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Molecular Biology of THE CELL

Sixth Edition

ALBERTS JOHNSON LEWIS MORGAN RAFF ROBERTS WALTER

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Garland Science
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Cover design: Cell biology is not only about the structure and function of the myriad molecules that comprise a cell, but also about how this complex chemistry is controlled. Understanding the cell's elaborate regulatory feedback networks will require quantitative approaches.

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Julian Hart Lewis

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Preface

Since the last edition of this book appeared, more than five million scientific papers have been published. There has been a parallel increase in the quantity of digital information: new data on genome sequences, protein interactions, molecular structures, and gene expression—all stored in vast databases. The challenge, for both scientists and textbook writers, is to convert this overwhelming amount of information into an accessible and up-to-date understanding of how cells work.

Help comes from a large increase in the number of review articles that attempt to make raw material easier to digest, although the vast majority of these reviews are still quite narrowly focused. Meanwhile, a rapidly growing collection of online resources tries to convince us that understanding is only a few mouse-clicks away. In some areas this change in the way we access knowledge has been highly successful—in discovering the latest information about our own medical problems, for example. But to understand something of the beauty and complexity of how living cells work, one needs more than just a wiki- this or wiki- that; it is enormously hard to identify the valuable and enduring gems from so much confusing landfill. Much more effective is a carefully wrought narrative that leads logically and progressively through the key ideas, components, and experiments in such a way that readers can build for themselves a memorable, conceptual framework for cell biology—a framework that will allow them to critically evaluate all of the new science and, more importantly, to understand it. That is what we have tried to do in *Molecular Biology of the Cell*.

In preparing this new edition, we have inevitably had to make some difficult decisions. In order to incorporate exciting new discoveries, while at the same time keeping the book portable, much has had to be excised. We have added new sections, such as those on new RNA functions, advances in stem cell biology, new methods for studying proteins and genes and for imaging cells, advances in the genetics and treatment of cancer, and timing, growth control, and morphogenesis in development.

The chemistry of cells is extremely complex, and any list of cell parts and their interactions—no matter how complete—will leave huge gaps in our understanding. We now realize that to produce convincing explanations of cell behavior will require quantitative information about cells that is coupled to sophisticated mathematical/computational approaches—some not yet invented. As a consequence, an emerging goal for cell biologists is to shift their studies more toward quantitative description and mathematical deduction. We highlight this approach and some of its methods in a new section at the end of Chapter 8.

Faced with the immensity of what we have learned about cell biology, it might be tempting for a student to imagine that there is little left to discover. In fact, the more we find out about cells, the more new questions emerge. To emphasize that our understanding of cell biology is incomplete, we have highlighted some of the major gaps in our knowledge by including *What We Don't Know* at the end of each chapter. These brief lists include only a tiny sample of the critical unanswered questions and challenges for the next generation of scientists. We derive great pleasure from the knowledge that some of our readers will provide future answers.

The more than 1500 illustrations have been designed to create a parallel narrative, closely interwoven with the text. We have increased their consistency between chapters, particularly in the use of color and of common icons; membrane pumps and channels are a good example. To avoid interruptions to the text, some material has been moved into new, readily accessible panels. Most of the important protein structures depicted have now been redrawn and consistently colored. In each

case, we now provide the corresponding Protein Data Bank (PDB) code for the protein, which can be used to access online tools that provide more information about it, such as those on the RCSB PDB website (www.rcsb.org). These connections allow readers of the book to explore more fully the proteins that lie at the core of cell biology.

John Wilson and Tim Hunt have again contributed their distinctive and imaginative problems to help students gain a more active understanding of the text. The problems emphasize quantitative approaches and encourage critical thinking about published experiments; they are now present at the end of all chapters. The answers to these problems, plus more than 1800 additional problems and solutions, all appear in the companion volume that John and Tim have written, *Molecular Biology of the Cell, Sixth Edition: The Problems Book*.

We live in a world that presents us with many complex issues related to cell biology: biodiversity, climate change, food security, environmental degradation, resource depletion, and human disease. We hope that our textbook will help the reader better understand and possibly contribute to meeting these challenges. Knowledge and understanding bring the power to intervene.

We are indebted to a large number of scientists whose generous help we mention separately in the detailed acknowledgments. Here we must mention some particularly significant contributors. For Chapter 8, Hana El-Samad provided the core of the section on Mathematical Analysis of Cell Functions, and Karen Hopkin made valuable contributions to the section on Studying Gene Expression and Function. Werner Kuhlbrandt helped to reorganize and rewrite Chapter 14 (Energy Conversion: Mitochondria and Chloroplasts). Rebecca Heald did the same for Chapter 16 (The Cytoskeleton), as did Alexander Schier for Chapter 21 (Development of Multicellular Organisms), and Matt Welch for Chapter 23 (Pathogens and Infection). Lewis Lanier aided in the writing of Chapter 24 (The Innate and Adaptive Immune Systems). Hossein Amiri generated the enormous online instructor's question bank.

Before starting out on the revision cycle for this edition, we asked a number of scientists who had used the last edition to teach cell biology students to meet with us and suggest improvements. They gave us useful feedback that has helped inform the new edition. We also benefited from the valuable input of groups of students who read most of the chapters in page proofs.

Many people and much effort are needed to convert a long manuscript and a large pile of sketches into a finished textbook. The team at Garland Science that managed this conversion was outstanding. Denise Schanck, directing operations, displayed forbearance, insight, tact, and energy throughout the journey; she guided us all unerringly, ably assisted by Allie Bochicchio and Janette Scobie. Nigel Orme oversaw our revamped illustration program, put all the artwork into its final form, and again enhanced the back cover with his graphics skills. Tiago Barros helped us refresh our presentation of protein structures. Matthew McClements designed the book and its front cover. Emma Jeffcock again laid out the final pages, managing endless rounds of proofs and last-minute changes with remarkable skill and patience; Georgina Lucas provided her with help. Michael Morales, assisted by Leah Christians, produced and assembled the complex web of videos, animations, and other materials that form the core of the online resources that accompany the book. Adam Sendroff provided us with the valuable feedback from book users around the world that informed our revision cycle. Casting expert eyes over the manuscript, Elizabeth Zayatz and Sherry Granum Lewis acted as development editors, Jo Clayton as copyeditor, and Sally Huish as proofreader. Bill Johncocks compiled the index. In London, Emily Preece fed us, while the Garland team's professional help, skills, and energy, together with their friendship, nourished us in every other way throughout the revision, making the whole process a pleasure. The authors are extremely fortunate to be supported so generously.

We thank our spouses, families, friends, and colleagues for their continuing support, which has once again made the writing of this book possible.

Just as we were completing this edition, Julian Lewis, our coauthor, friend, and colleague, finally succumbed to the cancer that he had fought so heroically for ten years. Starting in 1979, Julian made major contributions to all six editions, and, as our most elegant wordsmith, he elevated and enhanced both the style and tone of all the many chapters he touched. Noted for his careful scholarly approach, clarity and simplicity were at the core of his writing. Julian is irreplaceable, and we will all deeply miss his friendship and collaboration. We dedicate this Sixth Edition to his memory.

