial conditions. New and imperfect copies of the original will be propagated. In time, therefore, the sequence of nucleotides in the original polynucleotide molecule will change until the information it once represented is entirely lost (Figure 1–6).

But polynucleotides are not just strings of symbols that carry information in an abstract way. They have chemical personalities that affect their behavior. The specific sequence of nucleotides governs the properties of the whole molecule, especially how it folds up in solution. Just as the nucleotides in a polynucleotide can pair with free complementary nucleotides in their environment to form a new polymer, so they can pair with complementary nucleotide residues within the polymer itself. A sequence GGGG in one part of a polynucleotide chain can form a relatively strong association with a CCCC sequence in another region of the molecule. Such associations produce various three-dimensional folds, and the molecule as a whole takes on a unique shape that depends entirely on the sequence of its nucleotides (Figure 1–7).

The three-dimensional folded structure of a polynucleotide affects both its stability and its ability to replicate, so that not all polynucleotide shapes will be equally successful in a replicating mixture. Some will be too long or too tightly folded to act as efficient templates. Others might be unstable under the prevailing conditions. In fact, it has been demonstrated in laboratory studies that replicating systems of RNA molecules undergo a form of natural selection and that different favorable sequences will eventually predominate, depending on the exact conditions.

A polynucleotide such as an RNA molecule therefore has two important characteristics: it carries information encoded in its nucleotide sequence that it passes on by the process of replication, and it has a unique folded structure that determines how it will function and respond to external conditions. These two features—one informational, the other functional—are the two essential ingredients required for evolution to occur. The nucleotide sequence of an RNA molecule is analogous to the hereditary information, or *genotype*, of an organism. The folded three-dimensional structure is analogous to the *phenotype*—the expression of the hereditary information upon which natural selection operates.

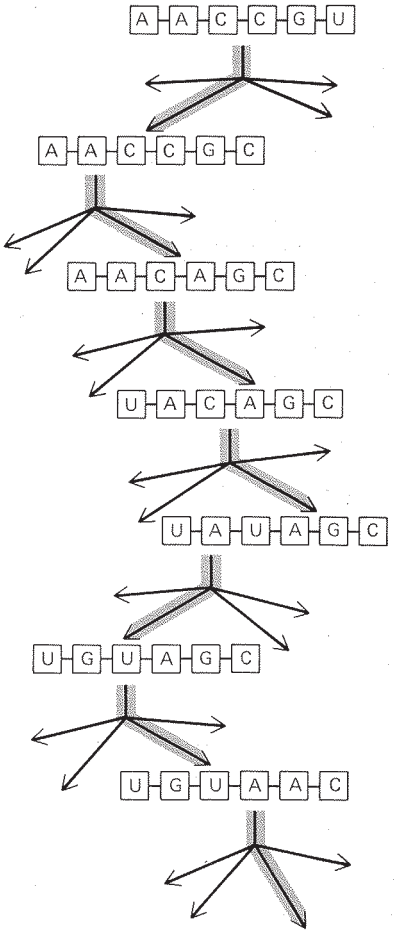


Figure 1–6 Changes in the sequence of an RNA molecule can occur through errors in replication. Here a particular "lineage" is traced in color showing how the RNA sequence AACCGU changes progressively to UGUAAC through a series of copying errors. Many other sequences will be generated at the same time, as indicated by the multiple arrows.

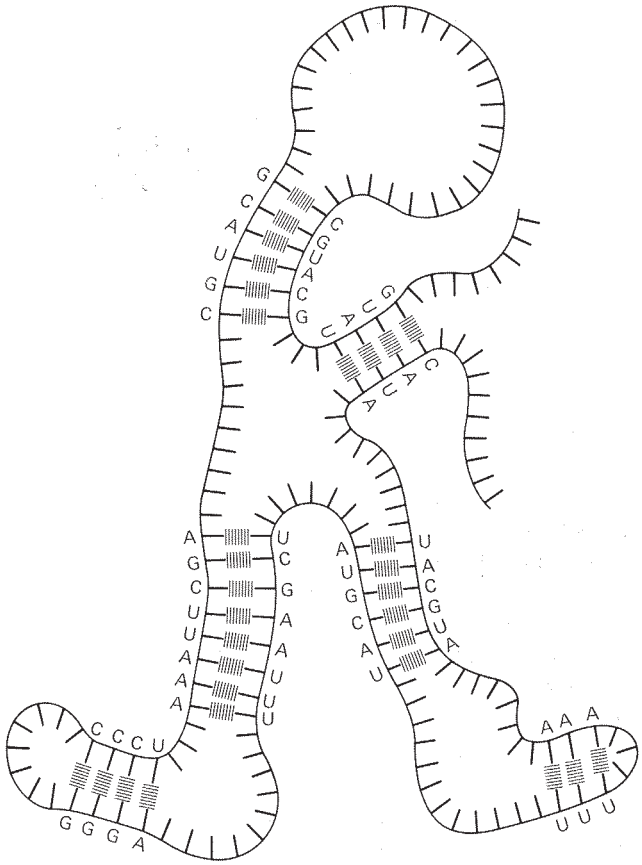


Figure 1–7 Nucleotide pairing between different regions of the same polynucleotide (RNA) chain causes the molecule to adopt a distinctive shape.

Information Flows from Polynucleotides to Polypeptides

The suggestion, therefore, is that between 3.5 and 4 billion years ago, somewhere on earth, self-replicating systems of polynucleotides began the process of evolution. Polymers with different nucleotide sequences competed for the available precursor materials to construct copies of themselves, just as organisms now compete; success depended on the accuracy and the speed with which the copies were made and on the stability of those copies.

However, while the structure of polynucleotides is well suited for information storage and replication, these molecules are not sufficiently versatile to provide all the structural and functional building blocks of a living cell. Polypeptides, on the other hand, are composed of many different amino acids, and, as will be discussed in Chapter 3, their diverse three-dimensional forms, which often bristle with reactive sites, make them ideally suited to a wide range of structural and chemical tasks. Even random polymers of amino acids produced by prebiotic synthetic mechanisms are likely to have had catalytic properties, some of which could have enhanced the replication of RNA molecules. Some classes of polypeptides would therefore have been extremely useful to a replicating system, especially if they could be tailor-made. Polynucleotides that helped guide the synthesis of specific polypeptides in their environment would have had a great advantage in the evolutionary struggle for survival (Figure 1–8).

Yet how could polynucleotides exert such control? How could the information encoded in their sequence specify the sequences of polymers of a different type? In present-day organisms, RNA directs the synthesis of polypeptides—that is, **protein synthesis**—but it is a process that requires remarkably elaborate biochemical machinery. One RNA molecule carries the

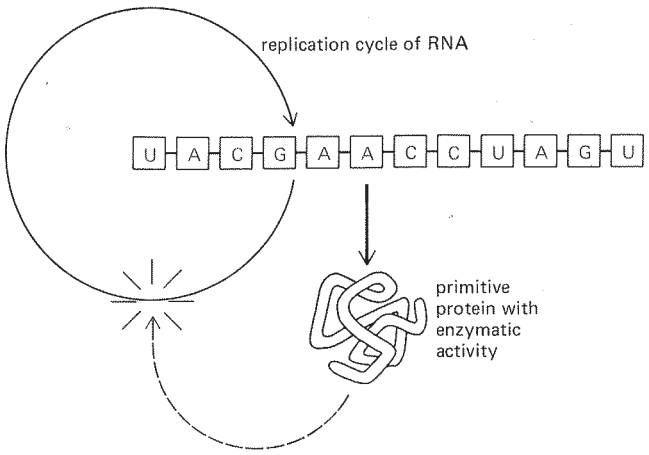


Figure 1–8 Proteins can act as efficient catalysts of chemical reactions such as the formation of nucleotides or their polymerization into RNA. Therefore, an RNA molecule that can direct the synthesis of an appropriate protein is able to accelerate its own replication, as illustrated schematically here.

genetic information for a particular polypeptide, while a set of other RNA molecules bind amino acids; the two types of RNA molecules form complementary base pairs with one another to enable sequences of nucleotides in the informational RNA molecule to direct the incorporation of specific amino acids into a growing polypeptide chain. Assembly of new proteins takes place on the surface of *ribosomes*—complex particles composed of several large RNA molecules and more than 50 different types of protein. How such a complex mechanism arose in evolution is still a mystery, although pieces of the puzzle are falling into place. One of the most fascinating sources of evidence is the genetic "dictionary," or *genetic code,* by which nucleotide triplets are translated into amino acids. Since the code is essentially the same in all living organisms, it must have become fixed at a very early stage in evolution, and it is likely to contain traces of the way that primordial translation was achieved.

Whatever the preliminary steps of evolution may have been, once RNA molecules were able to direct the synthesis of proteins, they had potentially at their disposal an enormous workshop of chemical tools. It was now possible in principle to synthesize enzymes that could catalyze a large range of chemical reactions, including the synthesis of more proteins and RNA molecules. Once the evolution of nucleic acids had thus advanced to the point of specifying enzymes to aid in their own manufacture, the proliferation of the replicating system would have been immensely speeded up. The potentially explosive nature of such an autocatalytic process can be seen today in the life cycle of some bacterial viruses: after they have entered a bacterium, such viruses direct the synthesis of proteins that catalyze selectively their own replication, so that within a short time they take over the entire cell (Figures 1–9 and 1–10).

Membranes Defined the First Cell

The appearance of protein synthesis controlled by nucleic acids was no doubt one of the crucial events leading to the formation of the first cell. Another must have been the development of an outer membrane. The proteins synthesized under the control of a certain species of RNA would not facilitate reproduction of that species of RNA unless they were retained in the neighborhood of the RNA; moreover, as long as these proteins were free to diffuse among the population of replicating RNA molecules, they could benefit equally any competing species of RNA that might be present. If a variant RNA arose that made a superior type of enzyme, the new enzyme could not contribute *selectively* to the survival of the variant RNA in its competition with its fellows. Selection of RNA molecules according to the quality of the proteins that they

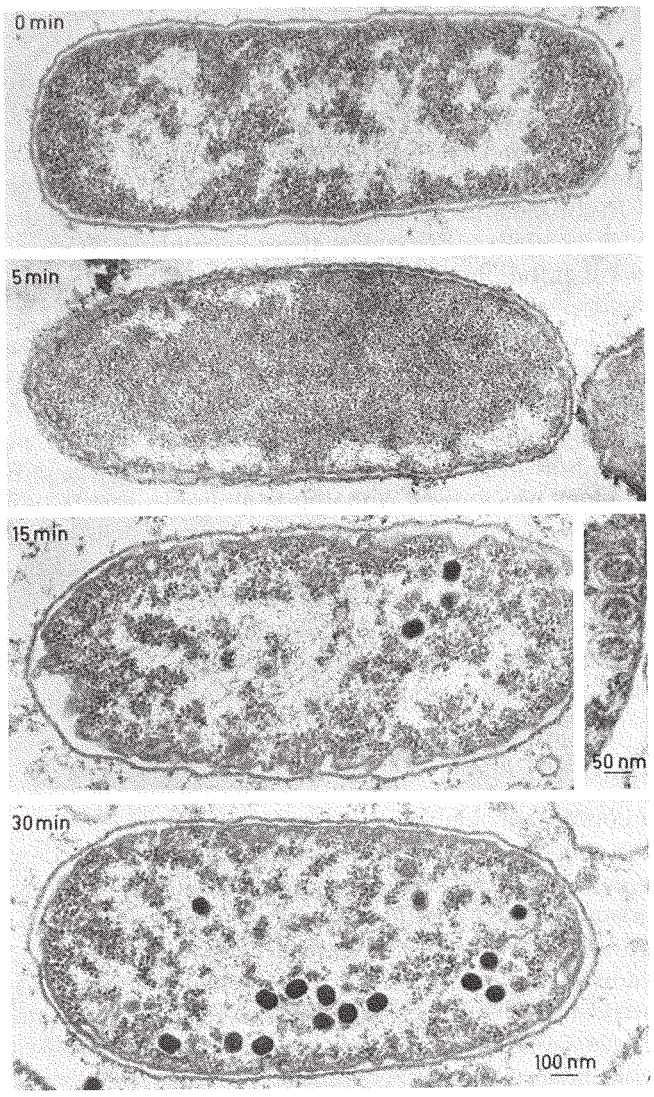
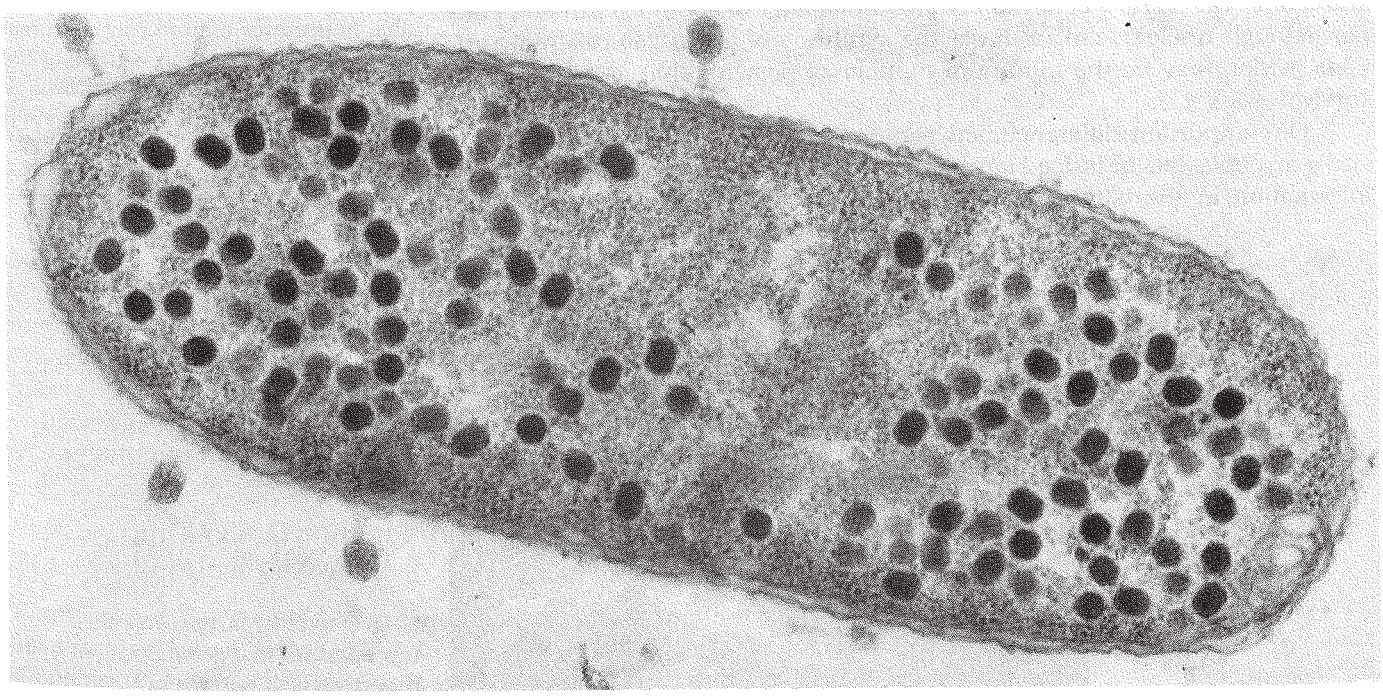


Figure 1–9 Sequence of electron micrographs showing the growth of a virus inside a bacterial cell. Infection begins when the virus attaches to the outside of the bacterium (see also Figure 1–10) and injects its DNA into the bacterial cell. Within 5 minutes, this DNA has directed the synthesis of a set of specific proteins, some of which degrade the DNA of the host bacterium, while others catalyze the replication of the viral DNA. The dense particles seen in the cell 15 minutes after infection are immature virus particles consisting of viral DNA packed into spherical shells of protein (the shells are first made separately, as shown in the inset). Virus particles continue to mature and accumulate in the cell, as seen in the 30-minute specimen. (Courtesy of E. Kellenberger.)

Figure 1–10 A higher magnification micrograph of a bacterial cell that has been infected with virus particles for more than an hour. The infectious cycle is almost complete, and the bacterial cell is about to burst open, releasing several hundred new infective virus particles to the surroundings. The virus shown in this micrograph and in the micrographs of Figure 1–9 is bacteriophage T4. (Courtesy of E. Kellenberger.)



generated could not begin until some form of compartment evolved to contain the proteins made by an RNA molecule and thereby make these proteins primarily available for its own use (Figure 1–11).

All present-day cells are surrounded by a **plasma membrane,** composed of phospholipids and proteins. In the electron microscope such membranes appear as sheets about 7 nm thick, with a distinctive three-layered appearance due to the tail-to-tail packing of the phospholipid molecules. Artificial membranes with a very similar appearance can be made in the test tube simply by mixing phospholipids and water together. Under suitable conditions such artificial membranes round up into closed vesicles with diameters between 1 and 10 μm. Although these vesicles are inert, like soap bubbles, it is easy to imagine that by enclosing a distinct population of molecules they could form a spatially isolated functional unit.

It has been postulated that the first cell was formed when phospholipid molecules in the prebiotic soup spontaneously assembled into such membranous structures, enclosing a self-replicating mixture of RNA and protein molecules. Once sealed within a closed membrane, RNA molecules could begin to evolve, not merely on the basis of their own structure, but also according to the proteins they could make: the nucleotide sequences of the RNA molecules could now become expressed in the character of the cell as a whole.

