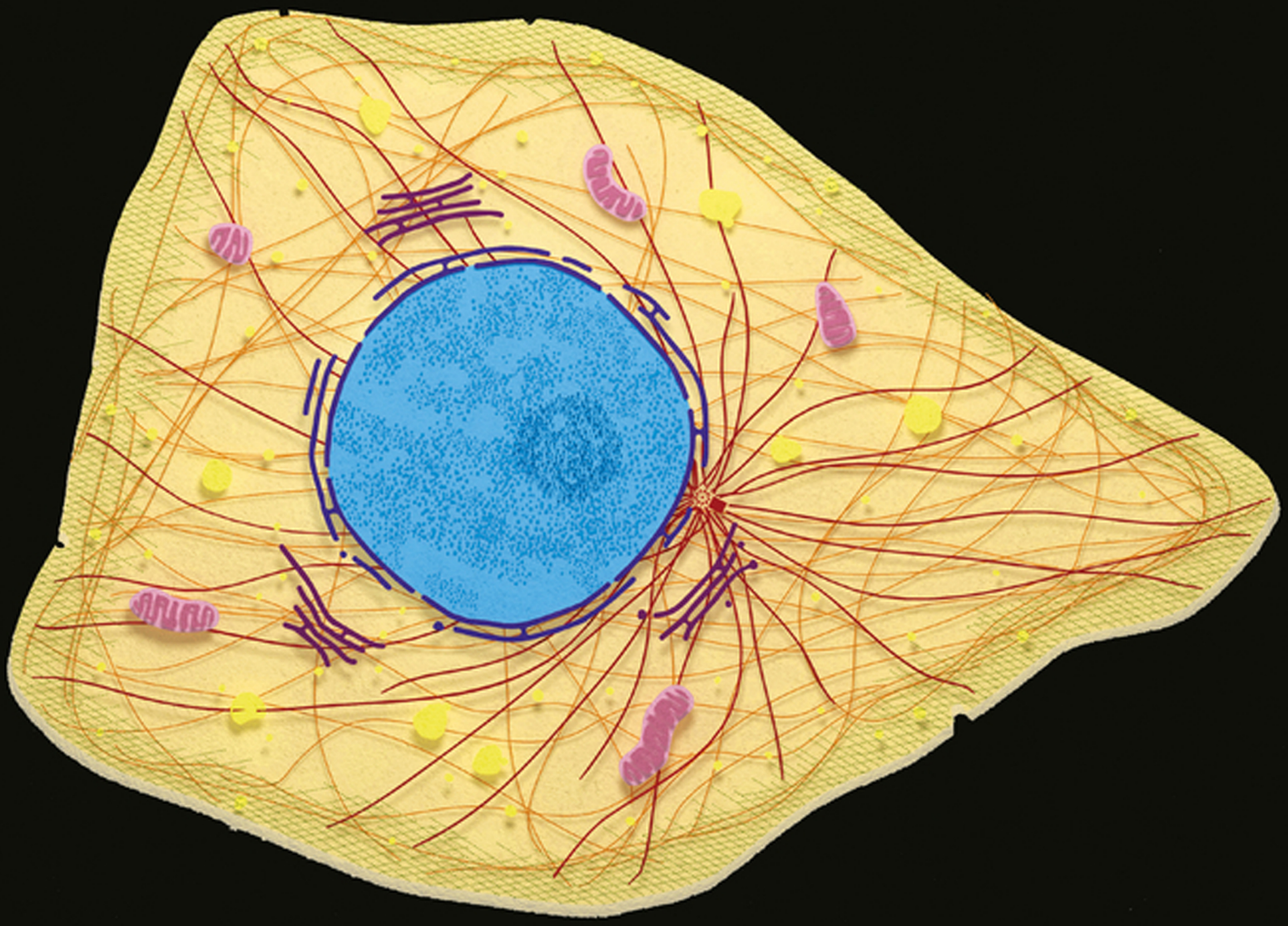
KARP'S CELL AND MOLECULAR BIOLOGY

CONCEPTS AND EXPERIMENTS

EIGHTH EDITION



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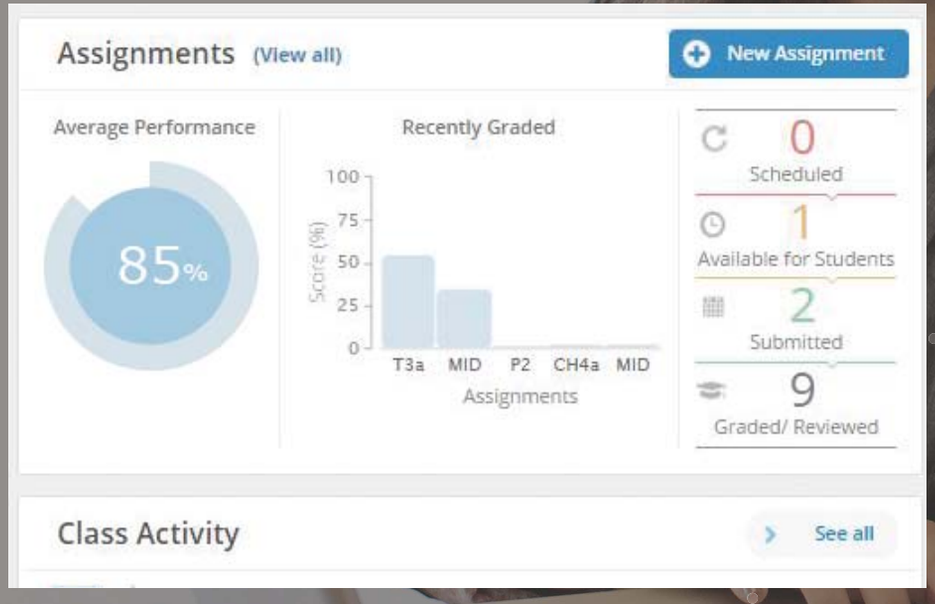

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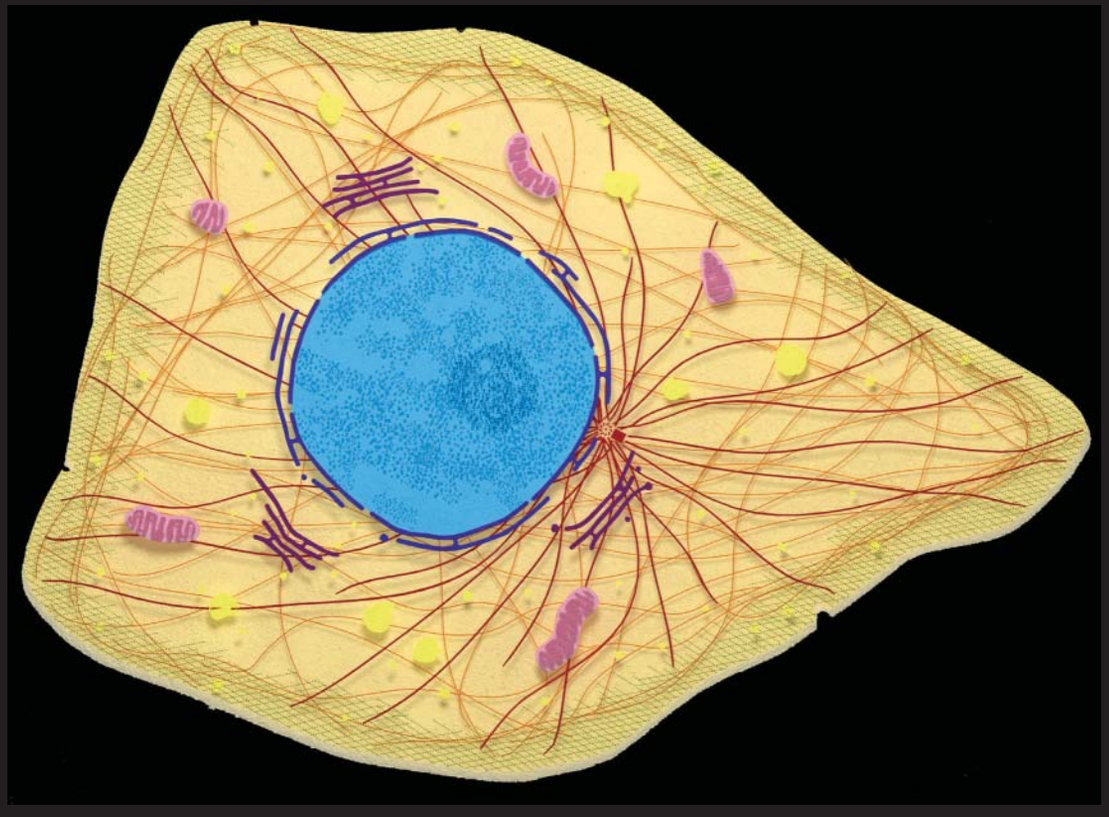

JANET IWASA ■ **WALLACE MARSHALL**

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About the Authors

JANET IWASA is a faculty member in the Biochemistry Department at the University of Utah. She received her bachelor's degree from Williams College and a Ph.D. in Cell Biology from the University of California, San Francisco, where she first became interested in the visualization of biological processes. As a postdoctoral fellow, she was awarded a fellowship from the National Science Foundation to create a multimedia exhibit with Nobel Laureate Jack Szostak (Harvard University) and the Museum of Science, Boston. She later joined Harvard Medical School as a faculty member in the Department of Cell Biology, where she utilized visualization tools to aid in scientific communication, exploration and outreach. Janet's award-winning illustrations and animations have appeared in scientific journals including Nature, Science and Cell, as well as in the New York Times.