Note to the Reader

Structure of the Book
Although the chapters of this book can be read independently of one another, they are arranged in a logical sequence of five parts. The first three chapters of Part I cover elementary principles and basic biochemistry. They can serve either as an introduction for those who have not studied biochemistry or as a refresher course for those who have. Part II deals with the storage, expression, and transmission of genetic information. Part III presents the principles of the main experimental methods for investigating and analyzing cells; here, a new section entitled "Mathematical Analysis of Cell Functions" in Chapter 8 provides an extra dimension in our understanding of cell regulation and function. Part IV describes the internal organization of the cell. Part V follows the behavior of cells in multicellular systems, starting with development of multicellular organisms and concluding with chapters on pathogens and infection and on the innate and adaptive immune systems.

End-of-Chapter Problems
A selection of problems, written by John Wilson and Tim Hunt, appears in the text at the end of each chapter. New to this edition are problems for the last four chapters on multicellular organisms. The complete solutions to all of these problems can be found in *Molecular Biology of the Cell, Sixth Edition: The Problems Book*.

References
A concise list of selected references is included at the end of each chapter. These are arranged in alphabetical order under the main chapter section headings. These references sometimes include the original papers in which important discoveries were first reported.

Glossary Terms
Throughout the book, boldface type has been used to highlight key terms at the point in a chapter where the main discussion occurs. Italic type is used to set off important terms with a lesser degree of emphasis. At the end of the book is an expanded glossary, covering technical terms that are part of the common currency of cell biology; it should be the first resort for a reader who encounters an unfamiliar term. The complete glossary as well as a set of flashcards is available on the Student Website.

Nomenclature for Genes and Proteins
Each species has its own conventions for naming genes; the only common feature is that they are always set in italics. In some species (such as humans), gene names are spelled out all in capital letters; in other species (such as zebrafish), all in lowercase; in yet others (most mouse genes), with the first letter in uppercase and rest in lowercase; or (as in *Drosophila*) with different combinations of uppercase and lowercase, according to whether the first mutant allele to be discovered produced a dominant or recessive phenotype. Conventions for naming protein products are equally varied.

This typographical chaos drives everyone crazy. It is not just tiresome and absurd; it is also unsustainable. We cannot independently define a fresh convention for each of the next few million species whose genes we may wish to study.

Moreover, there are many occasions, especially in a book such as this, where we need to refer to a gene generically—without specifying the mouse version, the human version, the chick version, or the hippopotamus version—because they are all equivalent for the purposes of our discussion. What convention then should we use?

We have decided in this book to cast aside the different conventions that are used in individual species and follow a uniform rule: we write all gene names, like the names of people and places, with the first letter in uppercase and the rest in lowercase, but all in italics, thus: *Apc*, *Bazooka*, *Cdc2*, *Dishevelled*, *Egl1*. The corresponding protein, where it is named after the gene, will be written in the same way, but in roman rather than italic letters: Apc, Bazooka, Cdc2, Dishevelled, Egl1. When it is necessary to specify the organism, this can be done with a prefix to the gene name.

For completeness, we list a few further details of naming rules that we shall follow. In some instances, an added letter in the gene name is traditionally used to distinguish between genes that are related by function or evolution; for those genes, we put that letter in uppercase if it is usual to do so (*LacZ*, *RecA*, *HoxA4*). We use no hyphen to separate added letters or numbers from the rest of the name. Proteins are more of a problem. Many of them have names in their own right, assigned to them before the gene was named. Such protein names take many forms, although most of them traditionally begin with a lowercase letter (actin, hemoglobin, catalase), like the names of ordinary substances (cheese, nylon), unless they are acronyms (such as GFP, for Green Fluorescent Protein, or BMP4, for Bone Morphogenetic Protein #4). To force all such protein names into a uniform style would do too much violence to established usages, and we shall simply write them in the traditional way (actin, GFP, and so on). For the corresponding gene names in all these cases, we shall nevertheless follow our standard rule: *Actin*, *Hemoglobin*, *Catalase*, *Bmp4*, *Gfp*. Occasionally in our book we need to highlight a protein name by setting it in italics for emphasis; the intention will generally be clear from the context.

For those who wish to know them, the table below shows some of the official conventions for individual species—conventions that we shall mostly violate in this book, in the manner shown.

	Species-Specific Convention		Unified Convention Used in This Book	
Organism	Gene	Protein	Gene	Protein
Mouse	*Hoxa4*	Hoxa4	*HoxA4*	HoxA4
	Bmp4	BMP4	*Bmp4*	BMP4
	integrin α-1, Itgα1	integrin α1	*Integrin α1, Itgα1*	integrin α1
Human	*HOXA4*	HOXA4	*HoxA4*	HoxA4
Zebrafish	*cyclops, cyc*	Cyclops, Cyc	*Cyclops, Cyc*	Cyclops, Cyc
Caenorhabditis	*unc-6*	UNC-6	*Unc6*	Unc6
Drosophila	*sevenless, sev* (named after recessive phenotype)	Sevenless, SEV	*Sevenless, Sev*	Sevenless, Sev
	Deformed, Dfd (named after dominant mutant phenotype)	Deformed, DFD	*Deformed, Dfd*	Deformed, Dfd
Yeast				
Saccharomyces cerevisiae (budding yeast)	*CDC28*	Cdc28, Cdc28p	*Cdc28*	Cdc28
Schizosaccharomyces pombe (fission yeast)	*Cdc2*	Cdc2, Cdc2p	*Cdc2*	Cdc2
Arabidopsis	*GAI*	GAI	*Gai*	GAI
E. coli	*uvrA*	UvrA	*UvrA*	UvrA

Molecular Biology of the Cell, Sixth Edition: The Problems Book
by John Wilson and Tim Hunt (ISBN: 978-0-8153-4453-7)
The Problems Book is designed to help students appreciate the ways in which experiments and simple calculations can lead to an understanding of how cells work. It provides problems to accompany Chapters 1–20 of *Molecular Biology of the Cell*. Each chapter of problems is divided into sections that correspond to those of the main textbook and review key terms, test for understanding basic concepts, pose research-based problems, and now include MCAT-style questions which help students to prepare for standardized medical school admission tests. *Molecular Biology of the Cell, Sixth Edition: The Problems Book* should be useful for homework assignments and as a basis for class discussion. It could even provide ideas for exam questions. Solutions for all of the problems are provided in the book. Solutions for the end-of-chapter problems for Chapters 1–24 in the main textbook are also found in *The Problems Book*.

RESOURCES FOR INSTRUCTORS AND STUDENTS

The teaching and learning resources for instructors and students are available online. The instructor's resources are password-protected and available only to adopting instructors. The student resources are available to everyone. We hope these resources will enhance student learning and make it easier for instructors to prepare dynamic lectures and activities for the classroom.

Instructor Resources

Instructor Resources are available on the Garland Science Instructor's Resource Site, located at www.garlandscience.com/instructors. The website provides access not only to the teaching resources for this book but also to all other Garland Science textbooks. Adopting instructors can obtain access to the site from their sales representative or by emailing science@garland.com.

Art of Molecular Biology of the Cell, Sixth Edition
The images from the book are available in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. Figures are searchable by figure number, by figure name, or by keywords used in the figure legend from the book.