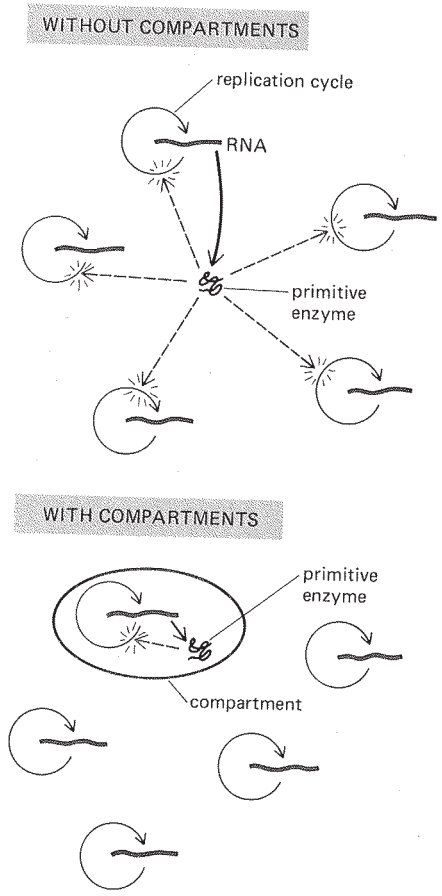


Figure 1–11 Schematic drawing showing the evolutionary advantage of cell-like compartments. In a mixed population of self-replicating RNA molecules capable of protein synthesis (as illustrated in Figure 1–8), any improved form of RNA that is able to produce a more useful protein must share this protein with all of its competitors. However, if the RNA is enclosed within a compartment, such as a lipid membrane, then any protein it makes is confined for its own use; the RNA can therefore be selected on the basis of its making a better protein.

Mycoplasmas Are the Simplest Living Cells

The picture we have presented is, of course, speculative: there are no fossil records that trace the origins of the first cell. Nevertheless, there is persuasive evidence from present-day organisms, and from experiments, that the broad features of this evolutionary story are correct. The prebiotic synthesis of small molecules, the self-replication of RNA molecules, the translation of RNA sequences into amino acid sequences, and the assembly of lipid molecules to form membrane-bounded compartments—all presumably occurred to generate the first cell 3.5 or 4 billion years ago.

It is useful to compare this putative first cell with the simplest present-day cells, the **mycoplasmas.** Mycoplasmas are small bacteriumlike organisms that normally lead a parasitic existence in close association with animal and plant cells (Figure 1–12). Some have a diameter of about 0.3 μm and contain enough nucleic acid to direct the synthesis of about 750 different proteins, which may be the minimum number of proteins that a cell needs to survive.

One important difference between the first cell as we have described it and a mycoplasma (or indeed any other present-day cell) is that the hereditary information in the latter is stored in DNA rather than RNA. Both types of

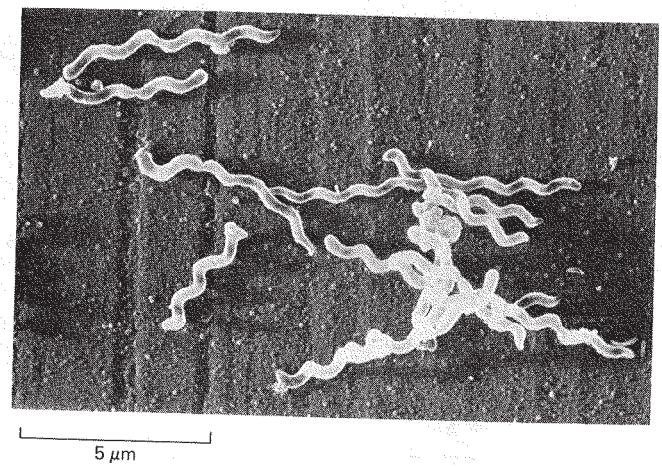


Figure 1–12 *Spiroplasma citrii,* a mycoplasma that grows in plant cells. (Courtesy of J. Burgess.)

polynucleotides are found in present-day cells, but they function in a collaborative manner, each having evolved to perform specialized tasks. Small chemical differences fit the two kinds of molecules for distinct functions. DNA serves as the permanent repository of genetic information. Unlike RNA, it exists principally in a double-stranded form composed of a pair of complementary polynucleotide molecules. Not only is genetic information that is stored in this way made more stable, but the double-stranded arrangement permits the operation of a repair mechanism: an intact strand serves as the template for the correction or repair of an associated damaged strand. DNA guides the synthesis of specific RNA molecules, again by the principle of complementary base-pairing, though now this pairing is between slightly different types of nucleotides. The resulting single-stranded RNA molecules then perform the two other primeval functions: they direct protein synthesis and in some situations they have a structural role not unlike that of proteins.

In addition to its various classes of polynucleotides, the mycoplasma cell contains many enzymes and structural proteins, some in its interior and some embedded in its membrane; these together synthesize essential small molecules that are not provided in the environment, redistribute the energy needed to drive biosynthetic reactions, and maintain appropriate chemical conditions inside the cell. The evolution of these latter metabolic functions will be discussed in the following section.

Summary

Living cells probably arose on earth by the spontaneous aggregation of molecules about 3.5 billion years ago. From our knowledge of present-day organisms and the molecules they contain, it seems that at least three steps must have occurred before the first cell emerged: (1) polymers of RNA capable of directing their own replication through complementary base-pairing interactions had to be formed; (2) mechanisms by which an RNA molecule could direct the synthesis of a protein had to be developed; and (3) a lipid membrane had to assemble to enclose the self-replicating mixture of RNA and protein molecules. At some later stage in the evolutionary process, DNA took the place of RNA as the hereditary material.

From Procaryotes to Eucaryotes[2]

It is thought that all organisms living now on earth derive from one single primordial cell born several billion years ago. This cell, outreproducing its competitors, took the lead in the process of cell division and evolution that would eventually cover the earth in green, change the composition of its atmosphere, and make it the home of intelligent life. The family resemblances between all organisms seem too strong to be explained in any other way. One important landmark along this evolutionary road occurred about 1.5 billion years ago, when there was a transition from small cells with a relatively simple internal structure—the so-called **procaryotes,** which include the various types of bacteria—to the larger and radically more complex *eucaryotic* cells such as are found in higher animals and plants.

Procaryotic Cells Are Structurally Simple But Biochemically Diverse

Bacteria are the simplest organisms found in most natural environments. They are spherical or rod-shaped cells, commonly several μm in linear dimension (Figure 1–13). They often possess a tough protective coat, called a

cell wall, beneath which a plasma membrane encloses a single cytoplasmic compartment containing DNA, RNA, proteins, and small molecules. In the electron microscope this cell interior appears as a more or less uniform matrix (see top panel of Figure 1–9).

Bacteria are small and can replicate quickly by simply dividing in two by *binary fission.* When food is plentiful, "survival of the fittest" generally means survival of those that can divide the fastest. Under optimal conditions, a single procaryotic cell can divide every 20 minutes and thereby give rise to 4 billion cells (approximately equal to the present human population on earth) in less than 11 hours. The ability to divide quickly enables populations of bacteria to adapt rapidly to changes in their environment. Under laboratory conditions, for example, a population of bacteria maintained in a large vat will evolve within a few weeks by spontaneous mutation and natural selection to utilize new types of sugar molecules as a carbon source.

In nature, bacteria live in an enormous variety of ecological niches, and they show a corresponding richness in their underlying biochemical composition. Two distantly related groups can be recognized: the *eubacteria,* which are the commonly encountered forms that inhabit soil, water, and living organisms; and the *archaebacteria,* which are found in such incommodious environments as bogs, ocean depths, salt brines, and hot acid springs (Figure 1–14).

There exist species of bacteria that can utilize virtually any type of organic molecule as food, including sugars, amino acids, fats, hydrocarbons, polypeptides, and polysaccharides. Some are even able to obtain their carbon atoms from CO_2 and their nitrogen atoms from N_2. Despite their relative simplicity, bacteria have survived for longer than any other organisms and still constitute the most abundant type of cell on earth.

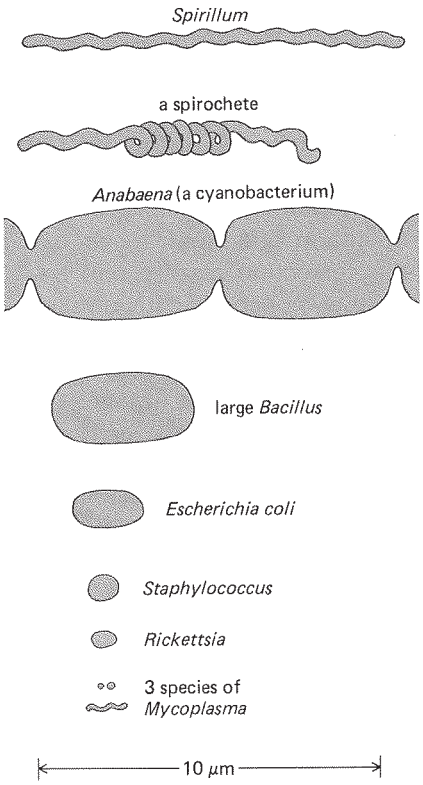


Figure 1–13 Some procaryotic cells drawn to scale.

Metabolic Reactions Evolve

A bacterium growing in a salt solution containing a single type of carbon source, such as glucose, must carry out a large number of chemical reactions. Not only must it derive from the glucose the chemical energy needed for many vital processes, it must also use the carbon atoms of glucose to synthesize every type of organic molecule that the cell requires. These reactions are catalyzed by hundreds of enzymes working in reaction "chains" so that the product of one reaction is the substrate for the next; such enzymatic chains, called *metabolic pathways,* will be discussed in the following chapter.

Originally, when life began on earth, there was probably little need for such metabolic reactions. Cells could survive and grow on the molecules in their surroundings—a legacy from the prebiotic soup. As these natural resources became exhausted, organisms that had developed enzymes to make

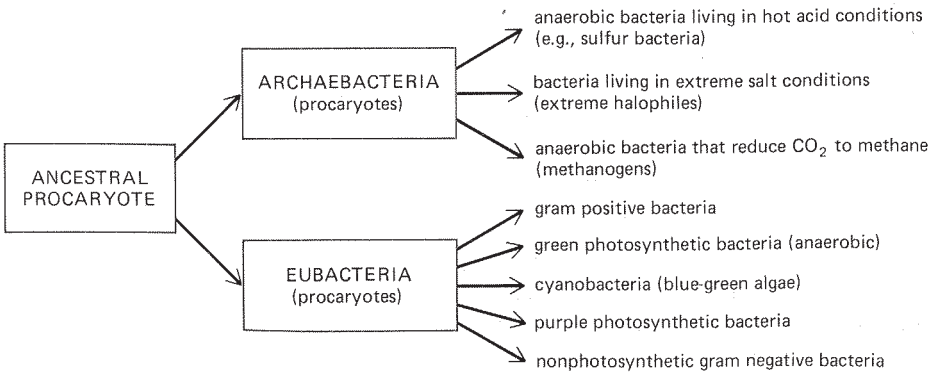


Figure 1–14 Family relationships between present-day bacteria (arrows indicate probable paths of evolution). The origin of eucaryotic cells is discussed later in the text.

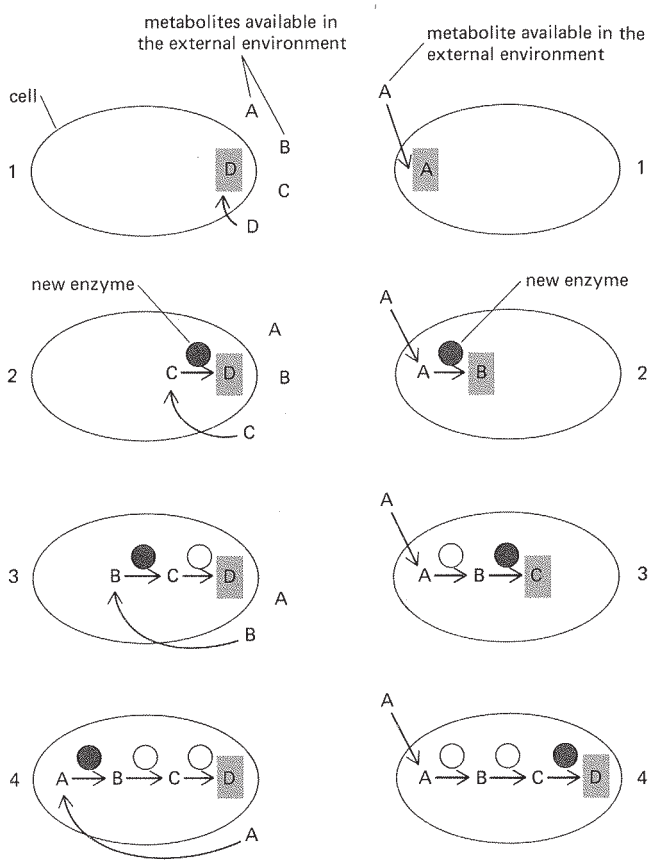


Figure 1–15 Schematic drawing showing two possible ways in which metabolic pathways might have evolved. The cell on the left is provided with a supply of related substances (A, B, C, D) produced by prebiotic synthesis. One of these, substance D, is metabolically useful. As the cell exhausts the available supply of D, a selective advantage is obtained by the evolution of a new enzyme that is able to produce D from the closely related substance C. By a series of similar steps, fundamentally important metabolic pathways may have evolved. On the right, a metabolically useful compound A is available in abundance. An enzyme appears in the course of evolution that, by chance, has the ability to convert substance A to substance B. Other changes then occur within the cell that enable it to make use of the new substance. The appearance of further enzymes can build up a long chain of reactions.

more organic molecules had a strong selective advantage. In this way, the complement of enzymes possessed by cells is thought to have gradually increased, generating the metabolic pathways of present organisms. Two plausible ways in which a metabolic pathway could arise in evolution are illustrated in Figure 1–15.

If metabolic reactions evolved by the sequential addition of new enzymatic reactions to existing ones, the most ancient reactions should, like the oldest rings in a tree trunk, be closest to the center of the "metabolic tree," where the most fundamental of the basic molecular building blocks are synthesized. This position in metabolism is firmly occupied by the transitions involving sugar phosphates, among which the most centrally placed of all is probably the sequence of reactions known as **glycolysis,** by which glucose can be degraded in the absence of oxygen (that is, *anaerobically*). The oldest metabolic pathways would have had to be anaerobic because there was no oxygen in the atmosphere of the primitive earth. Glycolysis occurs in virtually every living cell and drives the formation of the compound *adenosine triphosphate,* or *ATP,* which is used by all cells as a source of readily available chemical energy.

Connecting to the centrally placed reactions of sugar phosphates are hundreds of other chemical reactions. Some of these are responsible for the synthesis of small molecules, many of which in turn are utilized in further reactions to make the large polymers specific to the organism. Other reactions are used to degrade complex molecules, taken in as food, into simpler chemical units. One of the most striking features of these metabolic reactions is that they take place in all kinds of organisms. Certainly differences exist: the amino acid lysine is made in different ways in bacteria, in yeasts, and in green plants, and is not made at all in higher animals; and many specialized prod-

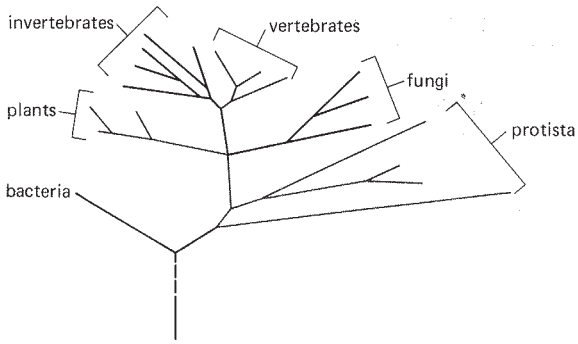


Figure 1–16 Evolutionary relationships of organisms deduced from the amino acid sequences of their cytochrome c (a protein involved in respiration). Each terminal branch of the tree represents a different species, and the total length of branches connecting any two species is proportional to the number of amino acids by which their cytochrome c differs. The evolutionary tree obtained in this way closely resembles that based on evidence from anatomical structures and the fossil record. (From M. O. Dayhoff and R. M. Schwartz. *Ann. N.Y. Acad. Sci.* 361:92–104, 1981.)

ucts of metabolism are restricted to certain genera or species. But in broad terms the majority of reactions and most of the enzymes that catalyze them are found in all living things, from bacteria to man; for this reason they are believed to have been present in the primitive ancestral cells that gave rise to all of these organisms.

The enzymes that catalyze the fundamental metabolic reactions, while continuing to serve the same essential functions, have undergone progressive modifications as organisms have evolved into divergent forms. For this reason, the amino acid sequence of the same type of enzyme in different living species provides an extremely valuable indication of the evolutionary relationship between these species (Figure 1–16). The evidence obtained closely parallels that from other sources, such as the fossil record. An even richer source of information is locked in the living cell in the sequences of nucleotides in DNA. Recently developed methods of analysis enable these *DNA sequences* to be determined in large numbers and compared between species; it is expected that they will enable the course of evolution to be followed with unprecedented accuracy.

Cyanobacteria Can Fix CO_2 and N_2

If the earliest metabolic steps evolved to fill the gaps in the supply of organic molecules from earlier prebiotic synthesis, what happened when such compounds were exhausted? A strong selective advantage would then belong to those organisms able to utilize carbon and nitrogen atoms (in the form of CO_2 and N_2) from the atmosphere. But while they are abundantly available, CO_2 and N_2 are also very stable. It therefore requires a large amount of energy as well as a number of complicated chemical reactions to convert them to a usable form—that is, into organic molecules, such as simple sugars.

In the case of CO_2, the mechanism that evolved to achieve this transformation was **photosynthesis,** in which radiant energy captured from the sun drives the conversion of CO_2 into organic compounds. The interaction of sunlight with a pigment molecule, *chlorophyll,* excites an electron to a more highly energized state. As the electron drops back to a lower energy level, the energy it gives up drives chemical reactions that are facilitated and directed by protein molecules.

One of the first sunlight-driven reactions was probably the phosphorylation of nucleotides to form the high-energy compound ATP. Another would have been the generation of "reducing power." The carbon and nitrogen atoms in atmospheric CO_2 and N_2 are in an oxidized and inert state. One way to make them more reactive, so that they participate in biosynthetic reactions, is to reduce them, that is, to give them a larger charge of electrons. In the process of reduction, electrons are removed from poor electron donors and transferred to a strong electron donor by chlorophyll in a reaction that requires light; the strong electron donor is then used to reduce CO_2 or N_2.