WALLACE MARSHALL is Professor of Biochemistry and Biophysics at the University of California San Francisco. A native Long-Islander, he received his bachelor's degrees in Electrical Engineering and Biochemistry from the State University of New York at Stony Brook, and his Ph.D. in Biochemistry from UC San Francisco, where he studied organization of chromosomes within the nucleus with John Sedat. He then moved to Yale University for postdoctoral studies with Joel Rosenbaum, where he became interested in questions of organelle size control and cell organization, using cilia, flagella, and centrioles as model systems. In 2003, he joined the faculty at UCSF where he continues to study questions of cellular organization in a variety of model organisms including green algae, yeast, ciliates, and mammalian cells. In addition to his cell biology research, Dr. Marshall teaches Human Metabolism for the UCSF School of Pharmacy, Cell Biology for the UCSF Graduate Division, and runs a two week lab course on cell behavior. In 2014, he served as Program Committee Chair organizing the annual meeting of the American Society for Cell Biology. He is currently co-director of the Physiology summer course at the Marine Biological Laboratory in Woods Hole, Massachusetts.

ABOUT THE COVER

The cover image shows an illustration, created by Janet Iwasa, of an idealized mammalian cell with different subcellular compartments highlighted and digitally rendered to appear as a paper cut-out. An interactive version of this illustration can be viewed at the website of the Cell Image Library (http://cellimagelibrary.org), where the selection of any compartment will allow the user to view microscopic images of that compartment taken from real cells.

Preface to the Eighth Edition

For the past two decades, Dr. Gerald Karp has written *Cell and Molecular Biology: Concepts and Experiments*. During this time, he has maintained a consistent focus on combining rigor with accessibility, so that even students without prior training in cell biology, molecular biology, or biochemistry have been able to learn cell biology not just as a collection of facts but as a process of discovery. The value of this approach is that the lessons learned extend far beyond the field of cell biology, and provide a way for students to learn how science works, how new experiments can overturn previous dogmas, and how new techniques can lead to groundbreaking discovery. This approach makes cell biology come alive.

After seven editions, Dr. Karp is ready to move on to other adventures. We are excited to take on the challenge of continuing Dr. Karp's unique approach to teaching cell biology, while continuing to put students first. Our goal for this revision was to build upon Karp's hallmark experimental approach by bringing in our own unique perspectives and harnessing today's technology. With our new ***Experimental Walkthrough*** feature, available in WileyPLUS Learning Space, students can see first-hand how key experimental techniques are performed in the lab. These offer a mix of video, which show how researchers carry out experiments, and 3D animations that show a molecular-level view of how the experiments work. These Walkthroughs provide context and a visual explanation that helps make these important experimental techniques more concrete.

A solid understanding of quantitative concepts is becoming increasingly important within cell biology, but is an area that many students struggle with. To address this issue, we have also added another new video feature, called ***Quantitative Tutorials***, to visually illustrate how to solve specific analytical questions at the end of each chapter. The Quantitative Tutorial provides an accessible, student-friendly review of basic mathematical concepts used within the context of a biological problem, and will expand the available resources for quantitative and physical concepts within this 8th edition.

One key feature of the past editions was to highlight how cell biology impacts our daily lives, in terms of medicine and other areas of society. The ***Human Perspectives*** sections highlight human interest stories to reinforce and review basic cell biology, and also provide examples of how fundamental discoveries have progressed into clinical practice. We have expanded this feature so that now every chapter has at least one Human Perspectives section. As part of this feature we report on the latest clinical trials for various cell biology-based therapies and drugs, a feature that we hope will inspire students who are pursuing careers in health sciences fields. In addition to the full Human Perspectives sections, each chapter is now introduced with a short "chapter opener" designed to generate enthusiasm about the science in each chapter through provocative issues or questions. We hope that this will give our readers the opportunity to think more about the links between science, society, and our place in the universe.

Working on the 8th edition side by side with Dr. Karp has given us renewed admiration for his writing and his ability to keep track of the cutting edge in the full range of topics that comprise cell and molecular biology. In this and future editions of *Karp's Cell and Molecular Biology: Concepts and Experiments*, we are dedicated to carrying out Dr. Karp's original mission of providing an interesting, modern and readable text that is grounded in the experimental approach. We welcome your ideas and feedback as we continue our work on this text, so please feel free to get in touch.

Janet Iwasa (jiwasa@gmail.com)
Wallace Marshall (Wallace.Marshall@ucsf.edu)

WileyPLUS Learning Space

WileyPLUS Learning Space connects the text to carefully-selected media examples such as video, animations, and diagrams, and provides students a multitude of tools and content for self-study and practice. Instructors can customize their course content for students, create online homework and quizzes, and have insight into student activity through data analytics and reporting features. To try it, visit http://www.wileypluslearningspace.com. Here are some of the resources available in WileyPLUS Learning Space:

- Experimental Walkthrough Videos
- Quantitative Tutorial Videos
- Cell View Animations
- Video Library
- Biology Basics Animations
- Instructor's Manual by Joel Piperberg, Millersville University
- Clicker Questions by Leocadia Paliulis, Bucknell University and Omar Quintero, University of Richmond
- Lecture PowerPoint Presentations by Edmund B. Rucker, University of Kentucky
- Testbank and Answer Key by Robert Seiser, Roosevelt University

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Gerald Karp, who dedicated many years to carefully and thoughtfully writing and editing this text, has left a remarkable legacy that we are grateful to inherit. In putting together this edition, we are thankful for his insight, wisdom and advice that was always cheerfully and generously provided to us.

We are grateful to many individuals at John Wiley & Sons who made this edition possible. Kevin Witt brought us on board at the beginning stages and infused us with his enthusiasm for the project. Bonnie Roth provided superb leadership, guidance and support throughout the writing and editing process. Carrie Thompson, Melissa Edwards, Beth Pearson, and Liz Baird helped to keep us on organized and on track with the text and the various media elements. Patty Donovan of SPI Global played a central role

in coordinating the production of the text, incorporating changes to the text and numerous illustrations and images. Billy Ray led the team in obtaining new images used in this edition. Maureen Eide skillfully designed the interior and front cover.

Janet Iwasa thanks Rob Savage, Dyche Mullins and Jack Szostak, for inspiring and guiding her along the path towards becoming a biologist. Janet is particularly grateful for the support of her family, Adam, Aki and Kenzo, and the lifelong encouragement of her parents, Kuni and Mieko.

Wallace Marshall thanks his scientific mentors, Rolf Sternglanz, John Sedat, and Joel Rosenbaum, for launching him in the direction that he went. He thanks his parents, Clifford and Adele Marshall for making him who he is. And he thanks his family, Jennifer and Wyeth, for continued inspiration and support.