Figure-Integrated Lecture Outlines
The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations. These will be useful for instructors who would like a head start creating lectures for their course. Like all of our PowerPoint presentations, the lecture outlines can be customized. For example, the content of these presentations can be combined with videos and questions from the book or Question Bank, in order to create unique lectures that facilitate interactive learning.

Animations and Videos
The 174 animations and videos that are available to students are also available on the Instructor's Website in two formats. The WMV-formatted movies are created for instructors who wish to use the movies in PowerPoint presentations on Windows® computers; the QuickTime-formatted movies are for use in PowerPoint for Apple computers or Keynote® presentations. The movies can easily be downloaded using the "download" button on the movie preview page. The movies are correlated to each chapter and callouts are highlighted in color.

Media Guide
This document provides an overview to the multimedia available for students and instructors and contains the text of the voice-over narration for all of the movies.

Question Bank
Written by Hossein Amiri, University of California, Santa Cruz, this greatly expanded question bank includes a variety of question formats: multiple choice,

short answer, fill-in-the-blank, true-false, and matching. There are 35–60 questions per chapter, and a large number of the multiple-choice questions will be suitable for use with personal response systems (that is, clickers). The Question Bank was created with the philosophy that a good exam should do much more than simply test students' ability to memorize information; it should require them to reflect upon and integrate information as a part of a sound understanding. This resource provides a comprehensive sampling of questions that can be used either directly or as inspiration for instructors to write their own test questions.

Diploma® Test Generator Software
The questions from the Question Bank have been loaded into the Diploma Test Generator software. The software is easy to use and can scramble questions to create multiple tests. Questions are organized by chapter and type and can be additionally categorized by the instructor according to difficulty or subject. Existing questions can be edited and new ones added. The Test Generator is compatible with several course management systems, including Blackboard®.

Medical Topics Guide
This document highlights medically relevant topics covered throughout *Molecular Biology of the Cell* and *The Problems Book*. It will be particularly useful for instructors with a large number of premedical, health science, or nursing students.

Blackboard and Learning Management System (LMS) Integration
The movies, book images, and student assessments that accompany the book can be integrated into Blackboard or other LMSs. These resources are bundled into a "Common Cartridge" or "Upload Package" that facilitates bulk uploading of textbook resources into Blackboard and other LMSs. The LMS Common Cartridge can be obtained on a DVD from your sales representative or by emailing science@garland.com.

Resources for Students

The resources for students are available on the *Molecular Biology of the Cell* Student Website, located at www.garlandscience.com/MBOC6-students.

Animations and Videos
There are 174 movies, covering a wide range of cell biology topics, which review key concepts in the book and illuminate subcellular processes. The movies are correlated to each chapter and callouts are highlighted in color.

Cell Explorer Slides
This application teaches cell morphology through interactive micrographs that highlight important cellular structures.

Flashcards
Each chapter contains a set of flashcards, built into the website, that allow students to review key terms from the text.

Glossary
The complete glossary from the book is available on the website and can be searched and browsed.

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In writing this book we have benefited greatly from the advice of many biologists and biochemists. We would like to thank the following for their suggestions in preparing this edition, as well as those who helped in preparing the first, second, third, fourth, and fifth editions. (Those who helped on this edition are listed first, those who helped with the first, second, third, fourth, and fifth editions follow.)

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INTRODUCTION TO THE CELL

CHAPTER 1

Cells and Genomes

IN THIS CHAPTER

The surface of our planet is populated by living things—curious, intricately organized chemical factories that take in matter from their surroundings and use these raw materials to generate copies of themselves. These living organisms appear extraordinarily diverse. What could be more different than a tiger and a piece of seaweed, or a bacterium and a tree? Yet our ancestors, knowing nothing of cells or DNA, saw that all these things had something in common. They called that something "life," marveled at it, struggled to define it, and despaired of explaining what it was or how it worked in terms that relate to nonliving matter.

The discoveries of the past century have not diminished the marvel—quite the contrary. But they have removed the central mystery regarding the nature of life. We can now see that all living things are made of cells: small, membrane-enclosed units filled with a concentrated aqueous solution of chemicals and endowed with the extraordinary ability to create copies of themselves by growing and then dividing in two.

Because cells are the fundamental units of life, it is to *cell biology*—the study of the structure, function, and behavior of cells—that we must look for answers to the questions of what life is and how it works. With a deeper understanding of cells and their evolution, we can begin to tackle the grand historical problems of life on Earth: its mysterious origins, its stunning diversity, and its invasion of every conceivable habitat. Indeed, as emphasized long ago by the pioneering cell biologist E. B. Wilson, "the key to every biological problem must finally be sought in the cell; for every living organism is, or at some time has been, a cell."

Despite their apparent diversity, living things are fundamentally similar inside. The whole of biology is thus a counterpoint between two themes: astonishing variety in individual particulars; astonishing constancy in fundamental mechanisms. In this first chapter, we begin by outlining the universal features common to all life on our planet. We then survey, briefly, the diversity of cells. And we see how, thanks to the common molecular code in which the specifications for all living organisms are written, it is possible to read, measure, and decipher these specifications to help us achieve a coherent understanding of all the forms of life, from the smallest to the greatest.