Comparison of the mechanisms of photosynthesis in various present-day bacteria suggests that one of the first sources of electrons was H_2S, from which the primary waste product would have been elemental sulfur. Much later the more difficult but ultimately more rewarding process of obtaining electrons from H_2O was accomplished, and O_2 began to accumulate in the earth's atmosphere as a waste product.

Cyanobacteria (also known as blue-green algae) are today a major route by which both carbon and nitrogen are converted into organic molecules and thus enter the *biosphere.* They include the most self-sufficient organisms that now exist. Able to "fix" both CO_2 and N_2 into organic molecules, they are, to a first approximation, able to live on water and air alone; the mechanisms by which they do this have probably remained essentially constant for over a billion years.

Bacteria Can Carry Out the Aerobic Oxidation of Food Molecules

Many people today are justly concerned about the environmental consequences of human activities. But in the past other organisms have caused revolutionary changes in the earth's environment (although very much more slowly). Nowhere is this more apparent than in the composition of the earth's atmosphere, which with the advent of photosynthesis has been transformed from a mixture containing practically no molecular oxygen to one in which oxygen represents 21% of the total.

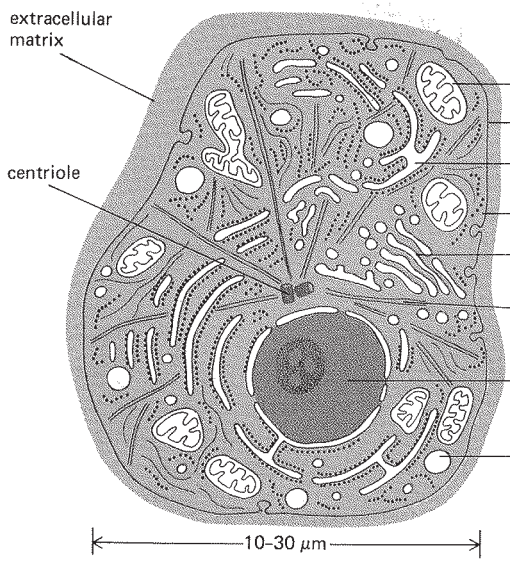
Since oxygen is an extremely reactive chemical that can interact with most cytoplasmic constituents, it was probably toxic to many early organisms, just as it is to many present-day anaerobic bacteria. However, this reactivity also provides a source of chemical energy, and, not surprisingly, this has been exploited by organisms during the course of evolution. By using oxygen, organisms are able to oxidize more completely the molecules they ingest. For example, in the presence of oxygen glucose can be completely degraded to CO_2 and H_2O, while in the absence of oxygen it can be broken down only to lactic acid or ethanol, the end products of anaerobic glycolysis. In this way much more energy can be derived from each gram of glucose. The energy release in the aerobic oxidation of food molecules—usually called **respiration**—is used to drive the synthesis of ATP in much the same way that photosynthetic organisms produce ATP from the energy of sunlight. In both processes there is a series of electron transfer reactions that generates a H^+ gradient between the outside and inside of a tiny membrane-bounded compartment; the H^+ gradient then serves to drive the synthesis of the ATP. Today, respiration is used by the great majority of organisms, including most procaryotes.

Eucaryotic Cells Contain Several Distinctive Organelles

As molecular oxygen accumulated in the atmosphere, what happened to the remaining anaerobic organisms with which life had begun? In a world that was rich in oxygen, which they could not use, they were at a severe disadvantage. Some, no doubt, became extinct. Others either developed a capacity for respiration or found niches from which oxygen was largely absent, where they could continue an anaerobic way of life. It seems, however, that a third class discovered a strategy for survival more cunning, and vastly richer in implications for the future: they are believed to have formed an intimate association with an aerobic type of cell, living with it in *symbiosis.* This is the most plausible explanation for the origin of present-day cells of the **eucaryotic** type (Panel A), with which this book will be chiefly concerned.

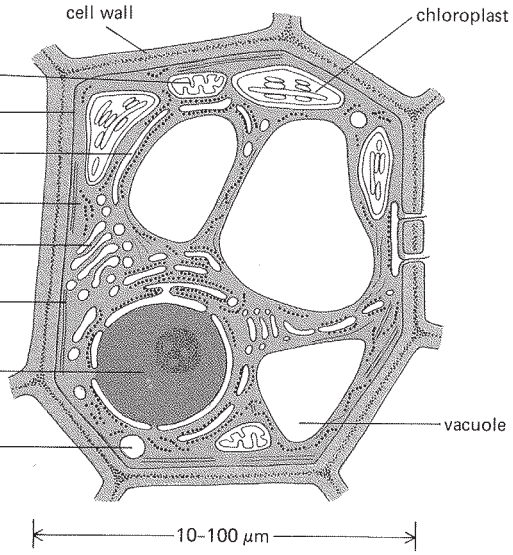
ANIMAL CELL

thin section of a generalized animal cell



PLANT CELL

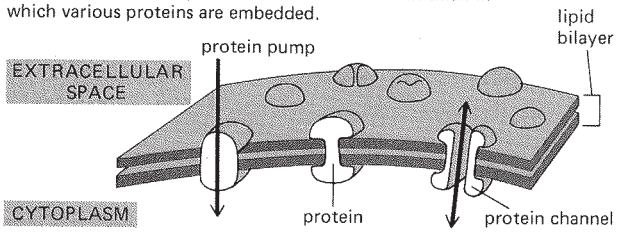
thin section of a generalized cell from a higher plant



THE MEMBRANE SYSTEM OF THE CELL

PLASMA MEMBRANE

The outer boundary of the cell is the plasma membrane, a continuous sheet of lipid molecules about 4–5 nm thick in which various proteins are embedded.

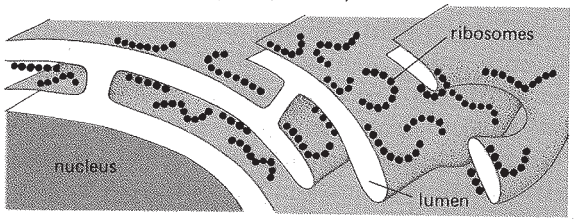


Some of these proteins serve as pumps and channels for transporting specific molecules into and out of the cell.

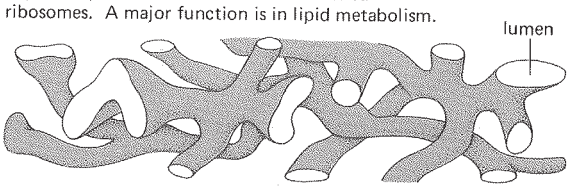
ENDOPLASMIC RETICULUM

Flattened sheets, sacs, and tubes of membrane extend throughout the cytoplasm of eucaryotic cells, enclosing a large intracellular space. The ER membrane is in structural continuity with the outer membrane of the nuclear envelope and it specializes in the synthesis and transport of lipids and membrane proteins.

The rough endoplasmic reticulum (rough ER) generally occurs as flattened sheets and is studded on its outer face with ribosomes engaged in protein synthesis.

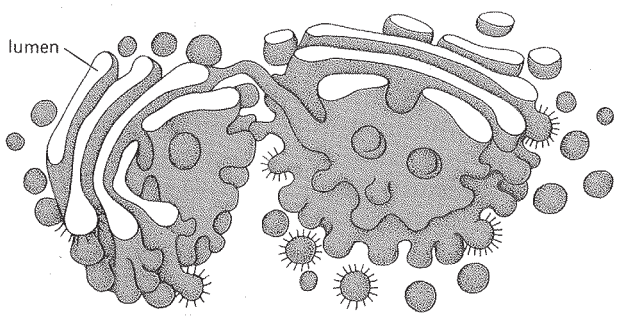


The smooth endoplasmic reticulum (smooth ER) is generally more tubular and lacks attached ribosomes. A major function is in lipid metabolism.

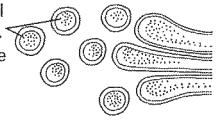


GOLGI APPARATUS

A system of stacked, membrane-bounded, flattened sacs involved in modifying, sorting, and packaging macromolecules for secretion or for delivery to other organelles.

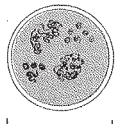


Around the Golgi apparatus are numerous small membrane-bounded vesicles (50 nm and larger). These are thought to carry material between the Golgi apparatus and different compartments of the cell.



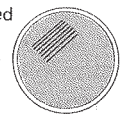
LYSOSOMES

membrane-bounded vesicles that contain hydrolytic enzymes involved in intracellular digestions



PEROXISOMES

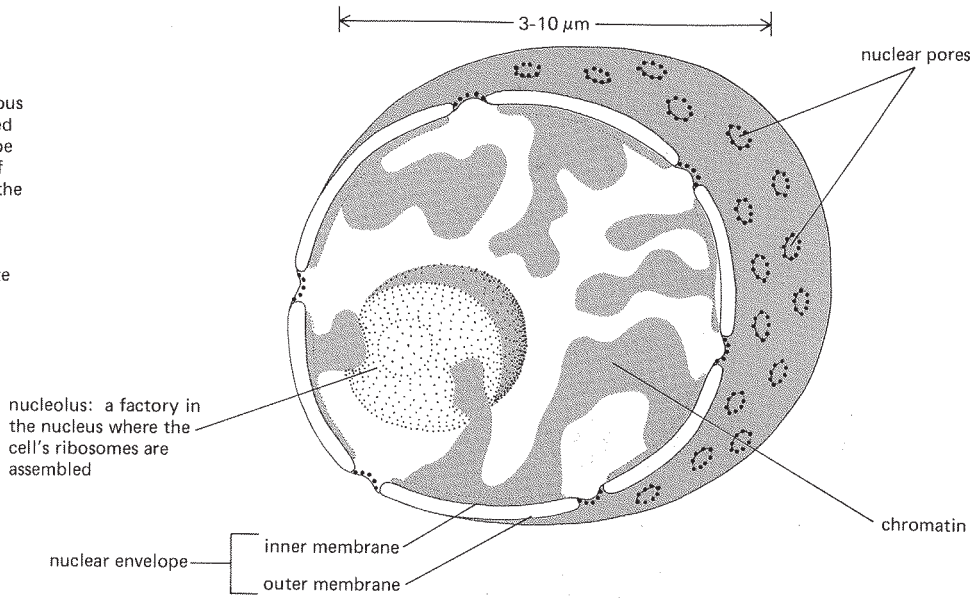
membrane-bounded vesicles containing oxidative enzymes that generate and destroy hydrogen peroxide



Panel A Eucaryotic cells: a survey of their principal organelles.

NUCLEUS

The nucleus is the most conspicuous organelle in the cell. It is separated from the cytoplasm by an envelope consisting of 2 membranes. All of the chromosomal DNA is held in the nucleus, packaged into chromatin fibers by its association with an equal mass of histone proteins. The nuclear contents communicate with the cytosol by means of openings in the nuclear envelope called nuclear pores.



CYTOSKELETON

In the cytosol, arrays of protein filaments form networks that give the cell its shape and provide a basis for its movements. In animal cells the cytoskeleton is often organized from an area near the nucleus that contains the cell's pair of centrioles. 3 main kinds of cytoskeletal filaments are:

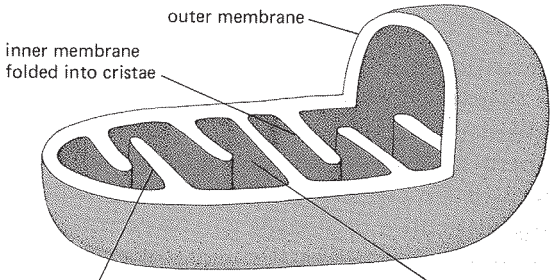
1. microtubules

2. actin filaments

3. intermediate filaments

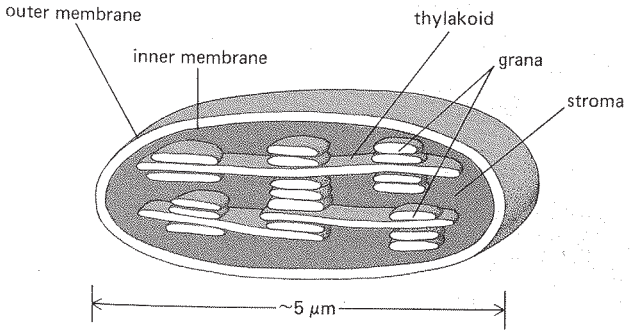
MITOCHONDRIA

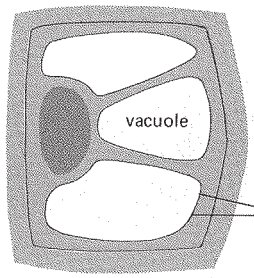
About the size of bacteria, mitochondria are the power plants of all eucaryotic cells, harnessing energy obtained by combining oxygen with food molecules to make ATP.



SPECIAL PLANT CELL ORGANELLES

chloroplasts—These chlorophyll-containing plastids are double-membrane-bounded organelles found in all higher plants. An elaborate internal membrane system contains the photosynthetic apparatus.

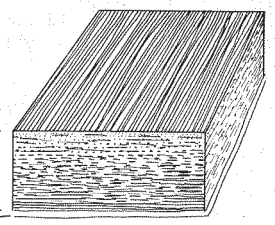




vacuole—A very large single-membrane-bounded vesicle occupying up to 90% of the cell volume, the vacuole functions in space-filling and also in intracellular digestion.

vacuole membrane (tonoplast)

cell wall—Plant cells are surrounded by a rigid wall composed of tough fibrils of cellulose laid down in a matrix of other polysaccharides.



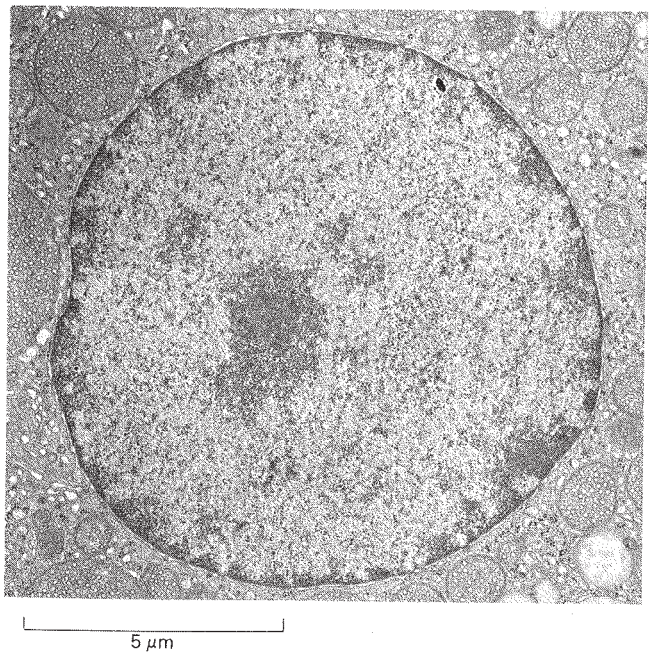


Figure 1–17 The nucleus contains most of the DNA of the eucaryotic cell. It is seen here in a thin section of a mammalian cell examined in the electron microscope. (Courtesy of Daniel S. Friend.)

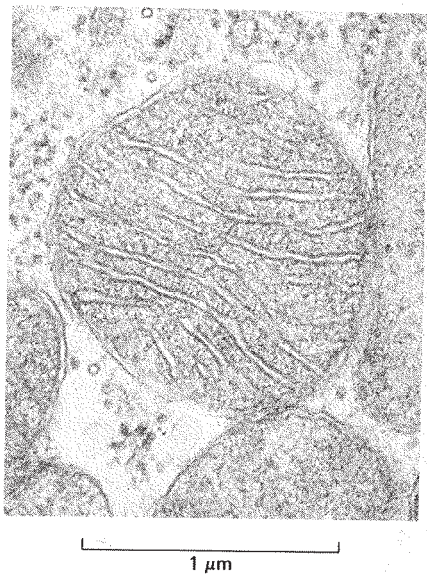


Figure 1–18 Mitochondria carry out the oxidative degradation of nutrient molecules in all eucaryotic cells. As seen in this electron micrograph, they possess a smooth outer membrane and a highly convoluted inner membrane. (Courtesy of Daniel S. Friend.)

Eucaryotic cells, by definition, and in contrast to procaryotic cells, have a *nucleus* ("caryon" in Greek), which contains most of the cell's DNA, enclosed by a double layer of membrane (Figure 1–17). The DNA is thereby kept in a compartment separate from the rest of the contents of the cell, the *cytoplasm*, where most of the cell's metabolic reactions occur. In the cytoplasm, moreover, many distinctive *organelles* can be recognized. Prominent among these are two types of small bodies, the *mitochondria* and *chloroplasts* (Figures 1–18 and 1–19). Each of these is enclosed in its own double layer of membrane that is chemically different from the membrane surrounding the nucleus. Mitochondria are an almost universal feature of eucaryotic cells, while chloroplasts are found only in those eucaryotic cells that are capable of photosynthesis—that is, in plants but not in animals or fungi. Both organelles are thought to have a symbiotic origin.