We also wish to thank all reviewers of this and previous editions:

STEVE ALAS
California State Polytechnic University, Pomona
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Northwestern University
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MRC Laboratory of Molecular Biology
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Nobel Prizes Awarded for Research in Cell and Molecular Biology Since 1958

Year	*Recipient**	*Prize*	*Area of Research*	*Pages in Text*
2015	Tomas Lindahl Paul Modrich Aziz Sancar	Chemistry	Mechanisms of DNA repair	532
2014	Eric Betzig W. E. Moerner Stefan Hell	Chemistry	Development of super-resolved fluorescence microscopy	699–700
2013	James E. Rothman Randy W. Schekman Thomas C. Südhof	M & P	Discoveries of machinery regulating vesicle traffic	263, 279
2012	John B. Gurdon	M & P**	Animal cloning, nuclear reprogramming	483
	Shinya Yamanaka		Cell reprogramming	20, 489
	Brian K. Kobilka Robert J. Lefkowitz	Chemistry	G protein-coupled receptors	588
2011	Bruce A. Beutler Jules A. Hoffmann	M & P	Innate immunity	664
	Ralph M. Steinman		Dendritic cells and Adaptive immunity	676
2009	Venkatraman Ramakrishnan Thomas A. Steitz Ada E. Yonath	Chemistry	Ribosome structure and function	453
	Eliazbeth H. Blackburn Carol W. Greider Jack W. Szostak	M & P	Telomeres and telomerase	475
2008	Francoise Barré-Sinoussi Luc Montagnier	M & P	Discovery of HIV	23
	Harald zur Hausen		Role of HPV in cancer	631
	Martin Chalfie Osamu Shimomura Roger Tsien	Chemistry	Discovery and development of GFP	260, 697
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2006	Andrew Z. Fire Craig C. Mello	M&P	RNA Interference	430
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	Aaron Ciechanover Avram Hershko Irwin Rose	Chemistry	Ubiquitin and proteasomes	509
2003	Peter Agre Roderick MacKinnon	Chemistry	Structure of membrane channels	143, 144
2002	Sydney Brenner John Sulston	M & P	Introduction of *C. elegans* as a model organism	16
	H. Robert Horvitz		Apoptosis in *C. elegans*	622
	John B. Fenn	Chemistry	Electrospray ionization in MS	717
	Koichi Tanaka		MALDI in MS	717
	Kurt Wüthrich		NMR analysis of proteins	55
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Year	*Recipient**	*Prize*	*Area of Research*	*Pages in Text*
2000	Arvid Carlsson	M & P	Synaptic transmission and signal transduction	164
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	Ferid Murad			
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1995	Edward B. Lewis	M & P	Genetic control of embryonic development	15
	Christiane Nüsslein-Volhard			
	Eric Wieschaus			
1994	Alfred Gilman	M & P	Structure and function of GTP-binding (G) proteins	593
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1993	Kary Mullis	Chemistry	Polymerase chain reaction (PCR)	726
	Michael Smith		Site-directed mutagenesis (SDM)	735
	Richard J. Roberts	M & P	Intervening sequences	420
	Phillip A. Sharp			
1992	Edmond Fischer	M & P	Alteration of enzyme activity by phosphorylation/ dephosphorylation	109, 600
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1991	Erwin Neher	M & P	Measurement of ion flux by patch-clamp recording	143
	Bert Sakmann			
1990	Joseph E. Murray	M & P	Organ and cell transplantation in human disease	684
	E. Donnall Thomas			
1989	J. Michael Bishop	M & P	Cellular genes capable of causing malignant transformation	633
	Harold Varmus			
	Thomas R. Cech	Chemistry	Ability of RNA to catalyze reactions	425, 450
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1987	Susumu Tonegawa	M & P	DNA rearrangements responsible for antibody diversity	681
1986	Rita Levi-Montalcini	M & P	Factors that affect nerve outgrowth	379
	Stanley Cohen			
1985	Michael S. Brown	M & P	Regulation of cholesterol metabolism and endocytosis	319
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1984	Georges Köhler	M & P	Monoclonal antibodies	738, 739
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	Niels K. Jerne		Antibody formation	666
1983	Barbara McClintock	M & P	Mobile elements in the genome	391, 392, 394
1982	Aaron Klug	Chemistry	Structure of nucleic acid-protein complexes	55
1980	Paul Berg	Chemistry	Recombinant DNA technology	692, 723
	Walter Gilbert		DNA sequencing technology	728
	Frederick Sanger			
	Baruj Bennacerraf	M & P	Major histocompatibility complex	684
	Jean Dausset			
	George D. Snell			
1978	Werner Arber	M & P	Restriction endonuclease technology	723
	Daniel Nathans			
	Hamilton O. Smith			
	Peter Mitchell	Chemistry	Chemiosmotic mechanism of oxidative phosphorylation	176
1976	D. Carleton Gajdusek	M & P	Prion-based diseases	63
1975	David Baltimore	M & P	Reverse transcriptase and tumor virus activity	633

Year	*Recipient**	*Prize*	*Area of Research*	*Pages in Text*
	Renato Dulbecco Howasrd M. Temin			
1974	Albert Claude Christian de Duve George E. Palade	M & P	Structure and function of internal components of cells	262
1972	Gerald Edelman Rodney R. Porter	M & P	Immunoglobulin structure	678
	Christian B. Anfinsen	Chemistry	Relationship between primary and tertiary structure of proteins	60
1971	Earl W. Sutherland	M & P	Mechanism of hormone action and cyclic AMP	590, 595, 596
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1969	Max Delbrück Alfred D. Hershey Salvador E. Luria	M & P	Genetic structure of viruses	23, 380
1968	H. Gobind Khorana Marshall W. Nirenberg	M & P	Genetic code	722-723
	Robert W. Holley		Transfer RNA structure	439
1966	Peyton Rous	M & P	Tumor viruses	632
1965	Francois Jacob Andre M. Lwoff Jacques L. Monod	M & P	Bacterial operons wand messenger RNA	406, 456
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1963	John C. Eccles Alan L. Hodgkin Andrew F. Huxley	M & P	Ionic basis of nerve membrane potentials	160
1962	Francis H. C. Crick James D. Watson Maurice H. F. Wilkins	M & P	Three-dimensional structure of DNA	374-377
	John C. Kendrew Max F. Perutz	Chemistry	Three-dimensional structure of globular proteins	56
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1960	F. MacFarlane Burnet Peter B. Medawar	M & P	Clonal selection theory of antibody formation	666
1959	Arthur Kornberg Severo Ochoa	M & P	Synthesis of DNA and RNA	518, 523
1958	George W. Beadle Joshua Lederberg Edward L. Tatum	M & P	Gene expression	405-406
	Frederick Sanger	Chemistry	Primary structure of proteins	53

*In a few cases, corecipients whose research was in an area outside of cell and molecular biology have been omitted from this list.

**Medicine and Physiology

Topics of Human Interest

NOTE: An f after a page denotes a figure; t denotes a table; fn denotes a footnote; HP denotes a Human Perspective; EP denotes an Experimental Pathway.

CHAPTER 1

Introduction to the Study of Cell and Molecular Biology

WE ARE CELLS

We are made of cells. Cells make up our skin, our organs, and our muscles. The brain, the seat of our thoughts and desires, is made of cells. Our blood vessels teem with cells. Fertilization is no more or less than a joining of two separate cells to produce a single new cell, which then multiplies to produce the embryo. When we grow from a tiny embryo into a large adult, we do so by adding more and more cells. When we get sick, it is often because our cells have run amok. And when we grow old, it is because our cells gradually give up the ghost. After we die and are buried, soon the only remnants of our existence are bones, teeth, and hair, structures that were sculpted in life by the ceaseless activity of cells. Many medicines work by changing how cells behave, and in recent years cells themselves are being used as medicines to cure sick people. Because all living things are made of one or more cells, the origin of life corresponds to the origin of cells. Starting with this chapter, we will explore what cells are and how they work, themes that will be expanded throughout this book.

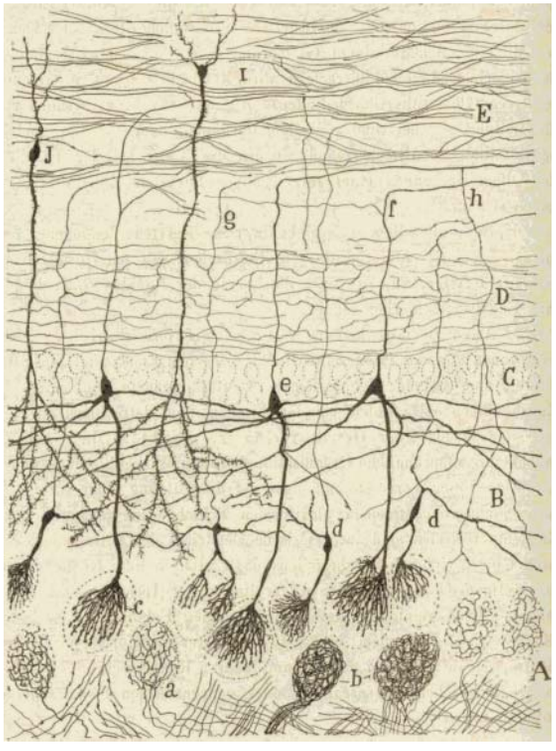


Diagram of nerve cells from the cat brain, hand-drawn by Santiago Ramón y Cajal. Ramón y Cajal was the first to recognize that the brain is made up of huge numbers of individual cells, rather than a continuous connected network as proposed by his competitor, Camillo Golgi. Ramón y Cajal and Golgi fought a protracted battle over this point, but eventually the meticulous detail of Ramón y Cajal's work convinced the world that the brain is indeed a collective of individual cells.

SOURCE: Histology of the Nervous System of Man and Vertebrates by Cajal (1995) Fig. "Neurons in the cat brain." By permission of Oxford University Press.