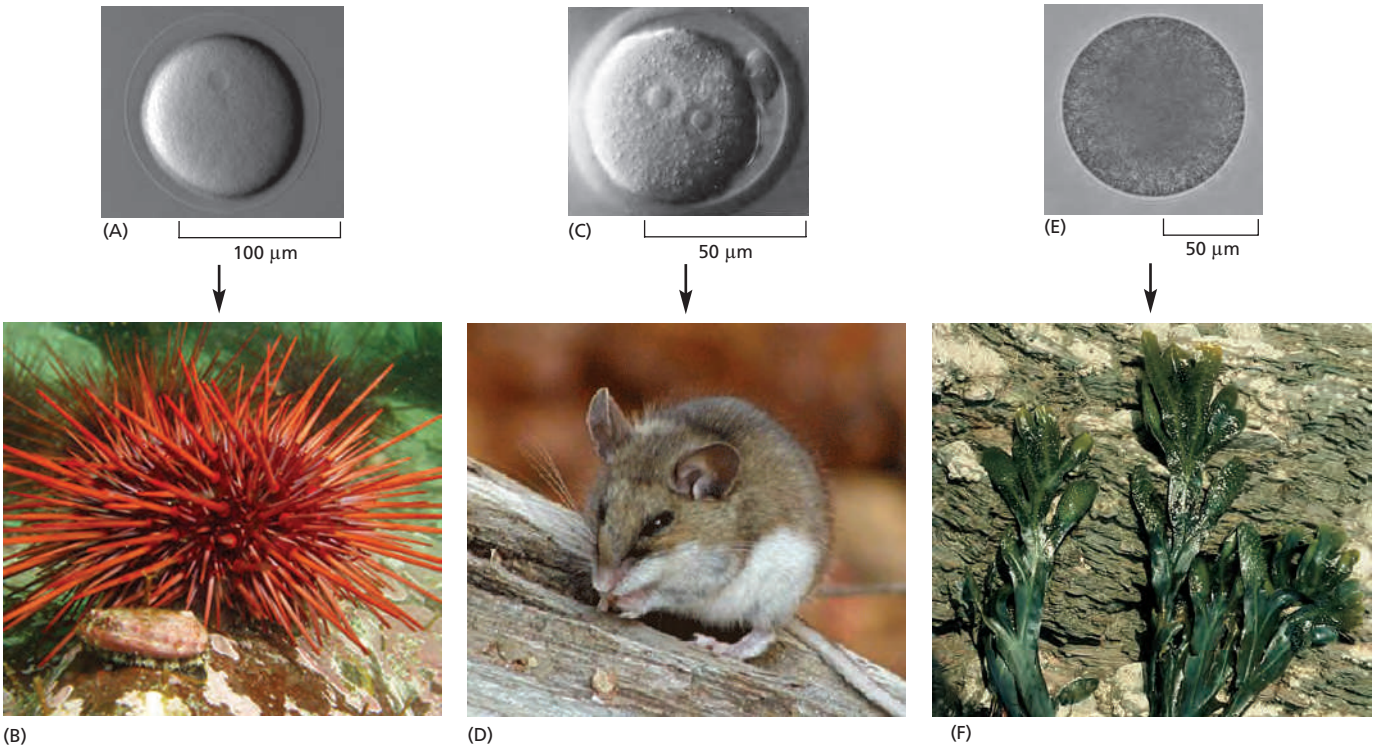


Figure 1–1 The hereditary information in the fertilized egg cell determines the nature of the whole multicellular organism. Although their starting cells look superficially similar, as indicated: a sea urchin egg gives rise to a sea urchin (A and B). A mouse egg gives rise to a mouse (C and D). An egg of the seaweed *Fucus* gives rise to a *Fucus* seaweed (E and F). (A, courtesy of David McClay; B, courtesy of M. Gibbs, Oxford Scientific Films; C, courtesy of Patricia Calarco, from G. Martin, *Science* 209:768–776, 1980. With permission from AAAS; D, courtesy of O. Newman, Oxford Scientific Films; E and F, courtesy of Colin Brownlee.)

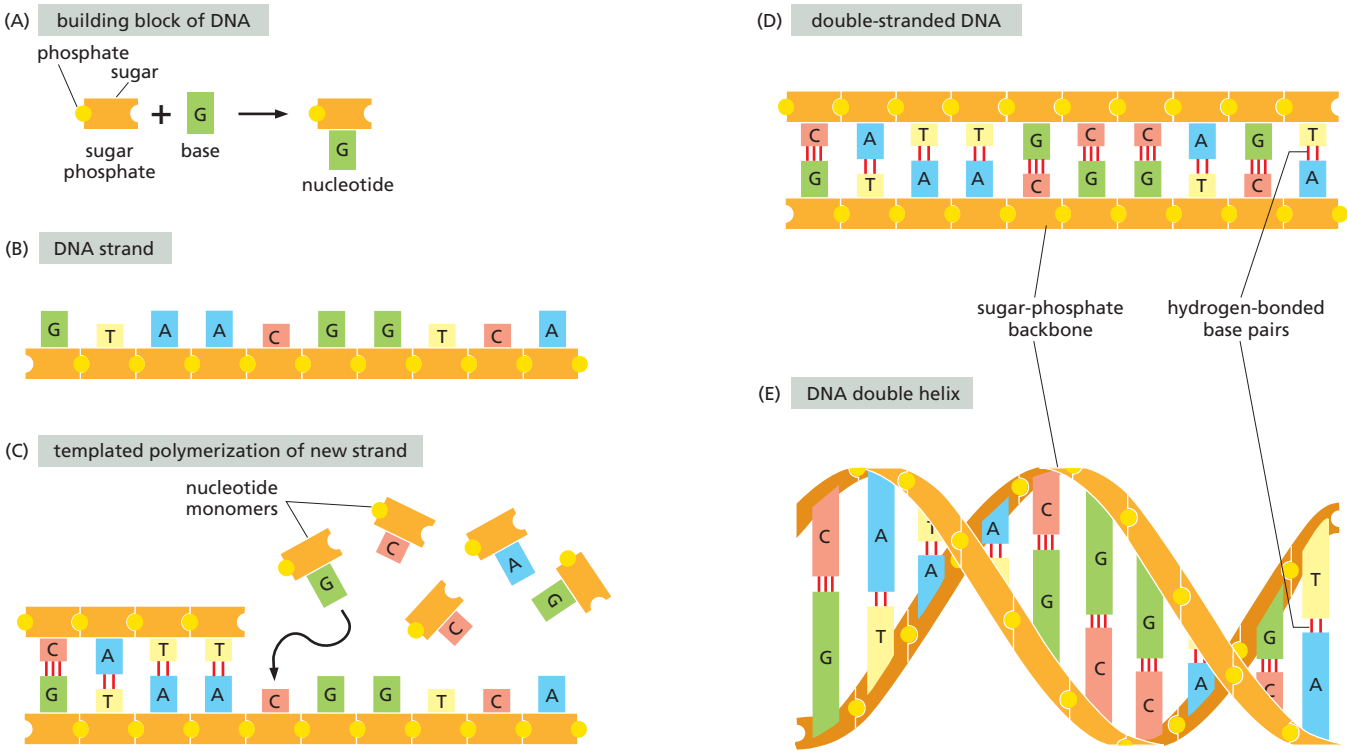
THE UNIVERSAL FEATURES OF CELLS ON EARTH

It is estimated that there are more than 10 million—perhaps 100 million—living species on Earth today. Each species is different, and each reproduces itself faithfully, yielding progeny that belong to the same species: the parent organism hands down information specifying, in extraordinary detail, the characteristics that the offspring shall have. This phenomenon of *heredity* is central to the definition of life: it distinguishes life from other processes, such as the growth of a crystal, or the burning of a candle, or the formation of waves on water, in which orderly structures are generated but without the same type of link between the peculiarities of parents and the peculiarities of offspring. Like the candle flame, the living organism must consume free energy to create and maintain its organization. But life employs the free energy to drive a hugely complex system of chemical processes that are specified by hereditary information.

Most living organisms are single cells. Others, such as ourselves, are vast multicellular cities in which groups of cells perform specialized functions linked by intricate systems of communication. But even for the aggregate of more than 10^{13} cells that form a human body, the whole organism has been generated by cell divisions from a single cell. The single cell, therefore, is the vehicle for all of the hereditary information that defines each species (**Figure 1–1**). This cell includes the machinery to gather raw materials from the environment and to construct from them a new cell in its own image, complete with a new copy of its hereditary information. Each and every cell is truly amazing.

All Cells Store Their Hereditary Information in the Same Linear Chemical Code: DNA

Computers have made us familiar with the concept of information as a measurable quantity—a million bytes (to record a few hundred pages of text or an image from a digital camera), 600 million bytes for the music on a CD, and so on. Computers have also made us well aware that the same information can be recorded in many different physical forms: the discs and tapes that we used 20 years ago for our electronic archives have become unreadable on present-day machines. Living



cells, like computers, store information, and it is estimated that they have been evolving and diversifying for over 3.5 billion years. It is scarcely to be expected that they would all store their information in the same form, or that the archives of one type of cell should be readable by the information-handling machinery of another. And yet it is so. All living cells on Earth store their hereditary information in the form of double-stranded molecules of DNA—long, unbranched, paired *polymer* chains, formed always of the same four types of *monomers*. These monomers, chemical compounds known as nucleotides, have nicknames drawn from a four-letter alphabet—A, T, C, G—and they are strung together in a long linear sequence that encodes the genetic information, just as the sequence of 1s and 0s encodes the information in a computer file. We can take a piece of DNA from a human cell and insert it into a bacterium, or a piece of bacterial DNA and insert it into a human cell, and the information will be successfully read, interpreted, and copied. Using chemical methods, scientists have learned how to read out the complete sequence of monomers in any DNA molecule—extending for many millions of nucleotides—and thereby decipher all of the hereditary information that each organism contains.