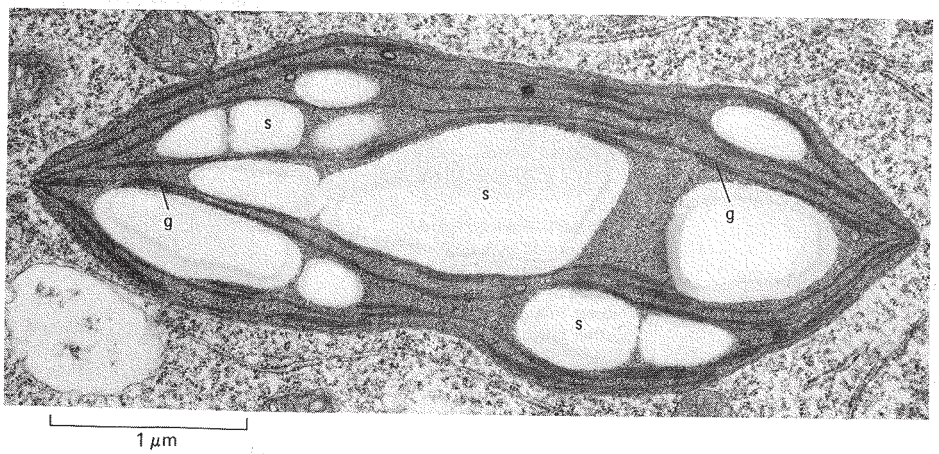


Figure 1–19 Electron micrograph of a chloroplast in a moss cell showing its extensive system of internal membranes. The flattened sacs of membrane contain chlorophyll and are arranged in stacks, or *grana* (g). This chloroplast also contains large accumulations of starch (s). (Courtesy of J. Burgess.)

Eucaryotic Cells Depend on Mitochondria for Their Oxidative Metabolism

Mitochondria show many similarities to free-living procaryotic organisms: for example, they often resemble bacteria in size and shape, they contain DNA, and they reproduce by dividing in two. By breaking up eucaryotic cells and separating their component parts, it is possible to show that mitochondria are responsible for respiration and that this process occurs nowhere else in the eucaryotic cell. Without mitochondria, the cells of animal and fungi would be anaerobic organisms, depending on the relatively inefficient and antique process of glycolysis for their energy. Many present-day bacteria can respire, and the mechanism by which they do so bears an unmistakable resemblance to that in mitochondria.

It seems probable, therefore, that eucaryotic cells are descendants of primitive anaerobic organisms, which survived in a world that had become rich in oxygen by engulfing aerobic bacteria. Rather than digest the bacteria, they nourished them and maintained them in symbiosis for the sake of their capacity to consume atmospheric oxygen and produce energy, just as we keep cows for their capacity to consume grass and produce milk. Of course, we cannot prove absolutely that this is what did happen, but certain present-day microorganisms provide strong evidence of the feasibility of such an evolutionary sequence: for example, an exceptional eucaryotic organism, the amoeba *Pelomyxa palustris*, lacks mitochondria and instead harbors aerobic bacteria in a permanent symbiotic relationship.

Chloroplasts May Be Descendants of Procaryotic Algae

Chloroplasts carry out photosynthesis in much the same way as procaryotic cyanobacteria, absorbing sunlight in the chlorophyll that is attached to their membranes. Some bear a close structural resemblance to the cyanobacteria, being similar in size and in the way that their chlorophyll-bearing membranes are stacked in layers (Figure 1–19). Moreover, chloroplasts reproduce by dividing and contain DNA. All this strongly suggests that chloroplasts have evolved from cyanobacteria that made their home inside eucaryotic cells, performing photosynthesis for their hosts in return for the sheltered and nourishing environment that their hosts provided for them. Symbiosis of photosynthetic cells with other cell types is, in fact, a common phenomenon, and a number of present-day eucaryotic cells can be observed to contain authentic cyanobacteria (Figure 1–20).

Figure 1–21 shows the evolutionary origins of the eucaryotes according to the symbiotic theory. It must be stressed, however, that mitochondria and chloroplasts show important differences from, as well as similarities to, present-day aerobic bacteria and cyanobacteria. Their quantity of DNA is very small, for example, and most of the molecules from which they are constructed are synthesized elsewhere in the eucaryotic cell and imported into the organelle. Assuming that they did originate as symbiotic bacteria, they have undergone large evolutionary changes and have become greatly dependent on their hosts.

Was the acquisition of mitochondria by some primitive anaerobic cell the crucial step in the genesis of the eucaryotes, bringing in its wake the evolution of their other special characteristics? We lack evidence to answer this question: existing eucaryotes have in common not only mitochondria but also a whole constellation of other features that distinguish them from procaryotes (Table 1–1). These function together to give eucaryotic cells a wealth of different capabilities, and it is impossible to say which of them evolved first.

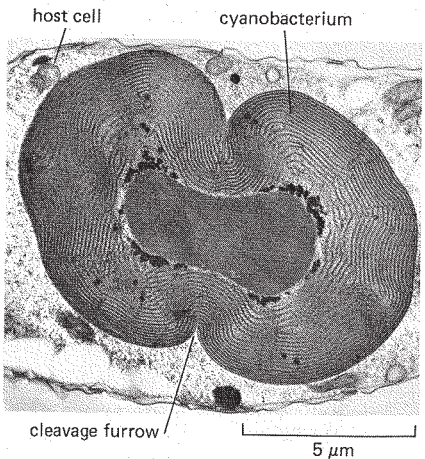


Figure 1–20 A close relative of present-day cyanobacteria that lives in a permanent symbiotic relationship inside another cell (the two organisms are known jointly as *Cyanophora paradoxa*). The "cyanobacterium" is undergoing cleavage. (Courtesy of Jeremy D. Pickett-Heaps.)

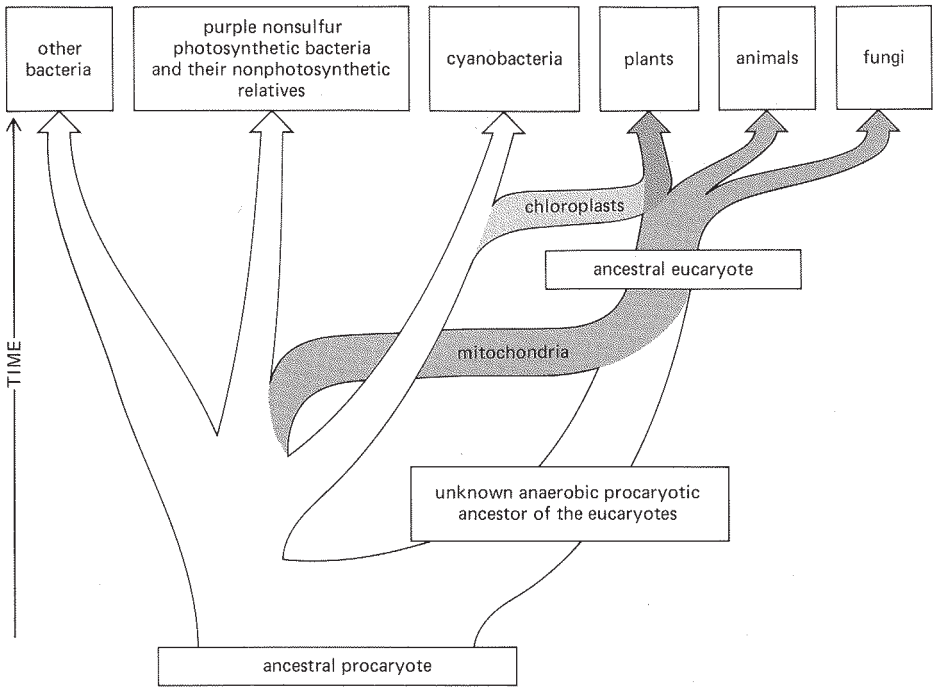


Figure 1–21 The postulated origin of the eucaryotes by symbiosis of aerobic with anaerobic procaryotes.

Table 1–1 Comparison of Procaryotic and Eucaryotic Organisms

	Procaryotes	**Eucaryotes**
Organisms	bacteria and cyanobacteria	protists, fungi, plants, and animals
Cell size	generally 1 to 10 μm in linear dimension	generally 10 to 100 μm in linear dimension
Metabolism	anaerobic or aerobic	aerobic
Organelles	few or none	nucleus, mitochondria, chloroplasts, endoplasmic reticulum, etc.
DNA	circular DNA in cytoplasm	very long DNA containing many noncoding regions; organized into chromosomes and bounded by nuclear envelope
RNA and protein	RNA and protein synthesized in same compartment	RNA synthesized and processed in nucleus; proteins synthesized in cytoplasm
Cytoplasm	no cytoskeleton, cytoplasmic streaming, endocytosis, or exocytosis	cytoskeleton composed of protein filaments; cytoplasmic streaming; endocytosis and exocytosis
Cell division	by binary fission	by mitosis (or meiosis)
Cellular organization	mainly unicellular	mainly multicellular, with differentiation of cells

Eucaryotic Cells Contain a Rich Array of Internal Membranes

Eucaryotic cells are usually much larger in volume than procaryotic cells, commonly by a factor of a thousand or more, and they carry a proportionately larger quantity of most cellular materials; for example, a human cell contains about 800 times as much DNA as a typical bacterium. This large size creates problems. Since all the raw materials for the biosynthetic reactions occurring in the interior of a cell must ultimately enter and leave by passing through the plasma membrane that covers its surface, and since the membrane is also the site of many important reactions, an increase of cell volume requires an increase of cell surface. But it is a fact of geometry that a simple scaling up of a structure increases the volume as the cube of the linear dimension, while the surface area is increased only as the square. Therefore, if the large eucaryotic cell is to keep as high a proportion of surface to volume as the procaryotic cell, it must supplement its surface area by means of convolutions, infoldings, and other elaborations of its membrane.

This probably explains in part the complex profusion of **internal membranes** that is a basic feature of all eucaryotic cells. Membranes surround the nucleus, the mitochondria, and (in plant cells) the chloroplasts. They form a labyrinthine compartment called the **endoplasmic reticulum** (Figure 1–22) where lipids and proteins of cell membranes as well as material destined for export from the cell are synthesized. They also form stacks of flattened sacs constituting the **Golgi apparatus** (Figure 1–23), which is likewise involved in the synthesis and transport of various organic molecules. Membranes surround **lysosomes,** in which stores of enzymes required for purposes of intracellular digestion are contained and so prevented from attacking the proteins and nucleic acids of the cell itself. In the same way, membranes surround **peroxisomes,** where dangerously reactive peroxides are generated and degraded. They also form small vesicles and, in plants, a large liquid-filled *vacuole.* All these membrane-bounded structures correspond to distinct internal compartments within the cytoplasm. In a typical animal cell, these compartments occupy nearly half of the total cell volume. The remaining compartment of the cytoplasm, which includes everything other than the membrane-bounded organelles, is usually referred to as the **cytosol.**

All of the membranous structures in our list lie in the interior of the cell. How, then, can they help to solve the problem we posed at the outset and provide the cell with a surface area that is adequate to its large volume? The answer depends on exchange between the internal membrane-bounded compartments and the outside of the cell. This is achieved by *endocytosis* and *exocytosis,* processes unique to eucaryotic cells. In endocytosis, portions of the external surface membrane invaginate and pinch off to form membrane-bounded cytoplasmic vesicles containing substances that were present in the external medium or were adsorbed onto the cell surface. Exocytosis is the reverse process, whereby membrane-bounded vesicles inside the cell fuse with the plasma membrane and release their contents into the external medium. In this way, membranes surrounding compartments deep inside the cell serve to increase the effective surface area of the cell for exchanges of matter with the external world.

As we shall see in later chapters, the various membranes and membrane-bounded compartments in eucaryotic cells have become highly specialized, some for secretion, some for absorption, some for specific biosynthetic processes, and so on.

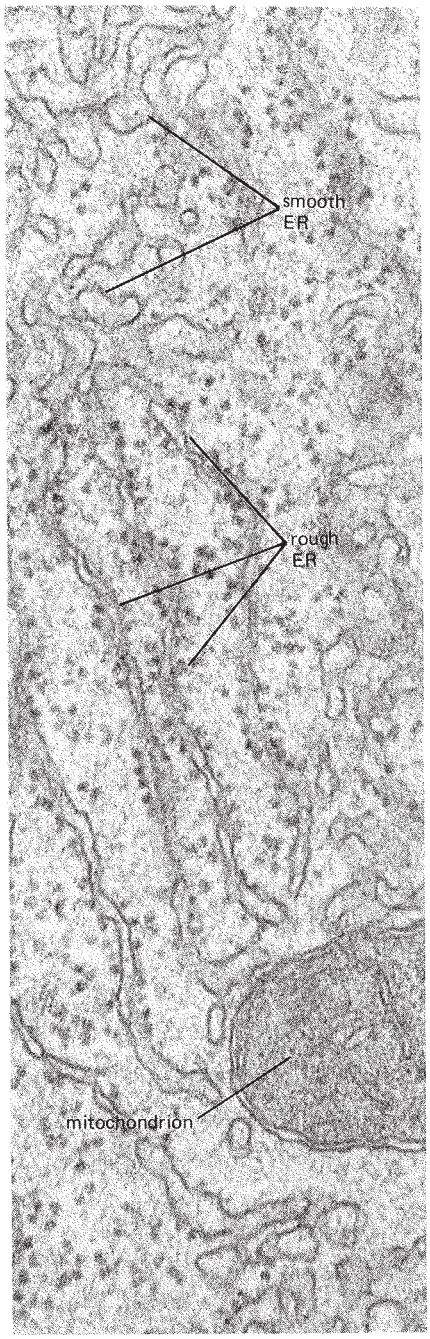


Figure 1–22 Electron micrograph of a thin section of a mammalian cell showing both smooth and rough regions of the endoplasmic reticulum (ER). (Courtesy of George Palade.)

Eucaryotic Cells Have a Cytoskeleton

The larger a cell is, and the more elaborate and specialized its internal structures, the greater its need to keep these structures in their proper places and

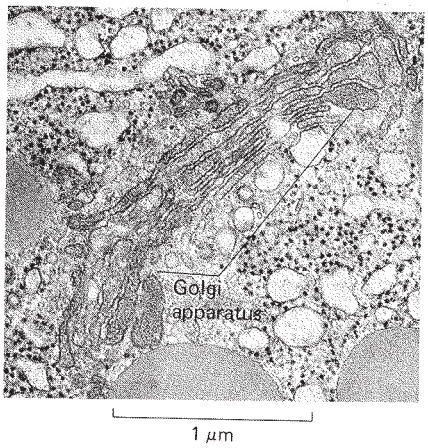


Figure 1–23 Electron micrograph of a thin section of a mammalian cell showing the Golgi apparatus, which is composed of flattened sacs of membrane arranged in multiple layers (see also Panel A, pages 16–17). The Golgi apparatus is involved in the synthesis and packaging of material destined to be secreted from the cell, as well as in the routing of newly synthesized proteins to the correct cellular compartment. (Courtesy of Daniel S. Friend.)

to control their movements. All eucaryotic cells have an internal skeleton, the **cytoskeleton,** that gives the cell its shape, its capacity to move, and its ability to arrange its organelles and transport them from one part of the cell to another. The cytoskeleton is composed of a network of protein filaments, two of the most important of which are *actin filaments* and *microtubules* (Figure 1–24). These two must date from a very early epoch in evolution since they are found almost unchanged in all eucaryotes. Both are involved in the generation of cellular movements; actin filaments, for example, participate in the contraction of muscle, while microtubules are the main structural and force-generating elements in *cilia* and *flagella*—the long projections on some cell surfaces, which beat like whips and serve as instruments of propulsion.

Actin filaments and microtubules are also essential for the internal movements that occur in the cytoplasm of all eucaryotic cells. Thus microtubules in the form of a *mitotic spindle* are a vital part of the usual machinery for partitioning DNA equally between the two daughter cells when a eucaryotic cell divides. Without microtubules, therefore, the eucaryotic cell could not reproduce. In this and other examples, movement by free diffusion would be either too slow or too haphazard to be useful. In fact, it has been suggested that most of the organelles in a eucaryotic cell are attached, directly or indirectly, to the cytoskeleton and that the only way they are able to move is along cytoskeletal tracks by an energy-requiring transport process.

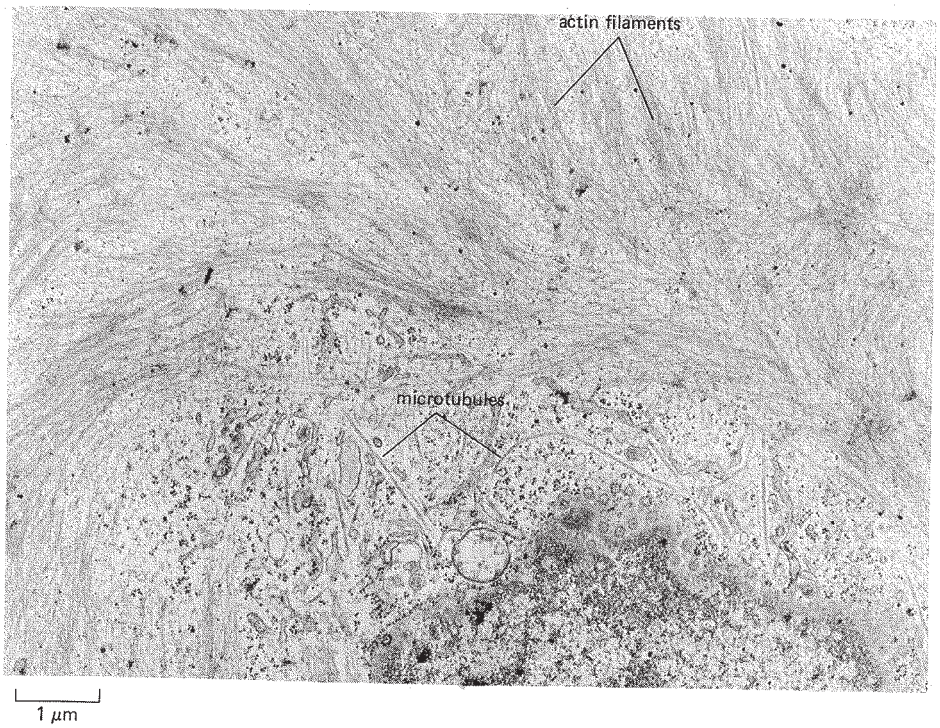


Figure 1–24 Microtubules and actin filaments, two prominent components of the cytoskeleton, are seen in this electron micrograph of an animal cell. (From B. S. Spooner, *Bioscience* 25:440–451, 1975. Copyright 1975 by the American Institute of Biological Sciences. Reprinted by permission of the copyright holder.)