CHAPTER OUTLINE

1.1 The Discovery of Cells

Cells, and the structures they comprise, are too small to be directly seen, heard, or touched. In spite of this tremendous handicap, cells are the subject of hundreds of thousands of publications each year, with virtually every aspect of their minuscule structure coming under scrutiny. In many ways, the study of cell and molecular biology stands as a tribute to human curiosity for seeking to discover and to human creative intelligence for devising the complex instruments and elaborate techniques by which these discoveries can be made. This is not to imply that cell and molecular biologists have a monopoly on these noble traits. At one end of the scientific spectrum, astronomers are utilizing an orbiting telescope to capture images of primordial galaxies that are so far from Earth they appear to us today as they existed more than 13 billion years ago, only a few hundred million years after the Big Bang. At the other end of the spectrum, nuclear physicists have recently forced protons to collide with one another at velocities approaching the speed of light, confirming the existence of a hypothesized particle—the Higgs boson—that is proposed to endow all other subatomic particles with mass. Clearly, our universe consists of worlds within worlds, all aspects of which make for fascinating study.

As will be apparent throughout this book, cell and molecular biology is *reductionist*; that is, it is based on the view that knowledge of the parts of the whole can explain the character of the whole. When viewed in this way, our feeling for the wonder and mystery of life may be replaced by the need to explain everything in terms of the workings of the "machinery" of the living system. To the degree to which this occurs, it is hoped that this loss can be replaced by an equally strong appreciation for the beauty and complexity of the mechanisms underlying cellular activity.

Microscopy

Because of their small size, cells can only be observed with the aid of a **microscope**, an instrument that provides a magnified image of a tiny object. We do not know when humans first discovered the remarkable ability of curved-glass surfaces to bend light and form images. Spectacles were first made in Europe in the thirteenth century, and the first compound (double-lens) light microscopes were constructed by the end of the sixteenth century. By the mid-1600s, a handful of pioneering scientists had used their handmade microscopes to uncover a world that would never have been revealed to the naked eye. The discovery of cells (**FIGURE 1.1a**) is generally credited to Robert Hooke, an English microscopist who, at age 27, was awarded the position of curator of the Royal Society of London, England's foremost scientific academy. One of the many questions Hooke attempted to answer was why stoppers made of cork (part of the bark of trees) were so well suited to holding air in a bottle. As he wrote in 1665: "I took a good clear piece of cork, and with a Pen-knife sharpen'd as keen as a Razor, I cut a piece of it off, and . . . then examining it with a *Microscope*, me thought I could perceive it to appear a little porous . . . much like a Honeycomb." Hooke called the pores *cells* because they reminded him of the cells inhabited by monks living in a monastery. In actual fact, Hooke had observed the empty cell walls of dead plant tissue, walls that had originally been produced by the living cells they surrounded.

Meanwhile, Antonie van Leeuwenhoek, a Dutchman who earned a living selling clothes and buttons, was spending his spare time grinding lenses and constructing simple microscopes of remarkable quality (Figure 1.1*b*). For 50 years, Leeuwenhoek sent letters to the Royal Society of London describing his microscopic observations—along with a rambling discourse on his daily habits and the state of his health. Leeuwenhoek was the first to examine a drop of pond water under the microscope and, to his amazement, observe the teeming microscopic "animalcules" that darted back and forth before his eyes. He was also the first to describe various forms of bacteria, which he obtained from water in which pepper had been soaked and from scrapings from his teeth. His initial letters to the Royal Society describing this previously unseen world were met with such skepticism that the society dispatched its curator, Robert Hooke, to confirm the observations. Hooke did just that, and Leeuwenhoek was soon a worldwide celebrity, receiving visits in Holland from Peter the Great of Russia and the queen of England.

(a)

(b)

FIGURE 1.1 The discovery of cells. (*a*) One of Robert Hooke's more ornate compound (double-lens) microscopes. (Inset) Hooke's drawing of a thin slice of cork, showing the honeycomb-like network of "cells." (*b*) Single-lens microscope used by Antonie van Leeuwenhoek to observe bacteria and other microorganisms. The biconvex lens, which was capable of magnifying an object approximately 270 times and providing a resolution of approximately 1.35 µm, was held between two metal plates.

SOURCE: (a) The Granger Collection, New York; inset Biophoto Associates/Getty Images, Inc.; (b) © Bettmann/Corbis

Cell Theory

It wasn't until the 1830s that the widespread importance of cells was realized. In 1838, Matthias Schleiden, a German lawyer turned botanist, concluded that, despite differences in the structure of various

tissues, plants were made of cells and that the plant embryo arose from a single cell. In 1839, Theodor Schwann, a German zoologist and colleague of Schleiden's, published a comprehensive report on the cellular basis of animal life. Schwann concluded that the cells of plants and animals are similar structures and proposed these two tenets of the **cell theory**:

- All organisms are composed of one or more cells.
- The cell is the structural unit of life.

Schleiden and Schwann's ideas on the *origin* of cells proved to be less insightful; both agreed that cells could arise from noncellular materials. Given the prominence that these two scientists held in the scientific world, it took a number of years before observations by other biologists were accepted as demonstrating that cells did not arise in this manner any more than organisms arose by spontaneous generation. By 1855, Rudolf Virchow, a German pathologist, had made a convincing case for the third tenet of the cell theory:

- Cells can arise only by division from a preexisting cell.

REVIEW

1. When Robert Hooke first described cells, what was he actually looking at?
2. What are the three componnents of cell theory?

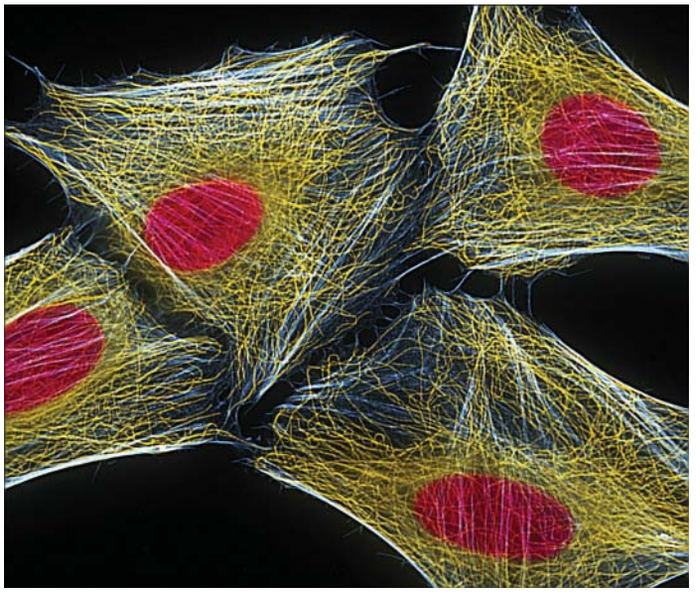


FIGURE 1.2 HeLa cells, such as the ones pictured here, were the first human cells to be kept in culture for long periods of time and are still in use today. Unlike normal cells, which have a finite lifetime in culture, these cancerous HeLa cells can be cultured indefinitely as long as conditions are favorable to support cell growth and division.

SOURCE: Torsten Wittmann/Photo Researchers, Inc.

1.2 Basic Properties of Cells

Just as plants and animals are alive, so too are cells. Life, in fact, is the most basic property of cells, and cells are the smallest units to exhibit this property. Unlike the parts of a cell, which simply deteriorate if isolated, whole cells can be removed from a plant or animal and cultured in a laboratory where they will grow and reproduce for extended periods of time. If mistreated, they may die. Death can also be considered one of the most basic properties of life, because only a living entity faces this prospect. Remarkably, cells within the body generally die "by their own hand"—the victims of an internal program that causes cells that are no longer needed or cells that pose a risk of becoming cancerous to eliminate themselves.

The first culture of human cells was begun by George and Martha Gey of Johns Hopkins University in 1951. The cells were obtained from a malignant tumor and named HeLa cells after the donor, Henrietta Lacks. HeLa cells—descended by cell division from this first cell sample—are still being grown in laboratories around the world today (**FIGURE 1.2**). Because they are so much simpler to study than cells situated within the body, cells grown **in vitro** (i.e., in culture, outside the body) have become an essential tool of cell and molecular biologists. In fact, much of the information that will be discussed in this book has been obtained using cells grown in laboratory cultures.

We will begin our exploration of cells by examining a few of their most fundamental properties.

Cells Are Highly Complex and Organized

Complexity is a property that is evident when encountered, but difficult to describe. For the present, we can think of complexity in terms of order and consistency. The more complex a structure, the greater the number of parts that must be in their proper place, the less tolerance for errors in the nature and interactions of the parts, and the more regulation or control that must be exerted to maintain the system. Cellular activities can be remarkably precise. DNA duplication, for example, occurs with an error rate of less than one mistake every ten million nucleotides incorporated—and most of these are quickly corrected by an elaborate repair mechanism that recognizes the defect.