All Cells Replicate Their Hereditary Information by Templated Polymerization

The mechanisms that make life possible depend on the structure of the double-stranded DNA molecule. Each monomer in a single DNA strand—that is, each **nucleotide**—consists of two parts: a sugar (deoxyribose) with a phosphate group attached to it, and a *base*, which may be either adenine (A), guanine (G), cytosine (C), or thymine (T) (**Figure 1–2**). Each sugar is linked to the next via the phosphate group, creating a polymer chain composed of a repetitive sugar-phosphate backbone with a series of bases protruding from it. The DNA polymer is extended by adding monomers at one end. For a single isolated strand, these monomers can, in principle, be added in any order, because each one links to the next in the same way, through the part of the molecule that is the same for all of them. In the living cell, however, DNA is not synthesized as a free strand in isolation, but on a template formed by a preexisting DNA strand. The bases protruding from the

Figure 1–2 DNA and its building blocks. (A) DNA is made from simple subunits, called nucleotides, each consisting of a sugar-phosphate molecule with a nitrogen-containing side group, or base, attached to it. The bases are of four types (adenine, guanine, cytosine, and thymine), corresponding to four distinct nucleotides, labeled A, G, C, and T. (B) A single strand of DNA consists of nucleotides joined together by sugar-phosphate linkages. Note that the individual sugar-phosphate units are asymmetric, giving the backbone of the strand a definite directionality, or polarity. This directionality guides the molecular processes by which the information in DNA is interpreted and copied in cells: the information is always "read" in a consistent order, just as written English text is read from left to right. (C) Through templated polymerization, the sequence of nucleotides in an existing DNA strand controls the sequence in which nucleotides are joined together in a new DNA strand; T in one strand pairs with A in the other, and G in one strand with C in the other. The new strand has a nucleotide sequence *complementary* to that of the old strand, and a backbone with opposite directionality: corresponding to the GTAA... of the original strand, it has ...TTAC. (D) A normal DNA molecule consists of two such complementary strands. The nucleotides within each strand are linked by strong (covalent) chemical bonds; the complementary nucleotides on opposite strands are held together more weakly, by hydrogen bonds. (E) The two strands twist around each other to form a double helix—a robust structure that can accommodate any sequence of nucleotides without altering its basic structure (see Movie 4.1).

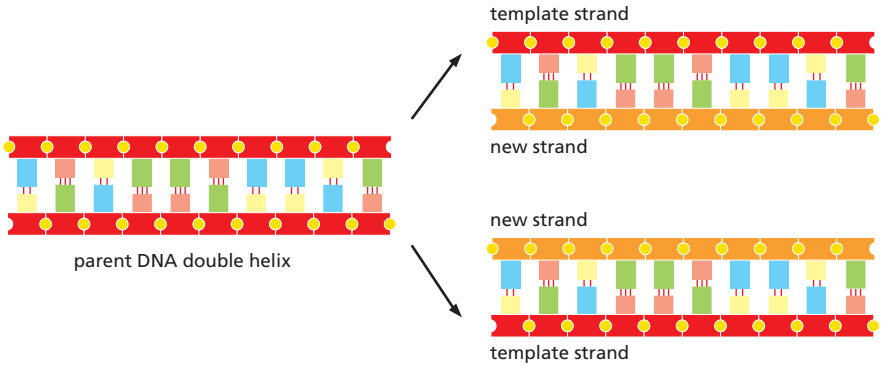


Figure 1–3 The copying of genetic information by DNA replication. In this process, the two strands of a DNA double helix are pulled apart, and each serves as a template for synthesis of a new complementary strand.

existing strand bind to bases of the strand being synthesized, according to a strict rule defined by the complementary structures of the bases: A binds to T, and C binds to G. This base-pairing holds fresh monomers in place and thereby controls the selection of which one of the four monomers shall be added to the growing strand next. In this way, a double-stranded structure is created, consisting of two exactly complementary sequences of As, Cs, Ts, and Gs. The two strands twist around each other, forming a DNA double helix (Figure 1–2E).

The bonds between the base pairs are weak compared with the sugar-phosphate links, and this allows the two DNA strands to be pulled apart without breakage of their backbones. Each strand then can serve as a template, in the way just described, for the synthesis of a fresh DNA strand complementary to itself—a fresh copy, that is, of the hereditary information (**Figure 1–3**). In different types of cells, this process of **DNA replication** occurs at different rates, with different controls to start it or stop it, and different auxiliary molecules to help it along. But the basics are universal: DNA is the information store for heredity, and *templated polymerization* is the way in which this information is copied throughout the living world.

All Cells Transcribe Portions of Their Hereditary Information into the Same Intermediary Form: RNA

To carry out its information-bearing function, DNA must do more than copy itself. It must also *express* its information, by letting the information guide the synthesis of other molecules in the cell. This expression occurs by a mechanism that is the same in all living organisms, leading first and foremost to the production of two other key classes of polymers: RNAs and proteins. The process (discussed in detail in Chapters 6 and 7) begins with a templated polymerization called **transcription**, in which segments of the DNA sequence are used as templates for the synthesis of shorter molecules of the closely related polymer **ribonucleic acid**, or **RNA**. Later, in the more complex process of **translation**, many of these RNA molecules direct the synthesis of polymers of a radically different chemical class—the *proteins* (**Figure 1–4**).

In RNA, the backbone is formed of a slightly different sugar from that of DNA—ribose instead of deoxyribose—and one of the four bases is slightly different—uracil (U) in place of thymine (T). But the other three bases—A, C, and G—are the same, and all four bases pair with their complementary counterparts in DNA—the A, U, C, and G of RNA with the T, A, G, and C of DNA. During transcription, the RNA monomers are lined up and selected for polymerization on a template strand of DNA, just as DNA monomers are selected during replication. The outcome is a polymer molecule whose sequence of nucleotides faithfully represents a portion of the cell's genetic information, even though it is written in a slightly different alphabet—consisting of RNA monomers instead of DNA monomers.

The same segment of DNA can be used repeatedly to guide the synthesis of many identical RNA molecules. Thus, whereas the cell's archive of genetic information in the form of DNA is fixed and sacrosanct, these *RNA transcripts* are

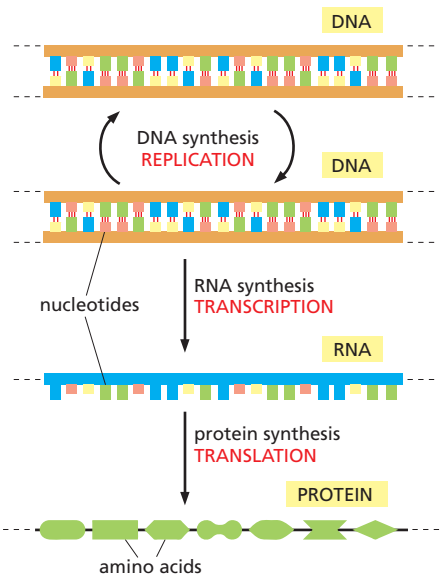


Figure 1–4 From DNA to protein. Genetic information is read out and put to use through a two-step process. First, in *transcription*, segments of the DNA sequence are used to guide the synthesis of molecules of RNA. Then, in *translation*, the RNA molecules are used to guide the synthesis of molecules of protein.