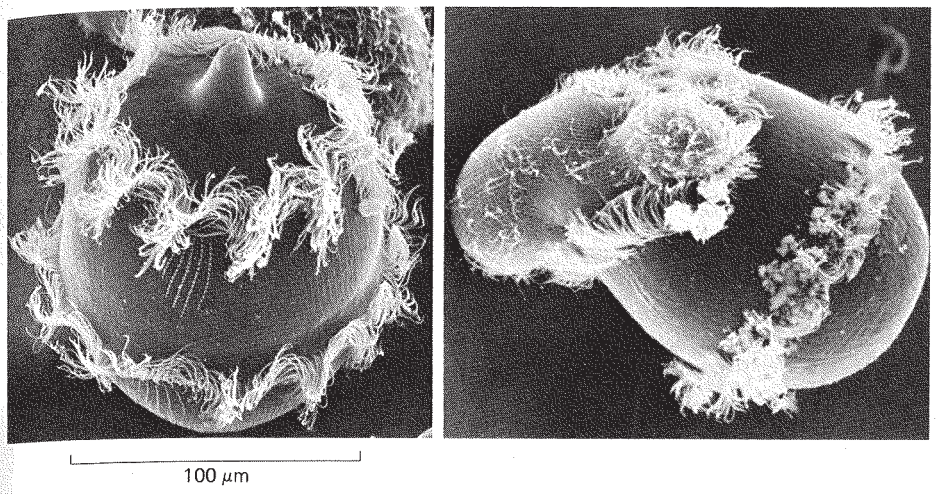


Figure 1–25 Scanning electron micrograph showing one protozoan eating another. Protozoans are single-cell animals that show an amazing diversity of form and behavior. *Didinium* (*left*), a ciliated protozoan, has two circumferential rings of motile cilia and a snoutlike protuberance at its leading end, with which it captures its prey. On the right, *Didinium* is shown engulfing another protozoan, *Paramecium*. (Courtesy of D. Barlow.)

Protozoa Include the Most Complex Cells Known

The complexity that can be achieved by a single eucaryotic cell is nowhere better illustrated than in *protists*. These are free-living, single-celled eucaryotes that exhibit a bewildering variety of different forms and behaviors: they can be photosynthetic or carnivorous, motile or sedentary. Their anatomy is often complex and includes such structures as sensory bristles, photoreceptors, flagella, leglike appendages, mouth parts, stinging darts, and musclelike contractile bundles. Although they are single cells, they can be as intricate and versatile as many multicellular organisms. This is particularly true of the group of protists known as **protozoa**—or "first animals."

Didinium is a carnivorous protozoan. It has a globular body, about 150 μm in diameter, encircled by two fringes of cilia; its front end is flattened except for a single protrusion rather like a snout (Figure 1–25). *Didinium* swims around at high speed in the water by means of the synchronous beating of its cilia. When it encounters a suitable prey, usually another type of protozoan, *Paramecium*, it releases numerous small paralyzing darts from its snout region. Then the *Didinium* attaches to and devours the *Paramecium*, inverting like a hollow ball to engulf the other cell, which is as large as itself. Most of this complex behavior—swimming, and paralyzing and capturing its prey—is generated by the cytoskeletal structures lying just beneath the plasma membrane. Included in this *cell cortex*, for example, are the parallel bundles of microtubules that form the core of each cilium and enable it to beat.

But the protozoa, for all their marvels, do not represent the peak of eucaryotic evolution. Greater things were achieved, not by concentrating every sort of complexity in a single cell, but by dividing the labor among different types of cells. *Multicellular organisms* evolved, in which cells closely related by ancestry became differentiated from one another, some developing one feature to a high degree, others another, so forming the specialized parts of one great cooperative enterprise.

Genes Can Be Switched On and Off

The various specialized cell types in a single higher plant or animal often appear radically different (Panel B). This seems paradoxical, since all of the cells in a multicellular organism are closely related, having recently descended from the same precursor cell—the fertilized egg. Common lineage implies similar genes; how then do the differences arise? In a few cases, cell specialization involves the loss of genetic material: an extreme example is the mam-

CELL TYPES

There are over 200 different types of cell in the human body. These are assembled into a variety of different types of tissue such as

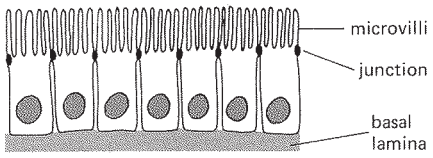
- epithelia
- connective tissue
- muscle
- nervous tissue

Most tissues contain a mixture of cell types.

EPITHELIA

Epithelial cells form coherent cell sheets called epithelia, which line the inner and outer surfaces of the body. There are many specialized types of epithelia.

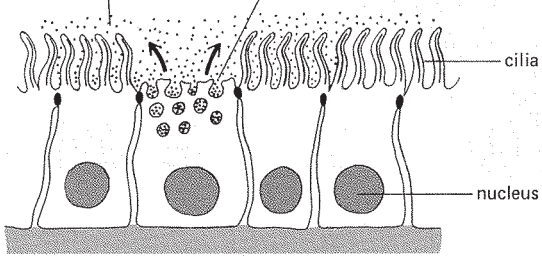
Absorptive cells have numerous hairlike microvilli projecting from their free surface to increase the area for absorption.



Adjacent epithelial cells are bound together by junctions that give the sheet mechanical strength and also make it impermeable to small molecules. The sheet rests on a basal lamina.

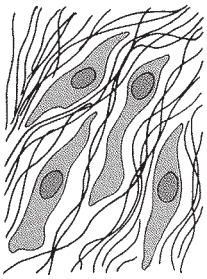
ciliated cells — cilia on their free surface beat in synchrony to move substances (such as mucus) over the epithelial sheet.

secretory cells — most epithelial layers have some cells that secrete substances onto the surface.



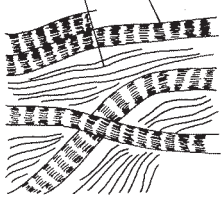
CONNECTIVE TISSUE

The spaces between organs and tissues in the body are filled with connective tissue made principally of a network of tough protein fibers embedded in a polysaccharide gel. This extracellular matrix is secreted mainly by fibroblasts.



fibroblasts in loose connective tissue

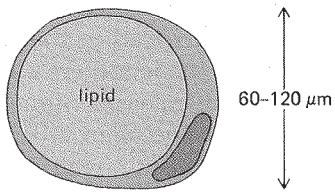
2 main types of extracellular protein fiber are collagen and elastin.



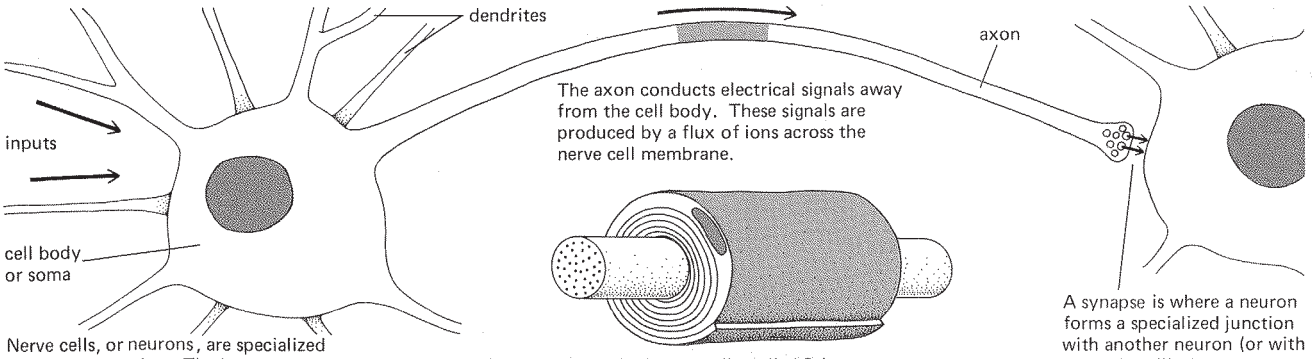
Bone is made by cells called osteoblasts. These secrete an extracellular matrix in which crystals of calcium phosphate are later deposited.

Calcium salts are deposited in the extracellular matrix.

Adipose cells are among the largest cells in the body. These cells are responsible for the production and storage of fat. The nucleus and cytoplasm are squeezed to the cell periphery by a large lipid droplet.



NERVOUS TISSUE



Nerve cells, or neurons, are specialized for communication. The brain and spinal cord, for example, are composed of a network of neurons among supporting glial cells.

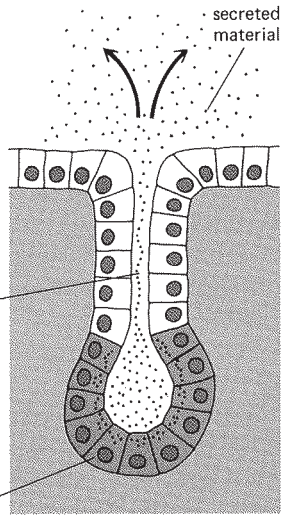
The axon conducts electrical signals away from the cell body. These signals are produced by a flux of ions across the nerve cell membrane.

Specialized cells, called Schwann cells, or oligodendrocytes, wrap around an axon to form a multilayered membrane sheath.

A synapse is where a neuron forms a specialized junction with another neuron (or with a muscle cell). At synapses, signals pass from one neuron to another (or from a neuron to a muscle cell).

Panel B Some of the different types of cells present in the vertebrate body.

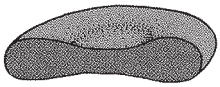
Secretory epithelial cells are often collected together to form a gland that specializes in the secretion of a particular substance. As illustrated, exocrine glands secrete their products (such as tears, mucus, and gastric juices) into ducts. Endocrine glands secrete hormones into the blood.



BLOOD

Erythrocytes (or red blood cells) are very small cells with no nucleus or internal membranes, and are stuffed full of the oxygen-binding protein hemoglobin.

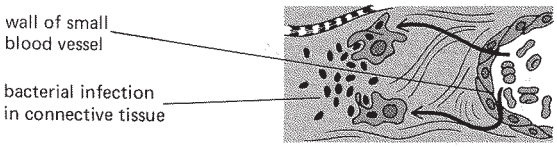
1 cm^3 of blood contains 5,000,000,000 erythrocytes.



Their normal shape is a biconcave disc.

white blood cells (leucocytes) — there is about 1 leucocyte for every 1000 red blood cells. Although they travel in the circulation, they can pass through the walls of blood vessels to do their work in the surrounding tissues. There are several different kinds, including:

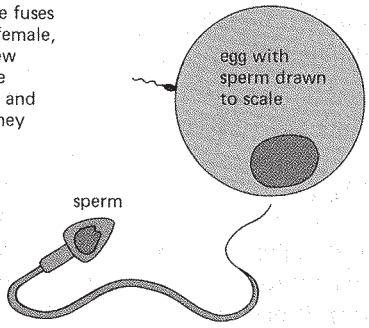
macrophages and neutrophils — these cells move to sites of infection where they ingest bacteria and debris.



lymphocytes — responsible for immune responses such as the production of antibody and the rejection of tissue grafts.

GERM CELLS

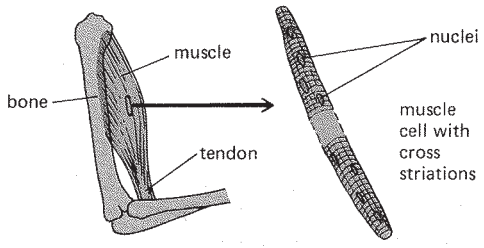
A sperm from the male fuses with an egg from the female, which then forms a new organism by successive divisions. Both sperm and egg are haploid, i.e., they carry only 1 set of chromosomes.



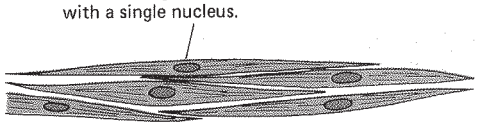
MUSCLE

Muscle cells produce mechanical force by their contraction. In vertebrates there are three main types:

skeletal muscle — this moves joints by its strong and rapid contraction. Each muscle is a bundle of muscle fibers, each of which is an enormous multinucleated cell.



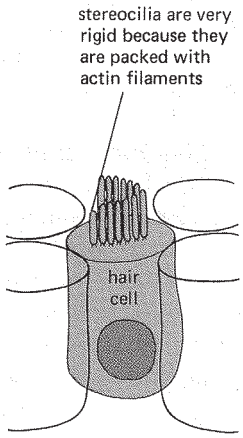
smooth muscle — present in digestive tract, bladder, arteries, and veins, it is composed of thin elongated cells (not striated) each with a single nucleus.

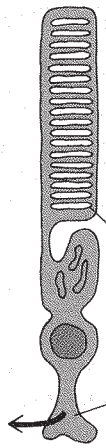


cardiac muscle — intermediate in character between skeletal and smooth muscle, it produces the heart beat. Adjacent cells are linked by electrically conducting junctions that cause the cells to contract in synchrony.

SENSORY CELLS

Among the most complex cells in the vertebrate body are those that detect external stimuli. Hair cells of the inner ear are primary detectors of sound. Modified epithelial cells, they carry special microvilli (stereocilia) on their surface. The movement of these in response to sound vibrations causes an electrical signal to pass to the brain.





Rod cells in the retina of the eye are nerve cells specialized to respond to light. The photosensitive region contains many membranous discs in whose membranes the light-sensitive pigment rhodopsin is embedded. Light causes an electrical signal to pass to other nerve cells.

malian red blood cell, which loses its entire nucleus in the course of differentiation. But the overwhelming majority of cells in most species of plants and animals retain all of the genetic information contained in the fertilized egg. Specialization depends not on the loss or acquisition of genes, but on changes in *gene expression*.

Even bacteria do not make all of their types of protein all of the time, but are able to adjust the level of synthesis according to external conditions. Proteins required specifically for the metabolism of lactose, for example, are made by some species of bacteria only when this sugar is available for use. Other bacteria, when conditions are unfavorable, arrest most of their normal metabolic processes and form *spores*, which have tough, impermeable outer walls and a cytoplasm of altered composition.

Eucaryotic cells have evolved far more sophisticated mechanisms for controlling gene expression, and these affect entire systems of interacting gene products. Groups of genes are activated or repressed in response to both external and internal signals. Membrane composition, cytoskeleton, secretory products, even metabolism—all these and other features must change in a coordinated manner when cells become differentiated. Compare, for example, a skeletal muscle cell specialized for contraction, with an *osteoblast*, which secretes the hard matrix of bone in the same animal (Panel B, pages 24–25). Such radical transformations of cell character reflect stable changes in gene expression. The controls that bring about such changes have evolved in eucaryotes to a degree unmatched in procaryotes.

Eucaryotic Cells Have Vastly More DNA Than They Need for the Specification of Proteins

Eucaryotic cells contain a very large quantity of DNA; as we have said, in human cells there is almost a thousand times more DNA than in typical bacteria. Yet it seems that only a small fraction of this DNA—perhaps 1% in human cells—carries the specifications for proteins that are actually made. Why then is the remaining 99% of the DNA there? One hypothesis is that much of it acts merely to increase the physical bulk of the nucleus. Another is that it is in large part parasitic—a collection of DNA sequences that have over the ages accumulated in the cell, exploiting the cell's machinery for their own reproduction, and bringing no benefit in return. Indeed, the DNA of many species has been shown to contain sequences called *transposable elements*, which have the ability to "jump" occasionally from one location to another in the DNA, and even to insert additional copies of themselves at new sites. Transposable elements could thus proliferate like a slow infection, becoming an ever larger proportion of the genetic material.

But evolution is opportunistic. Whatever the origins of the DNA that does not code for protein, it is certain that it now has some important functions. Part of this DNA is structural, enabling portions of the genetic material to become condensed or "packaged" in specific ways, as described in the next section, and some of the DNA is regulatory and helps to switch on and off the genes that direct the synthesis of proteins, thus playing a crucial role in the sophisticated control of gene expression in eucaryotic cells.

In Eucaryotic Cells the Genetic Material Is Packaged in Complex Ways

The length of DNA in eucaryotic cells is so great that the risk of entanglement and breakage becomes severe. Probably for this reason proteins unique to eucaryotes, the *histones*, have evolved to bind to the DNA and wrap it up into

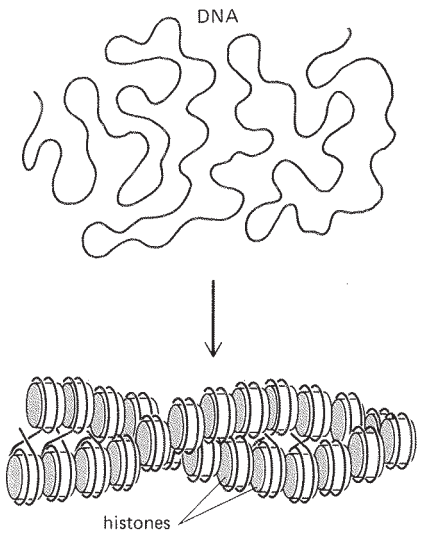


Figure 1–26 Schematic illustration of how the positively charged proteins called histones mediate the folding of DNA in chromosomes.

compact and manageable **chromosomes** (Figure 1–26). Tight packaging of the chromosomes is an essential part of the preparations for cell division in eucaryotes (Figure 1–27). All eucaryotes (with one minor exception) have histones bound to their DNA, and the importance of these proteins is reflected in the fact that they have been remarkably conserved in evolution: several of the histones of a pea plant are almost exactly the same, amino acid for amino acid, as those of a cow.