During the course of this book, we will have occasion to consider the complexity of life at several different levels. We will discuss the organization of atoms into small-sized molecules; the organization of these molecules into giant polymers; and the organization of different types of polymeric molecules into complexes, which in turn are organized into subcellular organelles and finally into cells. As will be apparent, there is a great deal of consistency at every level. Each type of cell has a consistent appearance when viewed under a high-powered electron microscope; that is, its organelles have a particular shape and location, from one individual of a species to another. Similarly, each type of organelle has a consistent composition of macromolecules, which are arranged in a predictable pattern. Consider the cells lining your intestine that are responsible for removing nutrients from your digestive tract. **FIGURE 1.3** illustrates the many different levels of organization present in such a tissue.

The epithelial cells that line the intestine are tightly connected to each other like bricks in a wall (Figure 1.3 inset 1). The apical ends of these cells, which face the intestinal channel, have long processes (*microvilli*) that facilitate absorption of nutrients (inset 2). The microvilli are able to project outward from the apical cell surface because they contain an internal skeleton made of filaments, which in turn are composed of protein (*actin*) monomers polymerized in a characteristic array (inset 3). At their basal ends, intestinal cells have large numbers of mitochondria (inset 4) that provide the energy required to fuel various membrane transport processes. Each mitochondrion is composed of a defined pattern of internal membranes,

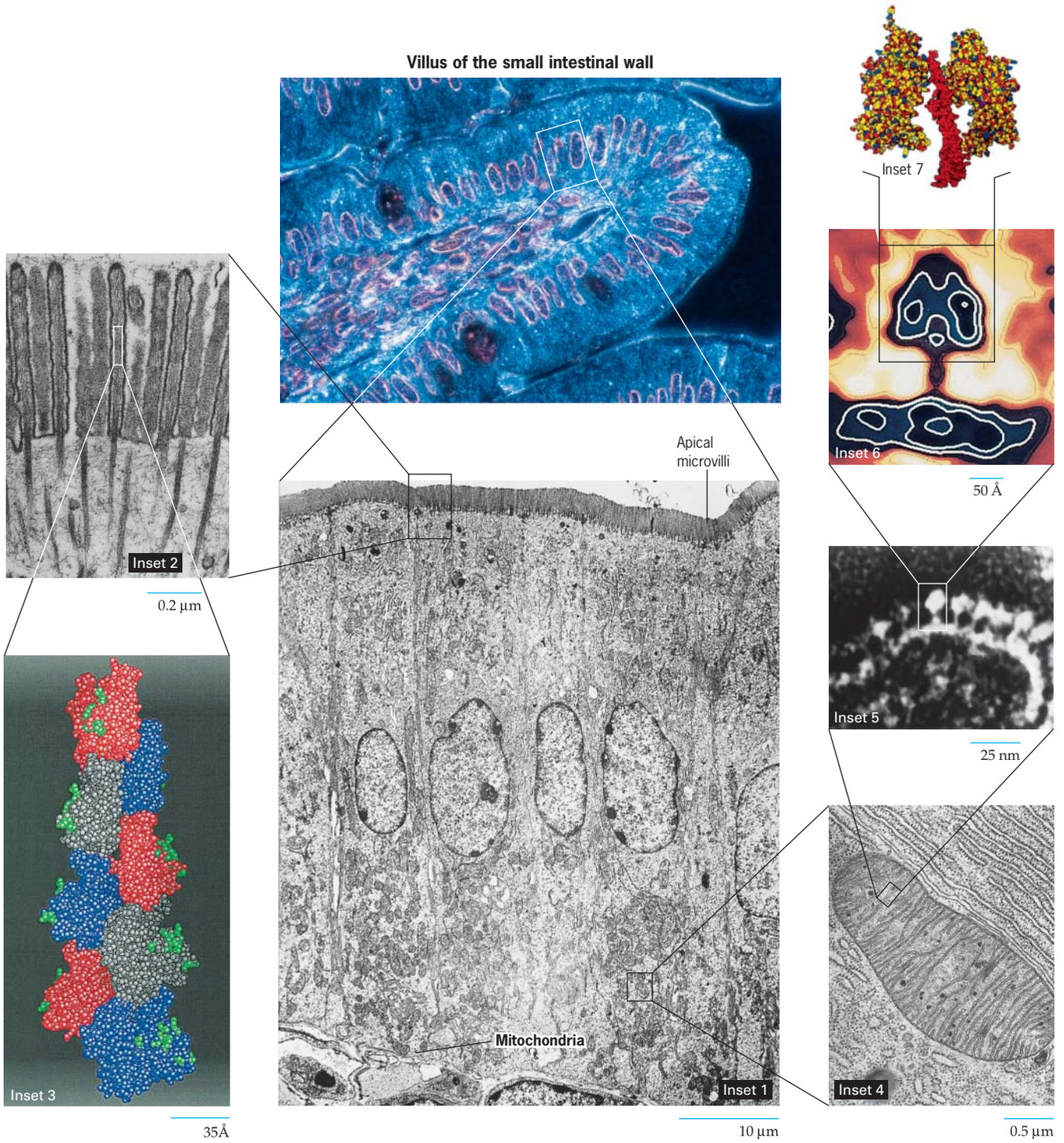


FIGURE 1.3 Levels of cellular and molecular organization. The brightly colored photograph of a stained section shows the microscopic structure of a villus of the wall of the small intestine, as seen through the light microscope. Inset 1 shows an electron micrograph of the epithelial layer of cells that lines the inner intestinal wall. The apical surface of each cell, which faces the channel of the intestine, contains a large number of microvilli involved in nutrient absorption. The basal region of each cell contains large numbers of mitochondria, where energy is made available to the cell. Inset 2 shows the apical microvilli; each microvillus contains a bundle of actin filaments. Inset 3 shows the actin protein subunits that make up each filament. Inset 4 shows an individual mitochondrion similar to those found in the basal region of the epithelial cells. Inset 5 shows a portion of an inner membrane of a mitochondrion including the stalked particles that project from the membrane and correspond to the sites where ATP is synthesized. Insets 6 and 7 show molecular models of the ATP- synthesizing machinery, which is discussed at length in Chapter 5.

SOURCE: Light micrograph Cecil Fox/Photo Researchers; inset 1 courtesy of Shakti P. Kapur, Georgetown University Medical Center; inset 2 from Mark S. Mooseker and Lewis G. Tilney, *J. Cell Biol*. 67:729, 1975, reproduced with permission of the Rockefeller University Press; inset 3 courtesy of Kenneth C. Holmes; inset 4 Keith R. Porter/Photo Researchers; inset 5 courtesy of Humberto Fernandez-Moran; inset 6 courtesy of Roderick A. Capaldi; inset 7 courtesy of Wolfgang Junge, Holger Lill, and Siegfried Engelbrecht, University of Osnabrück, Germany.

which in turn are composed of a consistent array of proteins, including an electrically powered ATP-synthesizing machine that projects from the inner membrane like a ball on a stick (insets 5–7).

One of the truly fascinating aspects of cells is that they achieve organization at many different scales using physical processes that are essentially random. Even though living cells are highly complex and ordered, it has become increasingly evident in recent years that random (*stochastic*) events play a critical role in all cellular activities. Many of the molecules within living cells are in a constant state of random movement, propelled by thermal energy they acquire from their environment. Cells have evolved the capacity to utilize this movement in highly directed ways. We can consider one example of this phenomenon, keeping in mind that many other cases could be described. Proteins are complex molecules often consisting of hundreds of amino acid building blocks and attaining molecular masses over a hundred thousand Daltons. Despite their huge size, proteins consist of a polypeptide chain that has to fold into a precisely defined three-dimensional (native) structure. If it fails to fold properly, the protein will lack meaningful function. In 1969, Cyrus Levinthal of Columbia University identified certain features of this folding process that became known as Levinthal's paradox. For one part of the paradox, Levinthal noted that, if protein folding depended solely on random molecular movements, it would require a period of time greater than the age of the universe for a protein to fold into its native structure. According to this scenario, the time it would take for a protein to fold properly might be compared to the period required for a monkey sitting at a piano to compose one of Beethoven's concertos. The paradox inherent in protein folding becomes evident knowing that, despite their enormous complexity, proteins actually acquire their native structures within fractions of a second. How is the paradox resolved? Even though folding of a protein is driven by random thermal motion, the process occurs in stepwise fashion so that the protein folds along pathways in which less structured intermediates guide the formation of better formed subsequent intermediates. In other words, the folding pathway allows proteins to rapidly "jump" from one step to the next until the native structure is reached. To carry over the solution of the protein folding paradox to the monkey at the piano, it would be as if every time the monkey tapped an appropriate key, that note would be recorded, allowing the monkey to move toward the next note in the concerto. As long as the monkey was an active player, the composition of the concerto could be accomplished quite rapidly. It can be said that these types of events are "biased." They depend upon random activities, but they lead to directed outcomes because they select for intermediate stages that lie on the path leading to the desired outcome.