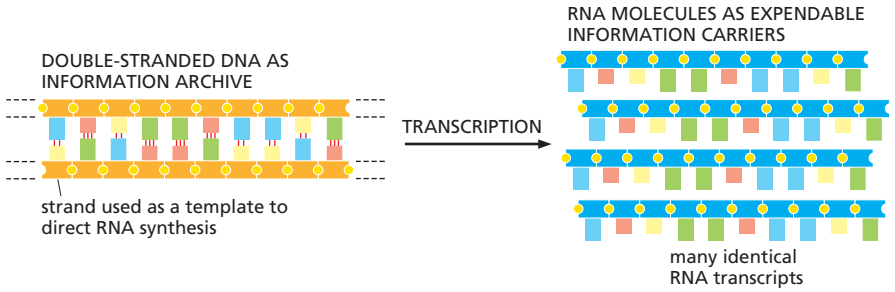


Figure 1–5 How genetic information is broadcast for use inside the cell. Each cell contains a fixed set of DNA molecules—its archive of genetic information. A given segment of this DNA guides the synthesis of many identical RNA transcripts, which serve as working copies of the information stored in the archive. Many different sets of RNA molecules can be made by transcribing different parts of a cell's DNA sequences, allowing different types of cells to use the same information store differently.

mass-produced and disposable (**Figure 1–5**). As we shall see, these transcripts function as intermediates in the transfer of genetic information. Most notably, they serve as **messenger RNA** (**mRNA**) molecules that guide the synthesis of proteins according to the genetic instructions stored in the DNA.

RNA molecules have distinctive structures that can also give them other specialized chemical capabilities. Being single-stranded, their backbone is flexible, so that the polymer chain can bend back on itself to allow one part of the molecule to form weak bonds with another part of the same molecule. This occurs when segments of the sequence are locally complementary: a ...GGGG... segment, for example, will tend to associate with a ...CCCC... segment. These types of internal associations can cause an RNA chain to fold up into a specific shape that is dictated by its sequence (**Figure 1–6**). The shape of the RNA molecule, in turn, may enable it to recognize other molecules by binding to them selectively—and even, in certain cases, to catalyze chemical changes in the molecules that are bound. In fact, some chemical reactions catalyzed by RNA molecules are crucial for several of the most ancient and fundamental processes in living cells, and it has been suggested that an extensive catalysis by RNA played a central part in the early evolution of life (discussed in Chapter 6).

All Cells Use Proteins as Catalysts

Protein molecules, like DNA and RNA molecules, are long unbranched polymer chains, formed by stringing together monomeric building blocks drawn from a standard repertoire that is the same for all living cells. Like DNA and RNA, proteins carry information in the form of a linear sequence of symbols, in the same way as a human message written in an alphabetic script. There are many different protein molecules in each cell, and—leaving out the water—they form most of the cell's mass.

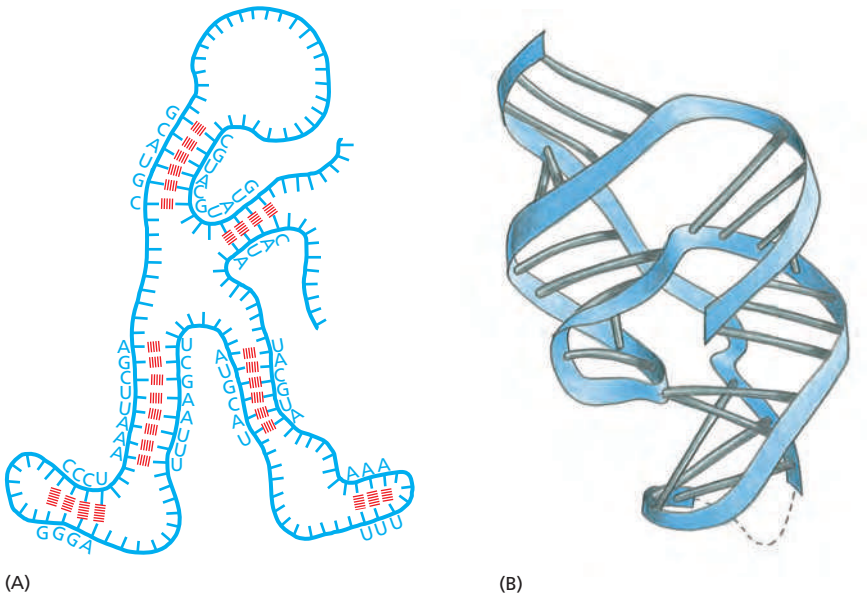


Figure 1–6 The conformation of an RNA molecule. (A) Nucleotide pairing between different regions of the same RNA polymer chain causes the molecule to adopt a distinctive shape. (B) The three-dimensional structure of an actual RNA molecule produced by hepatitis delta virus; this RNA can catalyze RNA strand cleavage. The *blue* ribbon represents the sugar-phosphate backbone and the bars represent base pairs (see Movie 6.1). (B, based on A.R. Ferré-D'Amaré, K. Zhou, and J.A. Doudna, *Nature* 395:567–574, 1998. With permission from Macmillan Publishers Ltd.)