Many other proteins besides histones are bound to the DNA in eucaryotic cells. By altering the opportunities of the DNA to interact with other molecules, some of these DNA-binding proteins alter the patterns of gene expression from one type of specialized cell to another. For example, since genes contained in a tightly packed mass of DNA are not expressed, gene expression can be controlled through changes in the packaging of the DNA.

The membranes enclosing the nucleus in eucaryotic cells protect the delicate control machinery associated with DNA, sheltering it from the rapid movements and from many of the chemical changes that take place in the cytoplasm. They also allow the segregation of two crucial steps in gene expression: (1) the copying of DNA sequences into RNA sequences (*DNA transcription*) and (2) the use of these RNA sequences, in turn, to direct the synthesis of specific proteins (*RNA translation*). In procaryotic cells, there is no compartmentalization—the translation of RNA sequences into protein begins as soon as they are transcribed, even before their synthesis is completed. In eucaryotes, however (except in mitochondria and chloroplasts, which in this respect as in others are closer to bacteria), the two steps in the path from gene to protein are kept strictly separate: transcription occurs in the nucleus, translation in the cytoplasm. The RNA has to leave the nucleus before it can be used to guide protein synthesis. While it is in the nucleus, it undergoes elaborate processing, in which some parts of the RNA molecule are discarded and other parts are modified.

Because of these complexities, the genetic material of a eucaryotic cell offers many more opportunities for control than are present in bacteria.

Summary

Present-day living cells are classified as procaryotic (bacteria and their close relatives) or eucaryotic. Procaryotic cells are believed to resemble most closely the earliest ancestral cell. Although they have a relatively simple structure, they are biochemically diverse: for example, all of the major metabolic pathways can be found in bacteria, including the three principal energy-yielding processes of glycolysis, respiration, and photosynthesis. Eucaryotic cells are larger and more complex than procaryotic cells and contain more DNA, together with components that allow this DNA to be handled in elaborate ways. The DNA of the eucaryotic cell is enclosed in a membrane-bounded nucleus, while the cytoplasm contains many other membrane-bounded organelles. These include mitochondria, which carry out the terminal oxidation of food molecules, and, in plant cells, chloroplasts, which carry out photosynthesis. Various lines of evidence suggest that mitochondria and chloroplasts are the descendants of earlier procaryotic cells that established themselves as internal symbionts of a larger anaerobic cell. Eucaryotic cells are also unique in containing a cytoskeleton of protein filaments that help organize the cytoplasm and provide the machinery for movement.

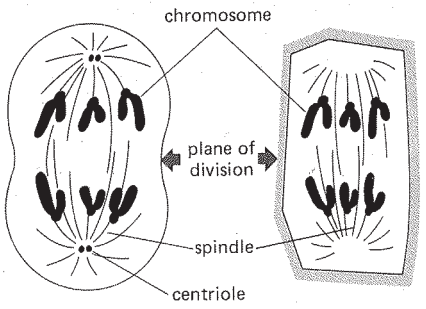


Figure 1–27 Schematic drawing of eucaryotic cells in mitosis. An animal cell is shown on the left and a plant cell on the right. The nuclear envelope has broken down, and the DNA, having replicated, has condensed into two complete sets of chromosomes. One set is distributed to each of the two newly forming cells by a mitotic spindle composed largely of microtubules.

From Single Cells to Multicellular Organisms[3]

Single-cell organisms, such as bacteria and protozoa, have been so successful in adapting to a variety of different environments that they comprise more than half of the total biomass on earth. Unlike higher animals, many of these unicellular organisms can synthesize all of the substances they need from a few simple nutrients, and some of them divide more than once every hour. What, then, was the selective advantage that led to the evolution of **multicellular organisms**?

The short answer is that multicellular organisms can exploit resources that no single cell could utilize so well. Multicellularity enables a tree, for example, to become physically large; to have roots in the ground, where one set of cells can take up water and nutrients; and to have leaves in the air, where another set of cells can efficiently capture the radiant energy from the sun. In the trunk of the tree are specialized cells that form channels for transporting water and nutrients between the roots and the leaves. Yet another set of specialized cells forms a layer of bark to prevent water loss and to provide a protected internal environment. The tree as a whole does not compete directly with unicellular organisms for its ecological niche; it has found a radically different way to survive and propagate.

As different animals and plants appeared, they changed the environment in which further evolution occurred. Survival in a jungle calls for different talents from those required for survival in the open sea. Innovations in movement, sensory detection, communication, social organization—all enabled eucaryotic organisms to compete, propagate, and survive in ever more complex ways.

Single Cells Can Associate to Form Colonies

It seems likely that an early step in the evolution of multicellular organisms was the association of unicellular organisms to form colonies. The simplest way of achieving this is for daughter cells to remain associated after each cell division. Even some procaryotic cells show such social behavior in a primitive form. Myxobacteria, for example, live in the soil and feed on insoluble organic molecules that they break down by secreting degradative enzymes. They stay together in loose colonies in which the digestive enzymes secreted by individual cells are pooled, thus increasing the efficiency of feeding. These cells indeed represent a peak of sophistication among procaryotes; for when food supplies are exhausted, the cells aggregate tightly together and form a multicellular *fruiting body*, within which the bacteria differentiate into spores that can survive even in extremely hostile conditions. When conditions are more favorable, the spores in a fruiting body germinate to produce a new swarm of bacteria.

Green algae (not to be confused with the procaryotic "blue-green algae" or cyanobacteria) are eucaryotes that exist as unicellular, colonial, or multicellular forms (Figure 1–28). Different species of green algae can be arranged in order of complexity, illustrating the kind of progression that probably occurred in the evolution of higher plants and animals. Unicellular green algae, such as *Chlamydomonas*, are similar to flagellated protozoa except that they possess chloroplasts, which enable them to carry out photosynthesis. In closely related genera, groups of flagellated cells live in colonies held together by a matrix of molecules secreted by the cells themselves. The simplest species (those of the genus *Gonium*) have the form of a concave disc made of 4, 8, 16, or 32 cells. Their flagella beat independently, but since they are all oriented in the same direction they are able to propel the colony through the water. Each cell is equivalent to every other, and each can divide to give rise to an

entirely new colony. Larger colonies are found in other genera, the most spectacular being *Volvox*, some of whose species have as many as 50,000 or more cells linked together to form a hollow sphere. In *Volvox*, the individual cells forming a colony are connected by fine cytoplasmic bridges so that the beating of their flagella is coordinated to propel the entire colony along like a rolling ball (Figure 1–28). Within the *Volvox* colony there is some division of labor between cells, with a small number of cells being specialized for reproduction and serving as precursors of new colonies. The other cells are so dependent on each other that they cannot live independently, and the organism dies if the colony is disrupted.

The Cells of a Higher Organism Become Specialized and Cooperate

In some ways, *Volvox* is more like a multicellular organism than a simple colony. All of its flagella beat in synchrony as it spins through the water, and the colony is structurally and functionally polarized and can swim toward a distant source of light. The reproductive cells are usually confined to one end of the colony, where they divide to form new miniature colonies, which are initially sheltered inside the parent sphere. Thus in a primitive way *Volvox* displays the two essential features of all multicellular organisms: its cells become *specialized* and they *cooperate.* By specialization and cooperation, the cells combine to form a coordinated single organism with richer capabilities than any one of its component parts.

Organized patterns of cell differentiation occur even in some procaryotes. For example, many kinds of cyanobacteria remain together after cell division, forming filamentous chains that can be as much as a meter in length. At regular intervals along the filament, individual cells take on a distinctive character and become able to incorporate atmospheric nitrogen into organic molecules. These few specialized cells perform nitrogen fixation for their neighbors and share the products with them. But eucaryotic cells appear to be very much better at this sort of organized division of labor; they, and not procaryotes, are the living units from which all the more complex multicellular organisms are constructed.

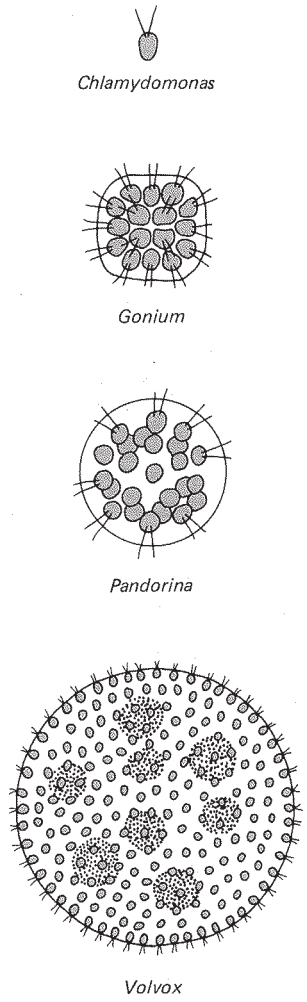


Figure 1–28 Four closely related genera of green algae, showing a progression from unicellular to colonial and multicellular organization.

Multicellular Organization Depends on Cohesion Between Cells

To form a multicellular organism, the cells must be somehow bound together, and eucaryotes have evolved a number of different devices that perform this function. In *Volvox*, as noted above, the cells do not separate entirely at cell division but remain connected by cytoplasmic bridges. In higher plants, the cells not only remain connected by cytoplasmic bridges (called *plasmodesmata*), but also are imprisoned in a rigid honeycomb of chambers walled with cellulose that the cells themselves have secreted (*cell walls*).

The cells of most animals do not have rigid walls, and cytoplasmic bridges are unusual. Instead, the cells are bound together by a relatively loose meshwork of large extracellular organic molecules (called the *extracellular matrix*) and by adhesions between their plasma membranes. In *sponges*, for example, which are commonly considered the most primitive of present-day animals, the body wall typically consists of a coherent sheet of cells comprising just five different specialized types; these form a system of channels and pores for the passage of water, from which food particles are filtered and ingested by the cells. Sponges grow indefinitely through cell proliferation, and their size and structure are not precisely fixed. They have no nervous system to coordinate the activities of their parts, and they have been described as "loose republics of cells"—to be contrasted with the more strictly disciplined cell

communities that constitute higher animals. Nevertheless, a sponge is far from being a totally chaotic structure. If the sponge is forced through a fine sieve so that its individual cells are mechanically separated from one another, the cells will often spontaneously reassemble into an intact sponge, aggregating initially into a large mass and then eventually rearranging themselves into a coherent multicellular sheet. Such sheets of cells are called **epithelia.**

Epithelial Sheets of Cells Enclose a Sheltered Internal Environment

Of all the ways in which animal cells are woven together into multicellular tissues, the epithelial arrangement is perhaps the most fundamentally important. The epithelial sheet has much the same significance for the evolution of complex multicellular organisms that the cell membrane has for the evolution of complex single cells.

The importance of epithelial sheets is well illustrated in another lowly group of animals, the *coelenterates.* These stand a rung higher in the scale of evolution than do the sponges, for they have a nervous system of sorts; but among animals with nervous systems, they are probably the most primitive. The group includes sea anemones, jellyfish, and corals, as well as the small freshwater organism *Hydra.* Coelenterates are constructed from two layers of epithelium, the outer layer being the *ectoderm,* the inner being the *endoderm.* The endodermal layer surrounds a cavity, the *coelenteron,* in which food is digested (Figure 1–29). The cells are bound together in such a way that the epithelial sheets not only have mechanical strength, but also can serve as a barrier to the passage of molecules; they thus prevent food from escaping and make it possible to set up specialized chemical conditions for its digestion. Among the endodermal cells are some that secrete digestive enzymes into the coelenteron, while other cells absorb and further digest the nutrient molecules that these enzymes release. By forming a tightly coherent epithelial sheet that prevents all these molecules from being lost to the exterior, the endodermal cells create for themselves an environment in the coelenteron that is suited to their own digestive tasks. Meanwhile the ectodermal cells, facing the exterior, remain specialized for encounters with the outside world. In the ectoderm, for example, are cells that contain, coiled inside them, a poison dart, which can be unleashed to paralyze the small animals that *Hydra* feeds on.

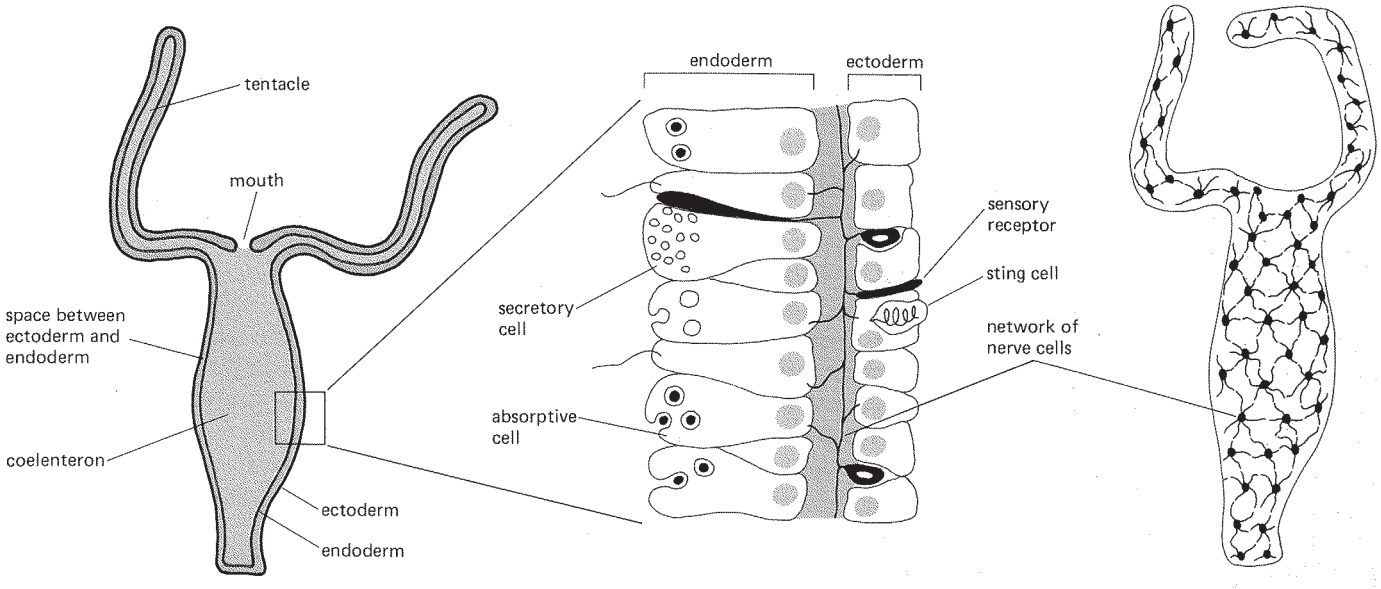


Figure 1–29 A schematic view of the body plan of *Hydra.* The outer layer of cells (ectoderm) is primarily protective, while cells of the inner layer (endoderm) are engaged principally in digestion. Sandwiched between these two layers is a net of interconnected nerve cells. (Note that in the right-hand figure the nerve cells are shown disproportionately large.)

Sandwiched between the ectoderm and the endoderm is another compartment, separate both from the coelenteron and from the outside world. It is in this narrow space that the nerve cells chiefly lie, pressed close against the inner face of the ectoderm. The animal can change its shape and move by contractions of musclelike cells in the ectoderm and endoderm. The nerve cells convey electrical signals to control and coordinate these contractions (Figures 1–30 and 1–31). As we shall see later, the concentrations of simple inorganic ions in the medium surrounding a nerve cell are crucial for its function. Most nerve cells—our own included—are designed to operate when bathed in a solution with an ionic composition similar to that of sea water. This presumably reflects the conditions under which the first nerve cells evolved. Most coelenterates still live in the sea, but not all. *Hydra,* in particular, lives in fresh water. It has evidently been able to colonize this new habitat only because its nerve cells are contained in a space that is sealed and isolated from the exterior by sheets of epithelial cells that maintain the internal environment necessary for nerve cell function.

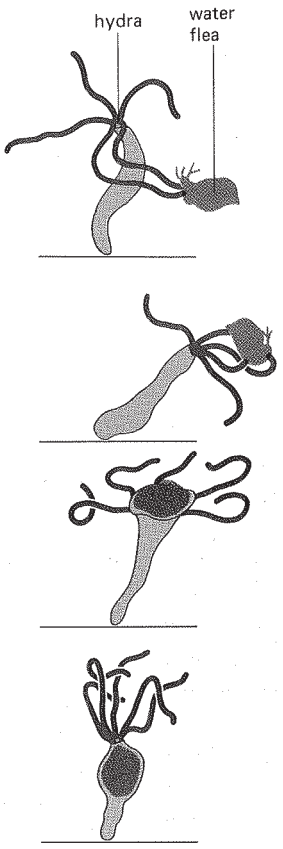


Figure 1–30 *Hydra* can perform a range of fairly complex activities. It is depicted here catching a small water flea in its tentacles and stuffing this prey into its coelenteron for digestion.

Cell-Cell Communication Controls the Spatial Pattern of Multicellular Organisms

The cells of *Hydra* are not only bound together mechanically and connected by junctions that seal off the interior from the exterior environment; they also communicate with one another along the length of the body. If one end of a *Hydra* is cut off, the remaining cells react to the absence of the amputated part by adjusting their characters and rearranging themselves so as to regenerate a complete animal. Evidently signals pass from one part of the organism to the other governing the development of its body pattern, with tentacles and a mouth at one end and a foot at the other. Moreover, these signals are independent of the nervous system. If a developing *Hydra* is treated with the drug colchicine, so that nerve cells are prevented from forming, the animal is unable to move, catch prey, or feed itself. However, its digestive system still functions normally, so it can be kept alive by anyone with the patience to stuff its normal prey into its mouth. In such force-fed animals the body pattern is maintained, and lost parts are regenerated just as well as in an animal that has an intact nervous system.