Fortunately for cell and molecular biologists, evolution has moved rather slowly at the levels of biological organization with which they are concerned. Whereas a human and a cat, for example, have very different anatomical features, the cells that make up their tissues, and the organelles that make up their cells, are very similar. The actin filament portrayed in Figure 1.3, inset 3, and the ATP-synthesizing enzyme of inset 6 are virtually identical to similar structures found in such diverse organisms as humans, snails, yeast, and redwood trees. Information obtained by studying cells from one type of organism often has direct application to other forms of life. Many of the most basic processes, such as the synthesis of proteins, the conservation of chemical energy, or the construction of a membrane, are remarkably similar in all living organisms.

Cells Possess a Genetic Program and the Means to Use It

Organisms are built according to information encoded in a collection of genes, which are constructed of DNA. The human genetic program contains enough information, if converted to words, to fill millions of pages of text. Remarkably, this vast amount of information is packaged into a set of chromosomes that occupies the space of a cell nucleus—hundreds of times smaller than the dot on this *i*.

Genes are more than storage lockers for information: They constitute the recipes for constructing cellular structures, the directions for running cellular activities, and the program for making more of themselves. The molecular structure of genes allows for changes in genetic information (mutations) that lead to variation among individuals, which forms the basis of biological evolution. Discovering the mechanisms by which cells use and transmit their genetic information has been one of the greatest achievements of science in recent decades.

Cells Are Capable of Producing More of Themselves

Just as individual organisms are generated by reproduction, so too are individual cells. Cells reproduce by division, a process in which the contents of a "mother" cell are distributed into two "daughter" cells. Prior to division, the genetic material is faithfully duplicated, and each daughter cell receives a complete and equal share of genetic information. In most cases, the two daughter cells have approximately equal volume. In some cases, however, as occurs when a human oocyte undergoes division, one of the cells can retain nearly all of the cytoplasm, even though it receives only half of the genetic material (**FIGURE 1.4**).

Cells Acquire and Utilize Energy

Every biological process requires the input of energy. Virtually all of the energy utilized by life on the Earth's surface arrives in the form of electromagnetic radiation from the sun. The energy of light is trapped by light-absorbing pigments present in the membranes of photosynthetic cells (**FIGURE 1.5**). Light energy is converted by photosynthesis

FIGURE 1.4 Cell reproduction. This mammalian oocyte has recently undergone a highly unequal cell division in which most of the cytoplasm has been retained within the large oocyte, which has the potential to be fertilized and develop into an embryo. The other cell is a nonfunctional remnant that consists almost totally of nuclear material (indicated by the blue-staining chromosomes, arrow).

SOURCE: Courtesy of Jonathan van Blerkom.

FIGURE 1.5 Acquiring energy. A living cell of the filamentous alga *Spirogyra*. The ribbon-like chloroplast, which is seen to zigzag through the cell, is the site where energy from sunlight is captured and converted to chemical energy during photosynthesis.
SOURCE: M. I. Walker/Photo Researchers, Inc.

into chemical energy that is stored in energy-rich carbohydrates, such as sucrose or starch. For most animal cells, energy arrives prepackaged, often in the form of the sugar glucose. In humans, glucose is released by the liver into the blood where it circulates through the body delivering chemical energy to all the cells. Once in a cell, the glucose is disassembled in such a way that its energy content can be stored in a readily available form (usually as ATP) that is later put to use in running all of the cell's myriad energy-requiring activities. Cells expend an enormous amount of energy simply breaking down and rebuilding the macromolecules and organelles of which they are made. This continual "turnover," as it is called, maintains the integrity of cell components in the face of inevitable wear and tear and enables the cell to respond rapidly to changing conditions.

Cells Carry Out a Variety of Chemical Reactions

Cells function like miniaturized chemical plants. Even the simplest bacterial cell is capable of hundreds of different chemical transformations, none of which occurs at any significant rate in the inanimate world. Virtually all chemical changes that take place in cells require *enzymes*—molecules that greatly increase the rate at which a chemical reaction occurs. The sum total of the chemical reactions in a cell represents that cell's **metabolism**.

Cells Engage in Mechanical Activities

Cells are sites of bustling activity. Materials are transported from place to place, structures are assembled and then rapidly disassembled, and, in many cases, the entire cell moves itself from one site to another. These types of activities are based on dynamic, mechanical changes within cells, many of which are initiated by changes in the shape of "motor" proteins. Motor proteins are just one of many types of molecular "machines" employed by cells to carry out mechanical activities.

Cells Are Able to Respond to Stimuli

Some cells respond to stimuli in obvious ways; a single-celled protist, for example, moves away from an object in its path or moves toward a source of nutrients. Cells within a multicellular plant or animal respond to stimuli less obviously. Most cells are covered with *receptors* that interact with substances in the environment in highly specific ways. Cells possess receptors to hormones, growth factors, and extracellular materials, as well as to substances on the surfaces of other cells. A cell's receptors provide pathways through which external stimuli can evoke specific responses in target cells. Cells may respond to specific stimuli by altering their metabolic activities, moving from one place to another, or even committing suicide.

Cells Are Capable of Self-Regulation

In recent years, a new term has been used to describe cells: *robustness*. Cells are robust, that is, hearty or durable, because they are protected from dangerous fluctuations in composition and behavior. Should such fluctuations occur, specific feedback circuits are activated that serve to return the cell to the appropriate state. In addition to requiring energy, maintaining a complex, ordered state requires constant regulation. The importance of a cell's regulatory mechanisms becomes most evident when they break down. For example, failure of a cell to correct a mistake when it duplicates its DNA may result in a debilitating mutation, or a breakdown in a cell's growth-control safeguards can transform the cell into a cancer cell with the capability of destroying the entire organism. We are gradually learning how a cell controls its activities, but much more is left to discover.

Consider the following experiment conducted in 1891 by Hans Driesch, a German embryologist. Driesch found that he could completely separate the first two or four cells of a sea urchin embryo and each of the isolated cells would proceed to develop into a normal embryo (**FIGURE 1.6**). How can a cell that is normally destined to

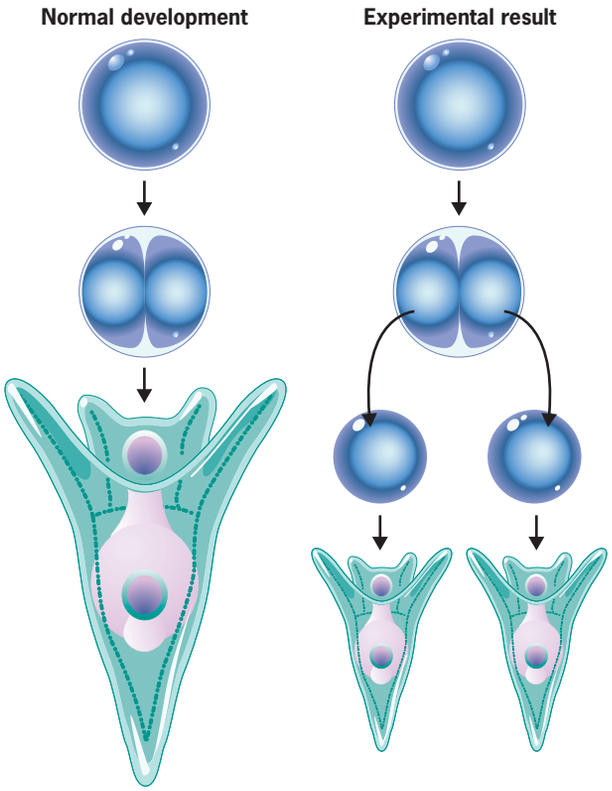


FIGURE 1.6 Self-regulation. The left panel depicts the normal development of a sea urchin in which a fertilized egg gives rise to a single embryo. The right panel depicts an experiment in which the cells of an early embryo are separated from one another after the first division, and each cell is allowed to develop in isolation. Rather than developing into half of an embryo, as it would if left undisturbed, each isolated cell recognizes the absence of its neighbor, regulating its development to form a complete (although smaller) embryo.

form only part of an embryo regulate its own activities and form an entire embryo? How does the isolated cell recognize the absence of its neighbors, and how does this recognition redirect the entire course of the cell's development? How can a part of an embryo have a sense of the whole? We are not able to answer these questions much better today than we were more than a hundred years ago when the experiment was performed.