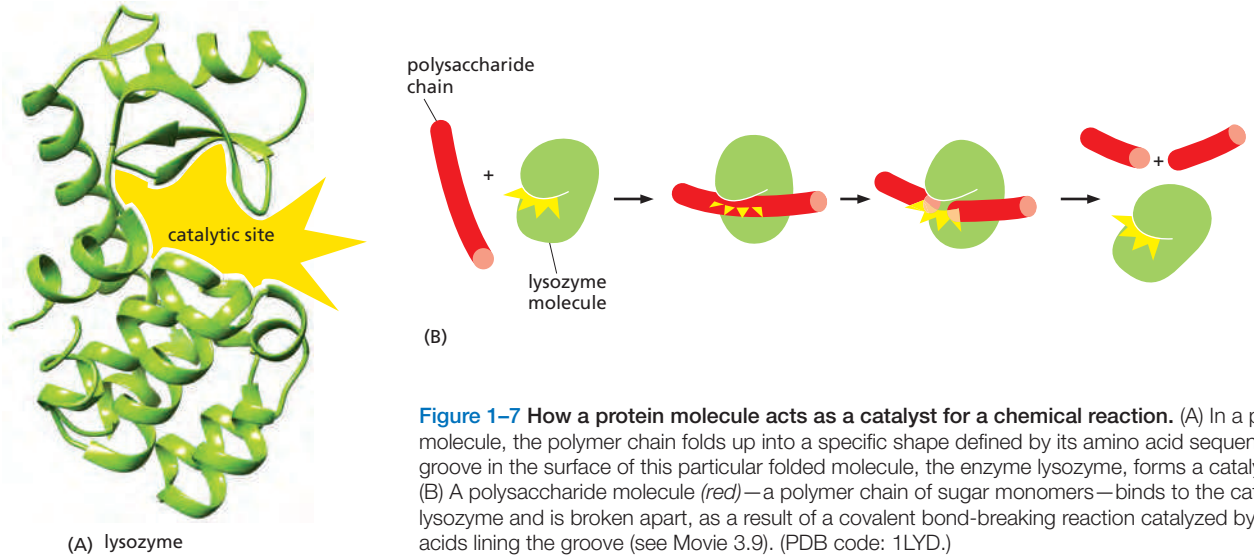


Figure 1–7 How a protein molecule acts as a catalyst for a chemical reaction. (A) In a protein molecule, the polymer chain folds up into a specific shape defined by its amino acid sequence. A groove in the surface of this particular folded molecule, the enzyme lysozyme, forms a catalytic site. (B) A polysaccharide molecule *(red)*—a polymer chain of sugar monomers—binds to the catalytic site of lysozyme and is broken apart, as a result of a covalent bond-breaking reaction catalyzed by the amino acids lining the groove (see Movie 3.9). (PDB code: 1LYD.)

The monomers of protein, the **amino acids**, are quite different from those of DNA and RNA, and there are 20 types instead of 4. Each amino acid is built around the same core structure through which it can be linked in a standard way to any other amino acid in the set; attached to this core is a side group that gives each amino acid a distinctive chemical character. Each of the protein molecules is a **polypeptide**, created by joining its amino acids in a particular sequence. Through billions of years of evolution, this sequence has been selected to give the protein a useful function. Thus, by folding into a precise three-dimensional form with reactive sites on its surface (**Figure 1–7**A), these amino-acid polymers can bind with high specificity to other molecules and can act as **enzymes** to catalyze reactions that make or break covalent bonds. In this way they direct the vast majority of chemical processes in the cell (Figure 1–7B).

Proteins have many other functions as well—maintaining structures, generating movements, sensing signals, and so on—each protein molecule performing a specific function according to its own genetically specified sequence of amino acids. Proteins, above all, are the main molecules that put the cell's genetic information into action.

Thus, polynucleotides specify the amino acid sequences of proteins. Proteins, in turn, catalyze many chemical reactions, including those by which new DNA molecules are synthesized. From the most fundamental point of view, a living cell is a self-replicating collection of catalysts that takes in food, processes this food to derive both the building blocks and energy needed to make more catalysts, and discards the materials left over as waste (**Figure 1–8**A). A feedback loop that connects proteins and polynucleotides forms the basis for this autocatalytic, self-reproducing behavior of living organisms (Figure 1–8B).

All Cells Translate RNA into Protein in the Same Way

How the information in DNA specifies the production of proteins was a complete mystery in the 1950s when the double-stranded structure of DNA was first revealed as the basis of heredity. But in the intervening years, scientists have discovered the elegant mechanisms involved. The translation of genetic information from the 4-letter alphabet of polynucleotides into the 20-letter alphabet of proteins is a complex process. The rules of this translation seem in some respects neat and rational but in other respects strangely arbitrary, given that they are (with minor exceptions) identical in all living things. These arbitrary features, it is thought, reflect frozen accidents in the early history of life. They stem from the chance properties of the earliest organisms that were passed on by heredity and have become so deeply embedded in the constitution of all living cells that they cannot be changed without disastrous effects.

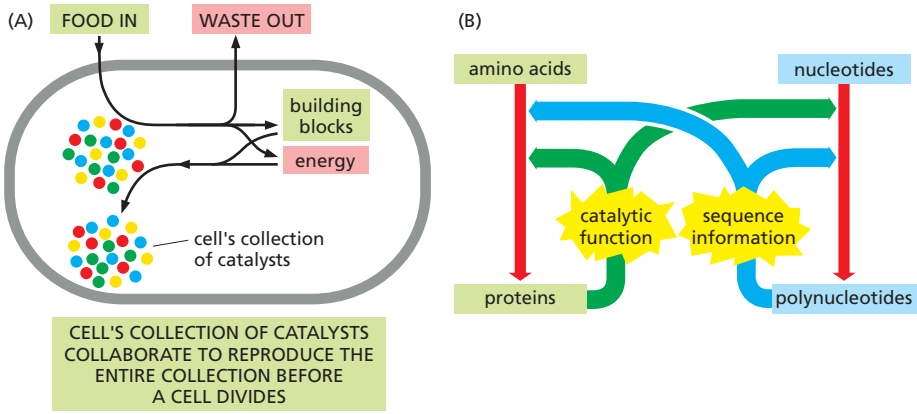


Figure 1–8 Life as an autocatalytic process. (A) The cell as a self-replicating collection of catalysts. (B) Polynucleotides (the nucleic acids DNA and RNA, which are nucleotide polymers) provide the sequence information, while proteins (amino acid polymers) provide most of the catalytic functions that serve—through a complex set of chemical reactions—to bring about the synthesis of more polynucleotides and proteins of the same types.

It turns out that the information in the sequence of a messenger RNA molecule is read out in groups of three nucleotides at a time: each triplet of nucleotides, or *codon*, specifies (codes for) a single amino acid in a corresponding protein. Since the number of distinct triplets that can be formed from four nucleotides is 4^3, there are 64 possible codons, all of which occur in nature. However, there are only 20 naturally occurring amino acids. That means there are necessarily many cases in which several codons correspond to the same amino acid. This *genetic code* is read out by a special class of small RNA molecules, the *transfer RNAs* (*tRNAs*). Each type of tRNA becomes attached at one end to a specific amino acid, and displays at its other end a specific sequence of three nucleotides—an *anticodon*—that enables it to recognize, through base-pairing, a particular codon or subset of codons in mRNA. The intricate chemistry that enables these tRNAs to translate a specific sequence of A, C, G, and U nucleotides in an mRNA molecule into a specific sequence of amino acids in a protein molecule occurs on the *ribosome*, a large multimolecular machine composed of both protein and *ribosomal RNA*. All of these processes are described in detail in Chapter 6.

Each Protein Is Encoded by a Specific Gene

DNA molecules as a rule are very large, containing the specifications for thousands of proteins. Special sequences in the DNA serve as punctuation, defining where the information for each protein begins and ends. And individual segments of the long DNA sequence are transcribed into separate mRNA molecules, coding for different proteins. Each such DNA segment represents one **gene**. A complication is that RNA molecules transcribed from the same DNA segment can often be processed in more than one way, so as to give rise to a set of alternative versions of a protein, especially in more complex cells such as those of plants and animals. In addition, some DNA segments—a smaller number—are transcribed into RNA molecules that are not translated but have catalytic, regulatory, or structural functions; such DNA segments also count as genes. A gene therefore is defined as the segment of DNA sequence corresponding to a single protein or set of alternative protein variants or to a single catalytic, regulatory, or structural RNA molecule.

In all cells, the *expression* of individual genes is regulated: instead of manufacturing its full repertoire of possible proteins at full tilt all the time, the cell adjusts the rate of transcription and translation of different genes independently, according to need. Stretches of *regulatory DNA* are interspersed among the segments that code for protein, and these noncoding regions bind to special protein molecules that control the local rate of transcription. The quantity and organization of the regulatory DNA vary widely from one class of organisms to another, but the basic strategy is universal. In this way, the **genome** of the cell—that is, the totality of its genetic information as embodied in its complete DNA sequence—dictates not only the nature of the cell's proteins, but also when and where they are to be made.