From humble ancestors resembling coelenterates the vastly more complex higher animals have evolved, and the latter owe their complexity to a more sophisticated exploitation of the same basic principles of cell cooperation that underlie the construction of *Hydra.* Epithelial sheets of cells line all external and internal surfaces in the body, creating sheltered compartments and controlled internal environments in which specialized functions are performed by differentiated cells. Specialized cells interact and communicate with one another, setting up signals to govern the character of each cell according to its place in the structure as a whole. To show how it is possible to generate multicellular organisms of such size, complexity, and precision as a human being, it is necessary, however, to consider more closely the sequence of events in **development.**

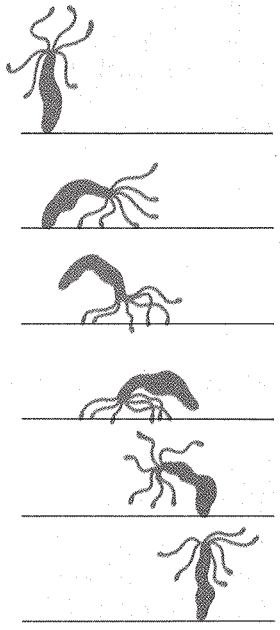


Figure 1–31 *Hydra* can swim, glide on its base, or, as shown here, travel by somersaulting.

Cell Memory Permits the Development of Complex Patterns

The cells of almost every multicellular organism are generated by repeated division from a single precursor cell; they constitute a *clone.* As proliferation continues and the clone grows, some of the cells, as we have seen, become differentiated from others, adopting a different structure, a different chemistry, and a different function, in response to cues from their neighbors. It is remarkable that eucaryotic cells and their progeny will usually persist in their

differently specialized states even after the influences that originally directed their differentiation have disappeared—in other words, these cells have a *memory*. Consequently, their final character is not determined simply by their final environment, but rather by the entire sequence of influences to which they have been exposed in the course of development. Thus as the body grows and matures, progressively finer and finer details of the adult body pattern become specified, creating an organism of gradually increasing complexity whose ultimate form is the expression of a long developmental history.

Basic Developmental Programs Tend to Be Conserved in Evolution

The structure of an animal is also the outcome of its evolutionary history, which, like development, presents a chronicle of progress from the simple to the complex. What then is the connection between the two perspectives, of evolution on the one hand and development on the other?

During evolution, many of the developmental devices that evolved in the simplest multicellular organisms have been conserved as basic principles for the construction of their more complex descendants. We have already mentioned, for example, the organization of cells into epithelia. It is notable also that some of the same basic specialized cell types, such as nerve cells, are found throughout nearly the whole of the animal kingdom, from *Hydra* to man. Furthermore, the early developmental stages of animals whose adult forms appear radically different are often surprisingly similar; it takes an expert eye to distinguish, for example, a young chick embryo from a young human embryo.

Such observations are not difficult to understand. Consider the process by which a new anatomical feature—say an elongated beak—appears in the course of evolution. A random mutation occurs that changes the amino acid sequence of a protein and hence its biological activity. This altered protein may, by chance, affect the cells responsible for the formation of the beak in such a way that they make one which is longer. But the mutation must also be compatible with the development of the rest of the organism: only then will it be propagated by natural selection. There would be little selective advantage in forming a longer beak if, in the process, the tongue was lost or the ears failed to develop. A catastrophe of this type is far more likely if the mutation affects events occurring early in development than if it affects those at the end. The early cells of an embryo are like cards at the bottom of a house of cards—a great deal depends on them and even small changes in their properties are likely to result in disaster. Fundamental steps have been "frozen" into developmental processes just as the genetic code or protein synthetic mechanisms have become frozen into the basic biochemical organization of the cell. In contrast, cells produced at the end of development have more freedom to change. It is presumably for this reason that the embryos of different species so often resemble each other in their early stages and, as they develop, seem sometimes to replay the steps of evolution.

Eucaryotic Organisms Possess a Complex Machinery for Reproduction

Within the multicellular organism there must be some cells that serve as precursors for a new generation. In higher plants and animals these cells have a highly specialized character and are called *germ cells*. The propagation of the species depends on them, and there is a powerful selection pressure to adjust the structure of the organism as a whole to provide the germ cells with the best chance of survival. Other cells may die, but as long as germ cells

survive, new organisms of the same sort will be produced. In this sense the most fundamental distinction to be drawn in a multicellular organism is the distinction between germ cells and the rest, that is, between germ cells and *somatic* cells.

Not all multicellular organisms reproduce by means of distinctive differentiated germ cells. Many simple animals, including sponges and coelenterates, can reproduce by budding off portions of their bodies, and many plants do likewise. Germ cells are, however, a necessity for **sexual reproduction.** This process is so familiar to us that we take it for granted, but it is by no means the obvious way to reproduce: it is far more complicated than asexual reproduction and requires a large diversion of resources. Two individuals of the same species but different sex produce germ cells of usually very different character—*eggs* from one, *sperm* from the other. An egg cell fuses with a sperm cell to form a *zygote*—the single precursor cell for the development of a new organism, whose genes represent a partly random reassortment of the genes of the two parents. While they may also reproduce in other ways, almost all eucaryotic species, unicellular as well as multicellular, are capable of reproducing sexually. Eucaryotic cells have evolved a complex machinery for sex; our lives revolve around it. Strong selective pressures must have operated to favor the evolution of sexual reproduction in preference to simpler strategies based on ordinary cell division. Although it is surprisingly difficult to say with certainty what those selection pressures were, it is at least plain that sexual reproduction brings new possibilities for manipulating and recombining the genes of a species. It may thus have played a crucial part in permitting the evolution of novel genes in novel combinations, and so in engendering the endless variety of forms and functions seen in plants and animals today.

The Cells of the Vertebrate Body Exhibit More Than 200 Different Modes of Specialization

The wealth of diverse specializations to be found among the cells of a higher animal is incomparably greater than any procaryote can show. In a vertebrate, more than 200 distinct **cell types** are plainly distinguishable, and many of these types of cells probably include, under a single name, a large number of more subtly different varieties. Panel B (pages 24–25) shows a small selection. In this profusion of specialized behaviors one can see displayed, in a single organism, the astonishing versatility of the eucaryotic cell. Each feature and each organelle of the prototype that we have outlined in Panel A (pages 16–17) is developed to an unusual degree or revealed with special clarity in one cell type or another. Much of current knowledge of the general properties of eucaryotic cells has depended on the study of such specialized types of cells, individually displaying to exceptionally good advantage particular features upon which all cells depend in some measure. To take one arbitrary example, consider the *neuromuscular junction,* where just three types of cells are involved: a muscle cell, a nerve cell, and a Schwann cell. Each has a very different role (Figure 1–32).

1. The muscle cell has made contraction its speciality. Its cytoplasm is packed with organized arrays of protein filaments, including vast numbers of actin filaments. There are also many mitochondria interspersed among the protein filaments, supplying ATP as fuel for the contractile apparatus.
2. The nerve cell stimulates the muscle to contract, conveying an excitatory signal to the muscle from the brain or spinal cord. The nerve cell therefore is extraordinarily elongated: its main body, containing the nucleus, may lie a meter or more from the junction with the muscle. The cytoskeleton is consequently well developed so as to maintain the unusual shape of the

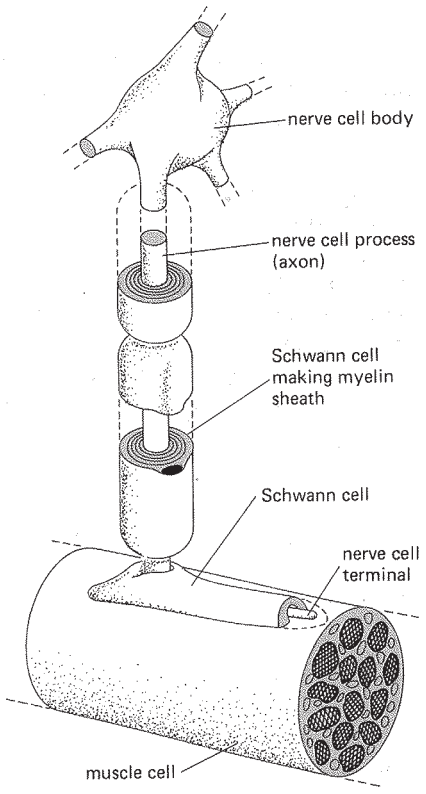


Figure 1–32 Schematic diagram showing a nerve cell, with its associated Schwann cells, contacting a muscle cell at a neuromuscular junction.

cell and to transport materials efficiently from one end of the cell to the other. The most crucial specialization of the nerve cell, however, is its plasma membrane, which contains proteins that act as ion *pumps* and ion *channels,* causing a movement of ions that is equivalent to a flow of electricity. Whereas all cells contain such pumps and channels in their plasma membranes, the nerve cell has exploited them in such a way that a pulse of electricity can propagate in a fraction of a second from one end of the cell to the other, conveying a signal for action.

3. Lastly, Schwann cells are specialists in the mass production of plasma membrane, which they wrap around the elongated portion of the nerve cell, laying down layer upon layer of membrane like a roll of tape, to form a *myelin sheath* that serves as insulation.

Cells of the Immune System Are Specialized for the Task of Chemical Recognition

Among all the cell systems that have evolved in higher animals, there are two that stand out in different ways as pinnacles of complexity and sophistication: the *immune system* of the vertebrate is one, the *nervous system* the other. Each of them far surpasses the performance of any artificial device—the vertebrate immune system in its capacity for chemical discrimination, the nervous system in its capacities for perception and control. Each system comprises a large number of different cell types and depends on interactions between them.

The protected and well-nourished environment in the interior of a multicellular animal is as inviting to foreign organisms as it is congenial to the animal's own cells. Hence there is a need for such animals to defend themselves against invading organisms—particularly viruses and bacteria. The primary task of the **immune system** is to destroy any such foreign microorganisms that may gain entry to the body.

Many eucaryotic cells have an ability to engulf and digest particles of matter from their surroundings. When the particles are relatively large, the process is termed *phagocytosis.* Among the differentiated cells in higher animals, there are professional phagocytic cells, such as *macrophages,* which specialize in this activity and can swallow up and destroy bacteria and other foreign cells. But there is a difficulty: it is good that the phagocytic cell should attack the foreign invader, but it would be disastrous if it were to attack also its own relatives and colleagues. The immune system therefore faces the problem of discriminating between the animal's own cells and those that are foreign—that is, of distinguishing between self and nonself.

The vertebrates have consequently evolved a specialized class of discriminatory cells, the *lymphocytes.* These are not themselves phagocytic; but they collaborate to provide the phagocytic cells with cues that tell them whether to attack or let live. In particular, certain of the lymphocytes (the B lymphocytes) manufacture specific protein molecules, or *antibodies,* that bind selectively to particular arrangements of atoms on the surfaces of invading organisms or on the toxic molecules that they produce. To brand a new type of invader as foreign, new types of antibody must be produced; and since the variety of possible invaders is vast and essentially unpredictable, the B lymphocytes must be capable of making an endless variety of antibodies. On the other hand, the system must not produce antibodies that bind to the animal's own cells and molecules.

The vast diversity of antibodies is generated by random changes in the DNA coding for the specific binding sites of antibody molecules. In this way, through a kind of specialized mutation, millions of genetically different lym-

phocytes are created, each able to proliferate to form a clone whose members all produce the same distinctive antibody. Of these many potential clones, the ones that make antibodies that react with self molecules are destroyed or suppressed (by mechanisms still poorly understood), while those that make antibodies against foreign molecules are selected to survive and multiply. Thus the genesis of an individual animal's immune system, like the process of evolution, depends on a strategy of random variation followed by selection.

Nerve Cells Allow a Rapid Adaptation to a Changing World

The immune system of vertebrates places them in a class apart. Lower animals apparently do not have lymphocytes to help defend against invading microorganisms. A **nervous system,** on the other hand, is found in almost all multicellular animals and fulfills a still more fundamental need—the need for a quick adaptative response to external events.

Evolution acts over many generations to optimize the structure of an organism according to the environment in which it lives. In most ecological niches, though, there occur changes that are far too rapid for evolutionary adaptation to keep pace. The most successful organism, therefore, will be one that is capable of another sort of adaptation, requiring no genetic mutation yet producing optimal behavior when circumstances change. If the sequence of environmental changes is perfectly predictable, like the alternation of night and day or of summer and winter, the organism can be genetically programmed to change autonomously according to the appropriate timetable. Thus the photosynthetic protist *Gonyaulax* (belonging to the group of cells known as *dinoflagellates*) shows a 24-hour rhythm in its photosynthetic activities, which continues even if the cell is maintained for weeks on end in conditions of constant lighting. Such biological clocks exist in many other organisms, but their mechanism remains a profound mystery.

Most environmental changes, however, are not so predictable. Bacteria in the gut, for example, will experience irregular fluctuations in the nature and quantity of food that is available to them, and any bacterium that can adjust its metabolism to these changes will have an advantage over one that cannot. These organisms consequently have evolved the ability to sense the concentrations of nutrients in their environment and to react by adjusting the rates at which they synthesize their metabolic enzymes. Special intracellular control molecules (such as *cyclic AMP*) serve to couple the environmental stimulus to the appropriate response.

In a multicellular organism, the signal that couples a sensation to a response must generally pass between cells. Thus metabolic adjustments are often mediated by hormones that are released by one set of cells and travel through the tissues to produce a response in other sets of cells. But hormones take time to travel a long distance, and in doing so they diffuse widely. If a chemical signal is to be delivered fast, it must be released close to its target; and in that way it can also have a precisely localized action. But if the chemical signal is to be released close to its target, how can it be used to couple a sensation to a response in a remote part of the body? The nerve cell provides the answer. At one end, it is itself sensitive to a chemical or physical stimulus; at the other end, it can in turn release a chemical signal or *neurotransmitter* that acts on other cells. Stimulation at one end triggers an electrical excitation, which is propagated rapidly to the other end and, on arriving there, triggers release of the neurotransmitter. This rapid signaling device enables multicellular animals to make rapid responses to the changing world around them. It also enables them to coordinate precisely the activities of widely separated parts of the body.

Developing Nerve Cells Must Assemble to Form a Nervous System

A single nerve cell of a human being is not very different from a single nerve cell of a worm. The superiority of the human nervous system lies in the enormous number of its cells and, above all, in the way that they are connected together to transmit, combine, and interpret sensory inputs and to coordinate complex patterns of activity. Similarly, the capabilities of a computer depend not so much on the nature of the individual switches or memory elements as on how many there are and the way they are linked together into a system. In the case of the computer, an external agent—the manufacturer—assembles the components in the proper configuration. But for the nervous system, as for the rest of the body, there is no external manufacturer: the cells must assemble into a functional system themselves, following instructions carried in their DNA and adjusting the final product according to the external world. To understand the cellular basis for the evolution of the nervous system, one must therefore look to the mechanisms by which nerve cells develop their fantastically intricate shapes and form their precisely ordered patterns of connections.

Nerve cells begin their existence like any other sort of cell, relatively small and compact. Long processes are then sent out from the body of the nerve cell toward the targets with which it must connect (Figure 1–33). Each such process, known as an *axon* or a *dendrite*, according to whether it carries signals away from the cell body or toward it, is constructed by means of a *growth cone* (Figure 1–34). This organelle, like so many others, represents a

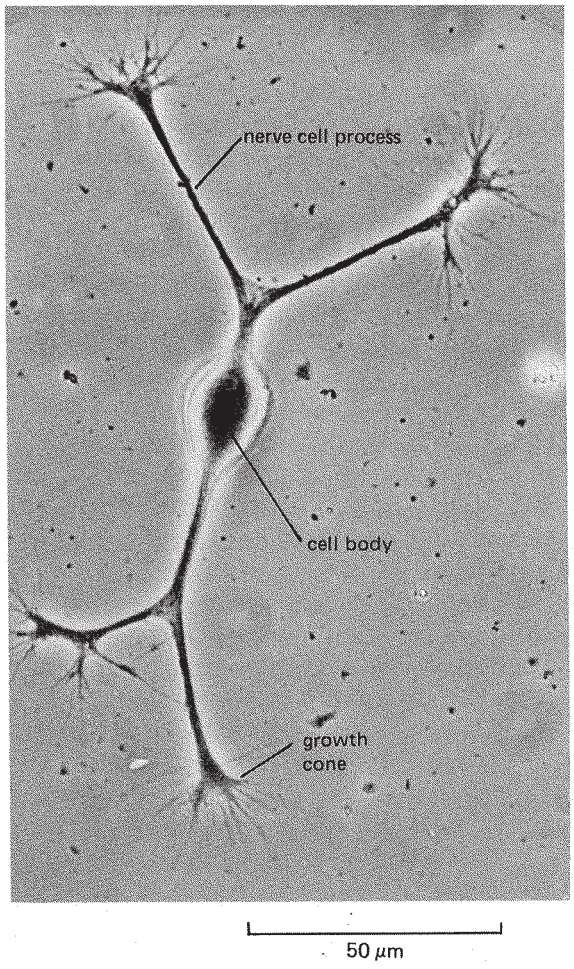


Figure 1–33 Light micrograph of a nerve cell that has been isolated from a chick embryo and put into a tissue-culture dish containing a nutrient solution. The cell is beginning to grow elongated processes. (Courtesy of Zoltan Gabor.)