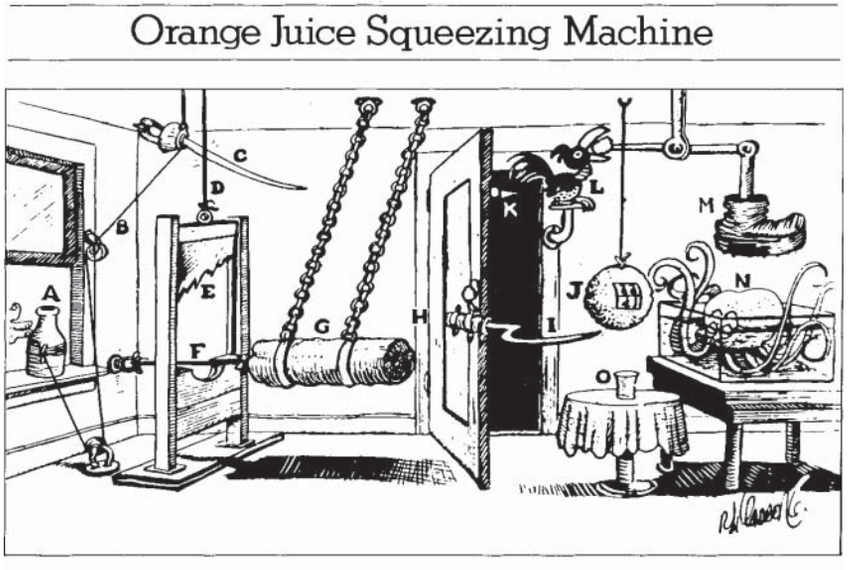
Throughout this book we will be discussing processes that require a series of ordered steps, much like the assembly-line construction of an automobile in which workers add, remove, or make specific adjustments as the car moves along. In the cell, the information for product design resides in the nucleic acids, and the construction workers are primarily proteins. It is the presence of these two types of macromolecules that, more than any other factor, sets the chemistry of the cell apart from that of the nonliving world. In the cell, the workers must act without the benefit of conscious direction. Each step of a process must occur spontaneously in such a way that the next step is automatically triggered. In many ways, cells operate in a manner analogous to the orange-squeezing contraption discovered by "The Professor" and shown in **FIGURE 1.7**. Each type of cellular activity requires a unique set of highly complex molecular tools and machines—the products of eons of natural selection and biological evolution. A primary goal of biologists is to understand the molecular structure and role of each component involved in a particular activity, the means by which these components interact, and the mechanisms by which these interactions are regulated.

Cells Evolve

How did cells arise? Of all the major questions posed by biologists, this question may be the least likely ever to be answered. It is presumed that cells evolved from some type of precellular life form, which in turn evolved from nonliving organic materials that were present in the primordial seas. Whereas the origin of cells is shrouded in near-total mystery, the evolution of cells can be studied by examining organisms that are alive today. If you were to observe the features of a bacterial cell living in the human intestinal tract (see **FIGURE 1.18a**) and a cell that is part of the lining of that tract (Figure 1.3), you would be struck by the differences between the two cells. Yet both of these cells, as well as all other cells that are present in living organisms, share many features, including a common genetic code, a plasma membrane, and ribosomes. According to one of the tenets of modern biology, all living organisms have evolved from a single, common ancestral cell that lived more than three billion years ago. Because it gave rise to all the living organisms that we know of, this ancient cell is often referred to as the *last universal common ancestor* (or *LUCA*). We will examine some of the events that occurred during the evolution of cells in the Experimental Pathway at the end of the chapter. Future chapters will explore biochemical aspects of the origin of life. Keep in mind that evolution is not simply an event of the past, but an ongoing process that continues to modify the properties of cells that will be present in organisms that have yet to appear. For example, evolution of drug resistance in bacteria is a major health concern and will be discussed in Section 3.8.

REVIEW

1. List the fundamental properties shared by all cells. Describe the importance of each of these properties.
2. Describe the features of cells that suggest that all living organisms are derived from a common ancestor.
3. What is the source of energy that supports life on Earth? How is this energy passed from one organism to the next?



Professor Butts steps into an open elevator shaft and when he lands at the bottom he finds a simple orange squeezing machine. Milkman takes empty milk bottle (**A**), pulling string (**B**) which causes sword (**C**) to sever cord (**D**) and allow guillotine blade (**E**) to drop and cut rope (**F**) which releases battering ram (**G**). Ram bumps against open door (**H**), causing it to close. Grass sickle (**I**) cuts a slice off end of orange (**J**)–at the same time spike (**K**) stabs "prune hawk" (**L**) he opens his mouth to yell in agony, thereby releasing prune and allowing diver's boot (**M**) to drop and step on sleeping octopus (**N**). Octopus awakens in a rage and, seeing diver's face which is painted on orange, attacks it and crushes it with tentacles, thereby causing all the juice in the orange to run into glass (**O**).

Later on you can use the log to build a log cabin where you can raise your son to be President like Abraham Lincoln.

FIGURE 1.7 Cellular activities are often analogous to this "Rube Goldberg machine" in which one event "automatically" triggers the next event in a reaction sequence.

SOURCE: Rube Goldberg is the ® and © of Rube Goldberg, Inc.

1.3 Characteristics That Distinguish Prokaryotic and Eukaryotic Cells

Once the electron microscope became widely available, biologists were able to examine the internal structure of a wide variety of cells. It became apparent from these studies that there were two basic classes of cells—prokaryotic and eukaryotic—distinguished by their size and the types of internal structures, or **organelles**, they contain (**FIGURE 1.8**). The existence of two distinct classes of cells, without any known intermediates, represents one of the most fundamental evolutionary divisions in the biological world. The structurally simpler **prokaryotic** cells include bacteria, whereas the structurally more complex **eukaryotic** cells include protists, fungi, plants, and animals.[1]

We are not sure when prokaryotic cells first appeared on Earth. Evidence of prokaryotic life has been obtained from rocks approximately 2.7 billion years of age. Not only do these rocks contain what appear to be fossilized microbes, they contain complex organic molecules that are characteristic of particular types of prokaryotic organisms, including cyanobacteria. It is unlikely that such molecules could have been synthesized abiotically, that is, without the involvement of living cells. Cyanobacteria almost certainly appeared by 2.4 billion

[1]Those interested in examining a proposal to do away with the concept of prokaryotic versus eukaryotic organisms can read a brief essay by N. R. Pace in *Nature* 441:289, 2006.