Life Requires Free Energy

A living cell is a dynamic chemical system, operating far from chemical equilibrium. For a cell to grow or to make a new cell in its own image, it must take in free energy from the environment, as well as raw materials, to drive the necessary synthetic reactions. This consumption of free energy is fundamental to life. When it stops, a cell decays toward chemical equilibrium and soon dies.

Genetic information is also fundamental to life, and free energy is required for the propagation of this information. For example, to specify one bit of information—that is, one yes/no choice between two equally probable alternatives—costs a defined amount of free energy that can be calculated. The quantitative relationship involves some deep reasoning and depends on a precise definition of the term "free energy," as explained in Chapter 2. The basic idea, however, is not difficult to understand intuitively.

Picture the molecules in a cell as a swarm of objects endowed with thermal energy, moving around violently at random, buffeted by collisions with one another. To specify genetic information—in the form of a DNA sequence, for example—molecules from this wild crowd must be captured, arranged in a specific order defined by some preexisting template, and linked together in a fixed relationship. The bonds that hold the molecules in their proper places on the template and join them together must be strong enough to resist the disordering effect of thermal motion. The process is driven forward by consumption of free energy, which is needed to ensure that the correct bonds are made, and made robustly. In the simplest case, the molecules can be compared with spring-loaded traps, ready to snap into a more stable, lower-energy attached state when they meet their proper partners; as they snap together into the bonded arrangement, their available stored energy—their free energy—like the energy of the spring in the trap, is released and dissipated as heat. In a cell, the chemical processes underlying information transfer are more complex, but the same basic principle applies: free energy has to be spent on the creation of order.

To replicate its genetic information faithfully, and indeed to make all its complex molecules according to the correct specifications, the cell therefore requires free energy, which has to be imported somehow from the surroundings. As we shall see in Chapter 2, the free energy required by animal cells is derived from chemical bonds in food molecules that the animals eat, while plants get their free energy from sunlight.

All Cells Function as Biochemical Factories Dealing with the Same Basic Molecular Building Blocks

Because all cells make DNA, RNA, and protein, all cells have to contain and manipulate a similar collection of small molecules, including simple sugars, nucleotides, and amino acids, as well as other substances that are universally required. All cells, for example, require the phosphorylated nucleotide *ATP* (*adenosine triphosphate*), not only as a building block for the synthesis of DNA and RNA, but also as a carrier of the free energy that is needed to drive a huge number of chemical reactions in the cell.

Although all cells function as biochemical factories of a broadly similar type, many of the details of their small-molecule transactions differ. Some organisms, such as plants, require only the simplest of nutrients and harness the energy of sunlight to make all their own small organic molecules. Other organisms, such as animals, feed on living things and must obtain many of their organic molecules ready-made. We return to this point later.

All Cells Are Enclosed in a Plasma Membrane Across Which Nutrients and Waste Materials Must Pass

Another universal feature is that each cell is enclosed by a membrane—the **plasma membrane**. This container acts as a selective barrier that enables the cell to concentrate nutrients gathered from its environment and retain the products it

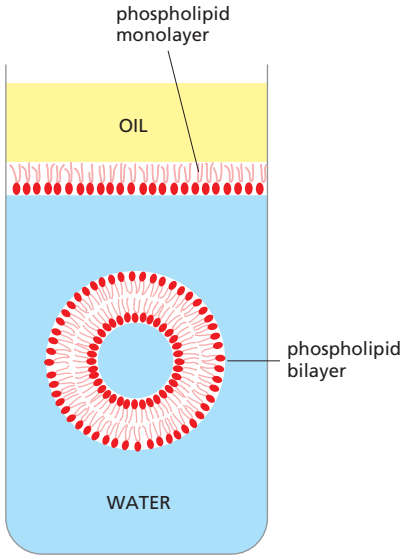


Figure 1–9 Formation of a membrane by amphiphilic phospholipid molecules. Phospholipids have a hydrophilic (water-loving, phosphate) head group and a hydrophobic (water-avoiding, hydrocarbon) tail. At an interface between oil and water, they arrange themselves as a single sheet with their head groups facing the water and their tail groups facing the oil. But when immersed in water, they aggregate to form bilayers enclosing aqueous compartments, as indicated.

synthesizes for its own use, while excreting its waste products. Without a plasma membrane, the cell could not maintain its integrity as a coordinated chemical system.

The molecules that form a membrane have the simple physicochemical property of being *amphiphilic*—that is, consisting of one part that is hydrophobic (water-insoluble) and another part that is hydrophilic (water-soluble). Such molecules placed in water aggregate spontaneously, arranging their hydrophobic portions to be as much in contact with one another as possible to hide them from the water, while keeping their hydrophilic portions exposed. Amphiphilic molecules of appropriate shape, such as the phospholipid molecules that comprise most of the plasma membrane, spontaneously aggregate in water to create a *bilayer* that forms small closed vesicles (**Figure 1–9**). The phenomenon can be demonstrated in a test tube by simply mixing phospholipids and water together; under appropriate conditions, small vesicles form whose aqueous contents are isolated from the external medium.

Although the chemical details vary, the hydrophobic tails of the predominant membrane molecules in all cells are hydrocarbon polymers ($-CH_2-CH_2-CH_2-$), and their spontaneous assembly into a bilayered vesicle is but one of many examples of an important general principle: cells produce molecules whose chemical properties cause them to *self-assemble* into the structures that a cell needs.

The cell boundary cannot be totally impermeable. If a cell is to grow and reproduce, it must be able to import raw materials and export waste across its plasma membrane. All cells therefore have specialized proteins embedded in their membrane that transport specific molecules from one side to the other. Some of these *membrane transport proteins*, like some of the proteins that catalyze the fundamental small-molecule reactions inside the cell, have been so well preserved over the course of evolution that we can recognize the family resemblances between them in comparisons of even the most distantly related groups of living organisms.

The transport proteins in the membrane largely determine which molecules enter the cell, and the catalytic proteins inside the cell determine the reactions that those molecules undergo. Thus, by specifying the proteins that the cell is to manufacture, the genetic information recorded in the DNA sequence dictates the entire chemistry of the cell; and not only its chemistry, but also its form and its behavior, for these too are chiefly constructed and controlled by the cell's proteins.

A Living Cell Can Exist with Fewer Than 500 Genes

The basic principles of biological information transfer are simple enough, but how complex are real living cells? In particular, what are the minimum requirements? We can get a rough indication by considering a species that has one of the smallest known genomes—the bacterium *Mycoplasma genitalium* (**Figure 1–10**). This organism lives as a parasite in mammals, and its environment provides it with many of its small molecules ready-made. Nevertheless, it still has to make all the large molecules—DNA, RNAs, and proteins—required for the basic processes of heredity. It has about 530 genes, about 400 of which are essential. Its genome of 580,070 nucleotide pairs represents 145,018 bytes of information—about as much as it takes to record the text of one chapter of this book. Cell biology may be complicated, but it is not impossibly so.

The minimum number of genes for a viable cell in today's environments is probably not less than 300, although there are only about 60 genes in the core set that is shared by all living species.