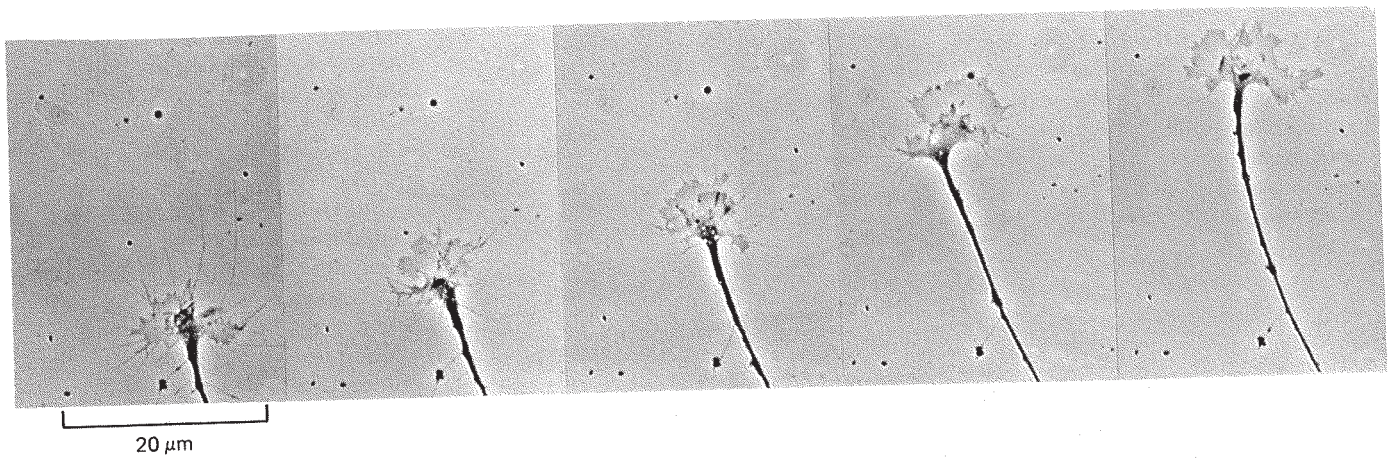


Figure 1–34 The tip of a nerve cell process extending along the surface of a tissue-culture dish as in the previous picture. Photographs taken at intervals of approximately 5 minutes show the elongation of the nerve cell process and the rapidly changing form of the growth cone. The remainder of the nerve cell lies to the bottom outside the micrograph; at this magnification the cell body would be 20 cm to 30 cm away. (Courtesy of Stephen Clark.)

specialization of an apparatus that is common to eucaryotic cells as a device for locomotion. However, instead of pulling the entire nerve cell along, the growth cone leaves the cell body behind and pulls out an elongating axon or dendrite. The growth cone seems to crawl forward through the tissues like a dog on a leash, sniffing its way along the path that will lead to its quarry. In some cases, growth cones appear to be guided simply by physical means, advancing through preestablished channels or along specified tracks in the extracellular matrix. It seems, however, that the evolution of complex nervous systems has depended to a large extent on the development of chemical markers, whereby a particular nerve cell can recognize its proper target from among a mass of others that are inappropriate.

Nerve Cell Connections Determine Patterns of Behavior

By mechanisms such as those just discussed, nervous systems of astonishing complexity are constructed. Look at the visual system of a fly, for example (Figures 1–35, 1–36, and 1–37); this entire structure is built to genetic specifications, and will develop even in the absence of light. Patterns of nerve connections, furthermore, constrain patterns of behavior. Without education, without need of experience, the male fly mates with the female, the spider

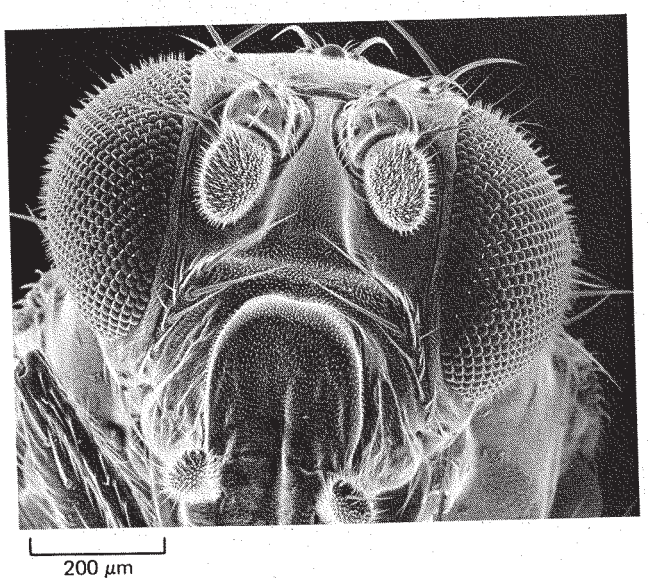


Figure 1–35 The head of a fruit fly (*Drosophila*) seen in a scanning electron microscope. Situated on either side of the head are two large compound eyes consisting of large numbers of units known as ommatidia. Each ommatidium has a separate lens that focuses the light onto a group of photosensitive receptor cells at its base (see Figure 1–36). (Courtesy of Rudi Turner and Anthony Mahowald.)

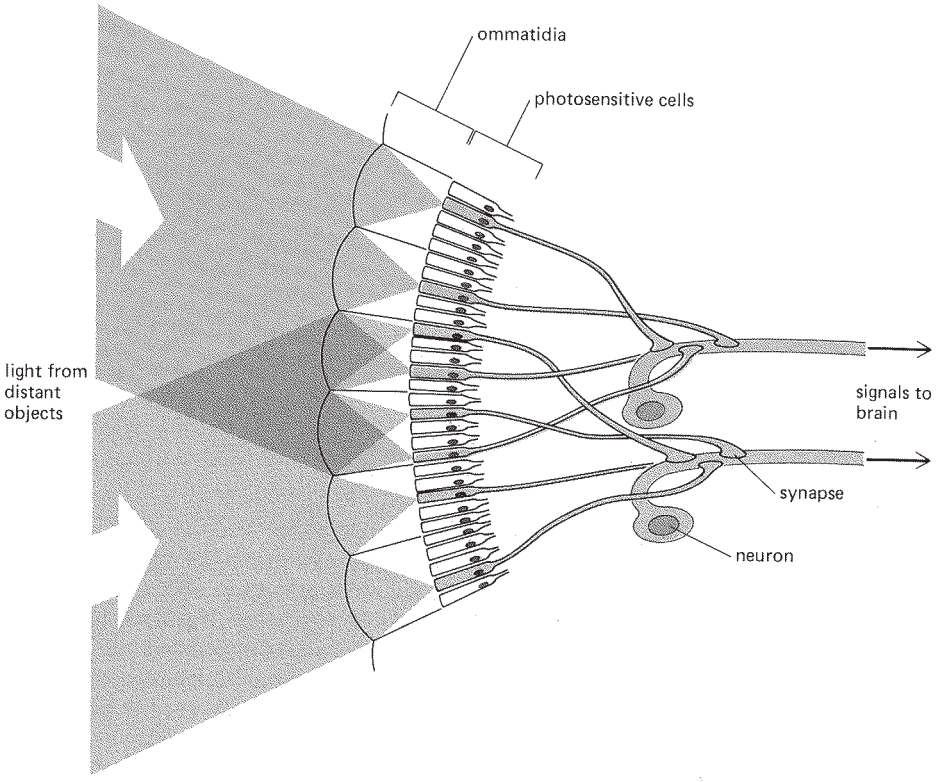


Figure 1–36 Schematic diagram of the neuronal connections in the outermost layer of the fly eye as seen in a vertical section. Light enters each of the ommatidia of the compound eye (see Figure 1–35) and is focused onto one of eight photosensitive receptor cells at its base (only five of which are shown here). Because of the curvature of the compound eye, light from a distant point source is focused onto a different photosensitive receptor cell in different ommatidia. The interweaving of the short axons of the photoreceptor cells, however, connects the photoreceptor cells that are "looking" at the same point to the same bundle of nerve axons that passes into the insect brain. More than a thousand such axon bundles are present in each fly eye, each of which is precisely wired in the course of development to the correct set of photoreceptor cells.

spins its web, the bird migrates to the south. All these activities are prescribed by the DNA of the species, acting through its control over the behavior of the individual cells, as they build the nervous system in the embryo and play their part in its functioning in the adult.

But not all behavior is genetically determined. The past experiences of an animal are important, as well as its DNA. Sensory deprivation during the development of a mammal can alter the microscopic structure of the brain, and mature animals of almost every species, from coelenterates to man, are to some degree capable of learning. Learning is by definition the outcome of experience, and therefore of electrical activity in nerve cells, and it must involve the production of lasting changes in neural connections. Beyond this, we understand very little of the mechanism. It is perhaps the central unsolved problem of neurobiology.

The brain connections that allow us to read and write and speak our native tongue are the outcome of education, and they represent an inheritance of a nongenetic kind. Learning and communication enable the human species to adapt itself over many generations, in a way that is possible for lower organisms only through genetic evolution. Yet even these sophisticated capacities, on which all our culture and society depend, can be seen to rest on the minutiae of cell behavior—on the rules by which nerve cells make lasting adjustments of their interconnections as a consequence of electrical activity.

Of course, we can no more understand the society or the multicellular organism by studying only single cells than we can understand the single cell by studying only isolated biological molecules. Yet if we do not understand the cell, we can never completely understand the organism. And if we do not understand the constituent molecules, we cannot properly understand the cell. Molecules, therefore, must be the starting point for our discussion of the living cell in the next chapter.

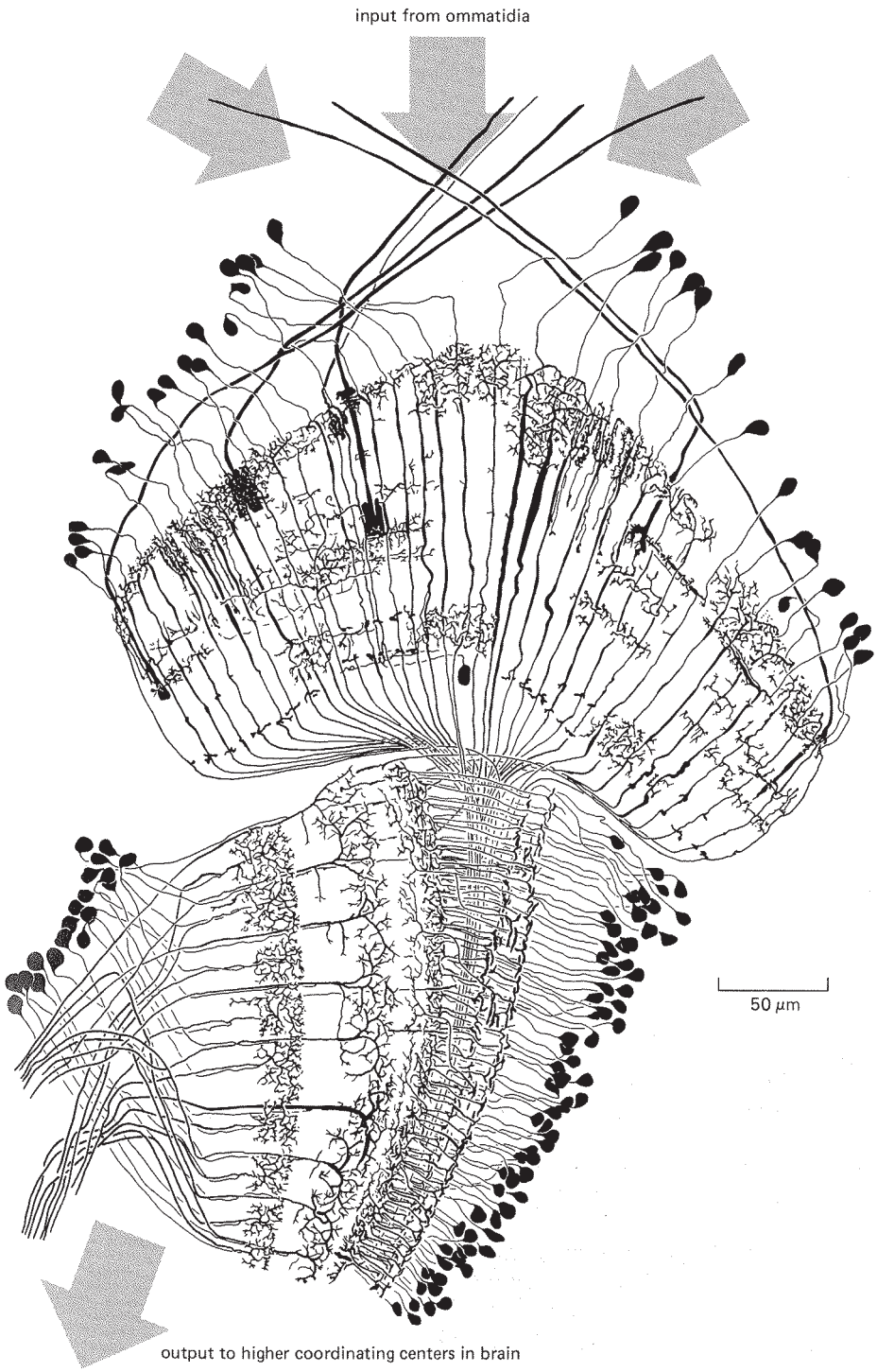
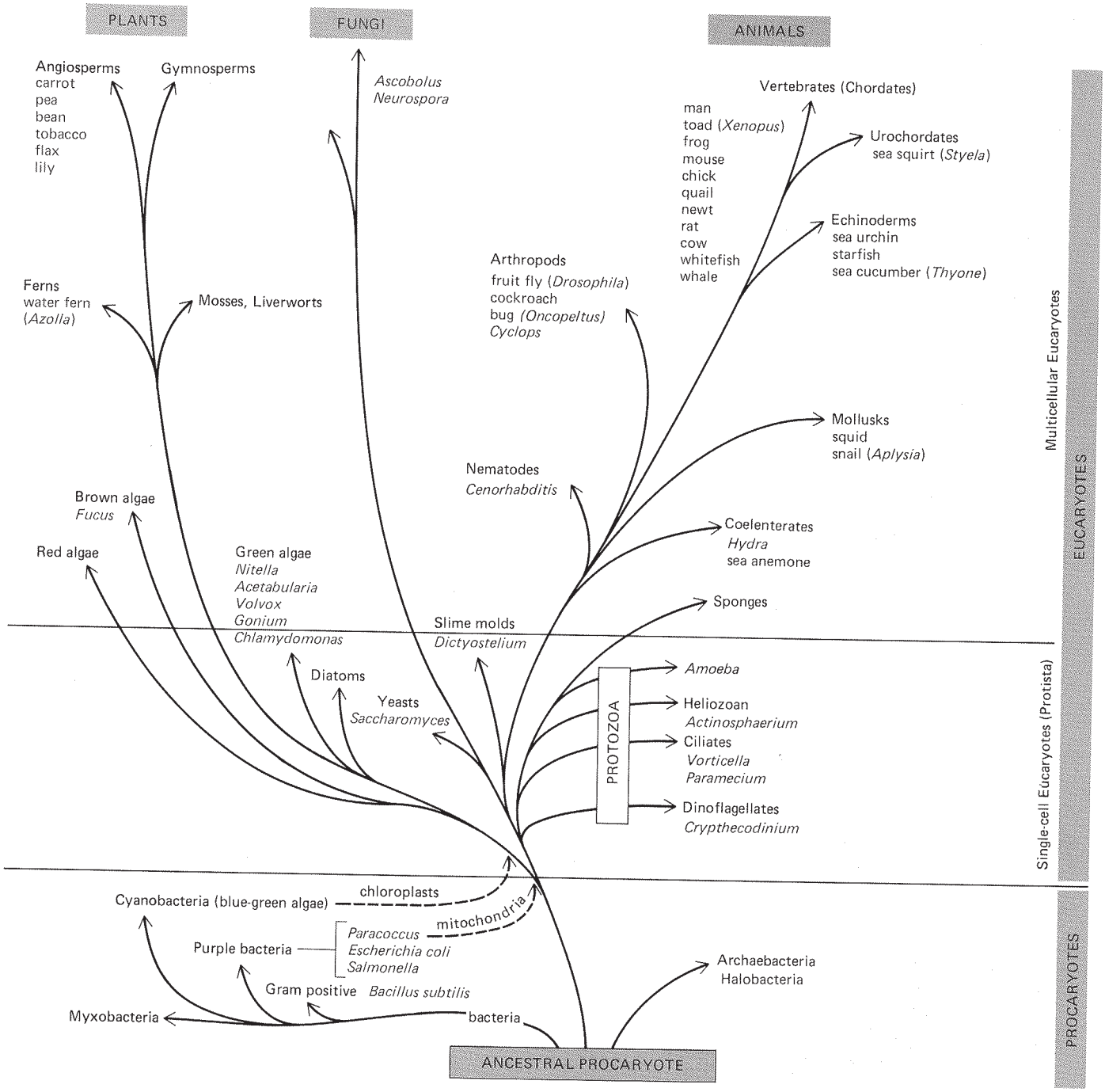


Figure 1–37 Portion of the brain of a fly, showing part of the network of nerve cells that process the input from the ommatidia (see Figure 1–36). (Redrawn from N. Strausfeld, Atlas of an Insect Brain. New York: Springer, 1976.)

Summary

The evolution of large multicellular organisms depended on the ability of eucaryotic cells to express their hereditary information in many different ways and to function cooperatively as a single organism. One of the earliest developments was probably that of epithelia, in which cells join together in sheets, separating the internal space of the animal from the exterior. In addition to



epithelial cells, primitive differentiated cell types would have included nerve cells, muscle cells, and connective tissue cells, all of which can be found in very simple present-day animals.

In the evolution of higher animals (Figure 1–38), the same fundamental developmental strategies were used to produce an increasing number of specialized cell types and more sophisticated methods of coordination between them. Two systems of cells in higher animals represent, in different ways, pinnacles of complexity in multicellular organization: one is the vertebrate immune system, the cells of which have the potential to produce millions of different protein antibodies; the other is the nervous system. In the lower animals

Figure 1–38 Evolutionary relationships among some of the organisms mentioned in this book. The branches of the tree show paths of common descent but (unlike the tree shown in Figure 1–16) do not indicate by their length the passage of time. (Note, similarly, that the vertical axis of the diagram shows major categories of organisms and not time.)

the pattern of connections between nerve cells is for the most part rigidly specified genetically, and behavioral patterns evolve by genetic mutation. In higher animals, up to and including humans, the performance and structure of the nervous system are increasingly subject to modification (learning) as a consequence of the capacity of nerve cells to alter their connections in response to electrical activity caused by environmental influences.

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