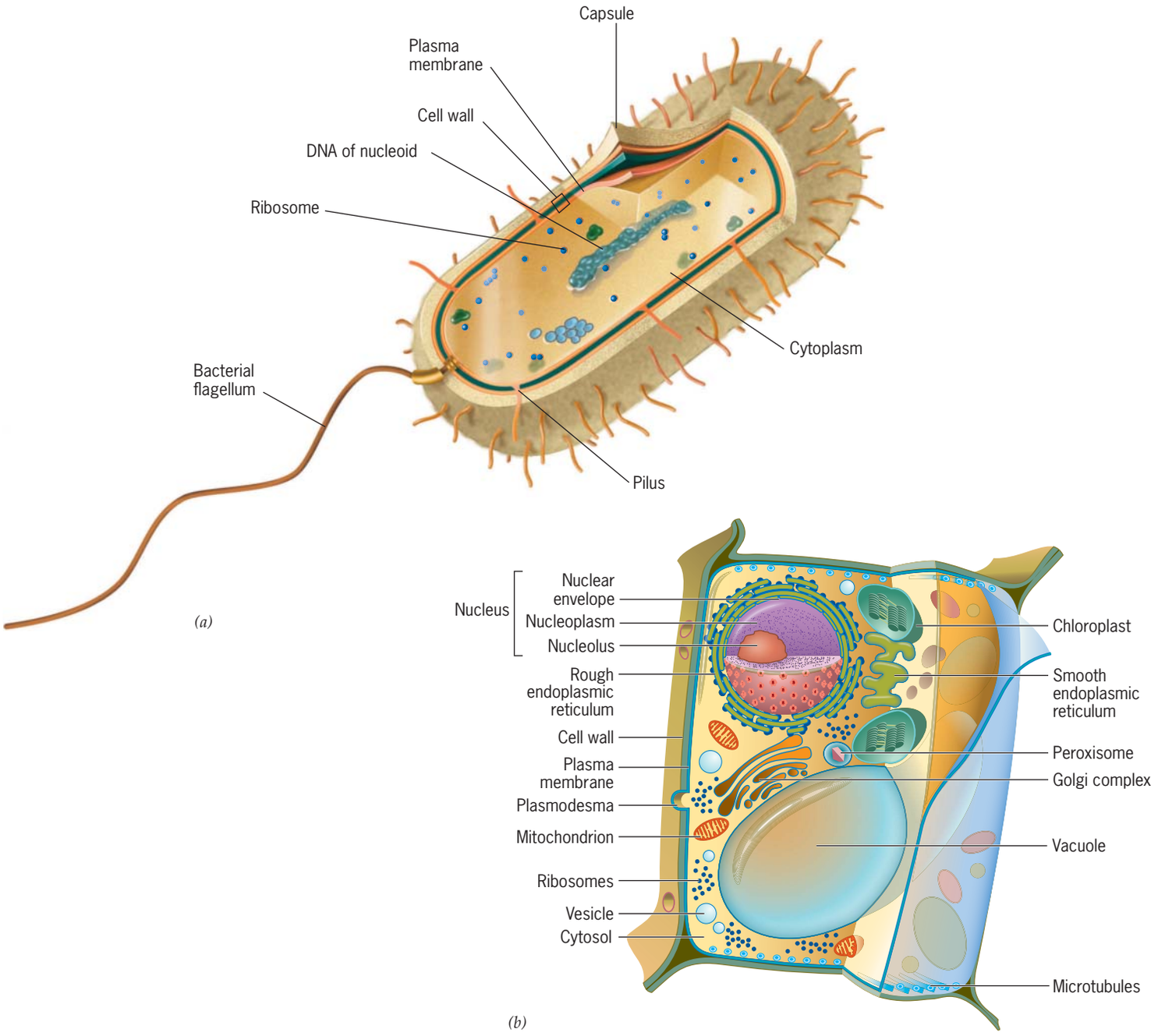


FIGURE 1.8 The structure of cells. Schematic diagrams of a "generalized" bacterial (*a*), plant (*b*), and animal (*c*) cell. Note: Organelles are not drawn to scale.

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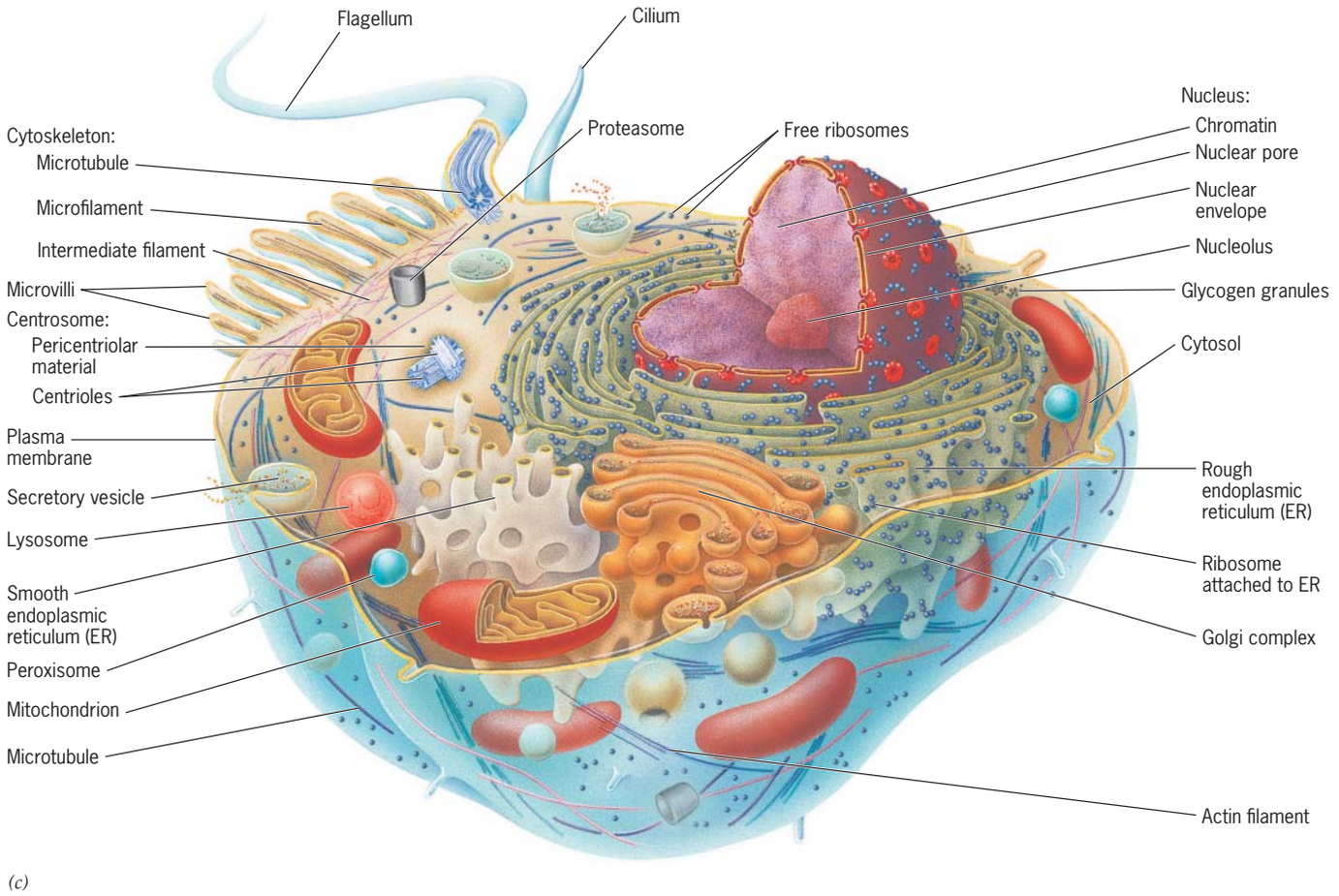

(c)

FIGURE 1.8 (*continued*)

years ago, because that is when the atmosphere became infused with molecular oxygen (O_2), which is a by-product of the photosynthetic activity of these prokaryotes. The dawn of the age of eukaryotic cells is also shrouded in uncertainty. Complex multicellular animals appear rather suddenly in the fossil record approximately 600 million years ago, but there is considerable evidence that simpler eukaryotic organisms were present on Earth more than one billion years earlier. The estimated time of appearance on Earth of several major groups of organisms is depicted in **FIGURE 1.9**. Even a superficial examination of Figure 1.9 reveals how "quickly" life arose following the formation of Earth and cooling of its surface and how long it took for the subsequent evolution of complex animals and plants.

The following brief comparison between prokaryotic and eukaryotic cells reveals many basic differences between the two types, as well as many similarities (see Figure 1.8). The similarities and differences between the two types of cells are listed in Table 1.1. The shared properties reflect the fact that eukaryotic cells almost certainly evolved from prokaryotic ancestors. Because of their common ancestry, both types of cells share an identical genetic language, a common set of metabolic pathways, and many common structural features. For example, both types of cells are bounded by plasma membranes of similar construction that serve as a selectively permeable barrier between the living and nonliving worlds. Both types of cells may be surrounded by a rigid, nonliving *cell wall* that protects the delicate life form within. Although the cell walls of prokaryotes and eukaryotes may have similar functions, their chemical composition is very different.

Internally, eukaryotic cells are much more complex—both structurally and functionally—than prokaryotic cells (Figure 1.8).

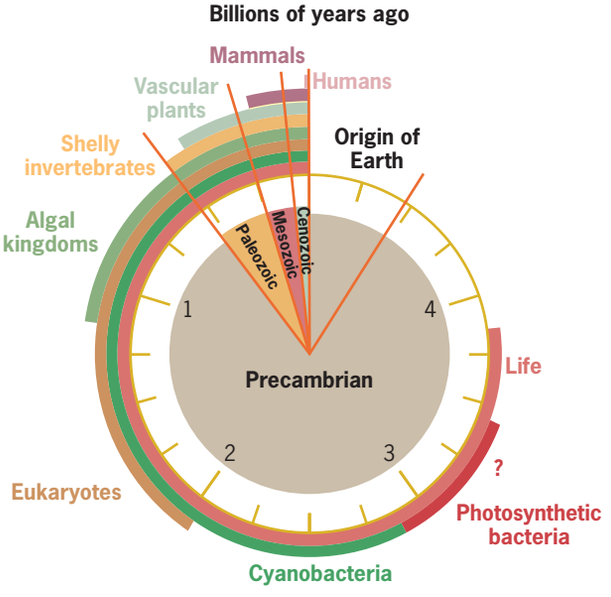

FIGURE 1.9 Earth's biogeologic clock. A portrait of the past five billion years of Earth's history showing a proposed time of appearance of major groups of organisms. Complex animals (shelly invertebrates) and vascular plants are relatively recent arrivals. The time indicated for the origin of life is speculative. In addition, photosynthetic bacteria may have arisen much earlier, hence the question mark. The geologic eras are indicated in the center of the illustration.

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