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Second Edition

Cell Biology: A Molecular Approach

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CELL BIOLOGY

A Molecular Approach

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and
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Preface

The name "molecular biology:" . . . implies not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below large-scale manifestations of classical biology for the corresponding molecular plan.

W. T. ASTBURY
Harvey Lecture, 1950

The topic of this book is cellular structure and function, with emphasis on understanding how and why, rather than simple description.

It has been said that a good textbook should tell what is known, what is uncertain about what is known, what is unknown, and how it might come to be known. With that admonition as a guide, I have made it my goal in this work to present a unified introduction to the present state of our knowledge about cell biology, and a framework into which new facts will fit as they become available.

I have been gratified at the acceptance of the first edition, and by the unselfish willingness of many users to tell me not only what they liked but what they would like to see changed. Largely on the basis of those suggestions, and also because of new directions in the thrust of recent research, many changes have been made in this edition. Primarily, they involve (1) a greatly expanded coverage of membrane structure and function, including consideration of cellular recognition, hormone receptors, and more coverage of endocytosis and secretion; (2) much new material on contractility and motility, especially on the contractile systems of non-muscle cells; and (3) a number of clinically relevant medical examples.

It was with considerable pleasure that the last category of changes was made. As a physician as well as a scientist, I have a special interest in the application of cell biology to medicine, and I firmly believe that cell biology is the cornerstone of scientific medicine. I feel that the medically relevant examples will help demonstrate that interaction without diluting the purpose of the text, which is to present basic cell biology—i.e., the study of processes that, for the most part, are common to all eukaryotic cells.

To hold the overall length within bounds, I have abbreviated the discussion of some topics that were covered in the first edition, and dropped others entirely. If I have interpreted the comments of previous users correctly, the missing material will be little mourned.

If, in spite of my attempts to contain the length of the text, it still seems overlong, I take refuge in a remark by Max Delbrück: "Any living cell carries with it the experiences of a billion years of experimentation by its ancestors. You cannot expect to explain so wise an old bird in a few simple words."

Robert D. Dyson

Acknowledgments

Though one name appears as author, many people contributed to making this book a reality. The following scientists were listed in the first edition: Richard Barsotti, Anita Bolinger, Janet Cardenas, Ernst Florey, Dean Fraser, Eric Holtzman, Benjamin Kaminer, Eugene Kennedy, John Menninger, Margot Pearson, and Ralph Quatrano. It is my pleasure again to acknowledge the debt I owe them. Expert advice and counsel specifically on the second edition were obtained from: K. R. Brasch, J. M. Cardenas, P. G. Satir, R. Sinclair, and M. Locke. In addition, scores of comments were received from users of the first edition, in their aggregate providing the basis for most of the changes made in this revision. To all of the above, I am very grateful. No one of these people, however, saw the manuscript in its final form, so it is both safe and fair to attribute any errors that remain solely to me.

There are, in addition, about 350 electron micrographs plus hundreds of other drawings and photographs that should be acknowledged. Where material was obtained from other sources, credit is given in the figure legend. The drawings for the first edition were produced mostly by Jacqueline Atzet. Revisions and new drawings for this edition were done by Vantage Art, Inc., of Massapequa, N.Y.

Last, but by no means least, I am grateful to Allyn and Bacon and its staff for putting together a finished textbook from the bits and pieces furnished them. In particular, Judy Fiske deserves enormous credit for her skill in editing and production, and for guiding the manuscript through a difficult schedule. William Roberts was the Senior Editor whose faith and encouragement made the first edition possible. Harvey Pantzis, whose good humor and understanding are always appreciated, played a similar role for this edition. An author could not hope for more talented or congenial people with which to work!

User's Guide

To me, we have been children, playing on the shore,
Picking up pretty pebbles from the beach . . .
While there beside us lay an Ocean,
Wide with undiscovered Truth.

SIR ISSAC NEWTON

It is the function of this User's Guide to help you obtain as many pebbles as possible from this book. About the ocean of undiscovered Truth, we can do very little; the most important thing is to realize it is there.

Organization. The book begins with an introductory chapter in which the structural features of cells and their organelles are described briefly. The purpose is one of orientation and perspective—it is easy to get so involved with the study of a given cellular component that you forget how this component fits into the overall structural pattern of the cell. You can minimize that problem if you would return from time to time to the descriptions in Chap. 1.

The organization of the rest of the topics is rather traditional: the chemical and biochemical aspects of cell physiology are treated in Chaps. 2–5, followed by an in-depth consideration of the structure and function of the various cellular components that were introduced in Chap. 1. The emphasis throughout is on membranes, their structure, function, and interactions. There is, in addition, a chapter-length appendix that treats physical methodologies used in cell biology. Emphasis, of course, is on microscopy in its various forms.

There has been a conscientious effort to produce a relatively complete index. The purpose was not only to enhance the use of the text as a reference, but also to eliminate the need for a glossary. It is my opinion that scientific terms are best defined in context. Those who prefer the dictionary approach have a number of excellent biological dictionaries from which to choose. A relatively complete and very inexpensive example is the *Dic-*

tionary of Biology by E. B. Steen (New York: Barnes and Noble, 1971).

Chapter Structure. Each chapter is divided into several major sections, with each of the various sections having its own summary and study guide. The objective was flexibility, and the hope that topics could be more easily arranged to suit the design of a particular course or preferences of its instructor.

The summaries are concise presentations of the most relevant points. They are for review. They are not intended to stand on their own and cannot substitute for a careful study of the text and examination of the illustrations.

The study guides are designed to help you determine how much you remember from the associated section. Most of the questions are straightforward, and test only recall. Where appropriate, problems have been included and the answers given. Occasionally, a question demands extrapolation from given material to new situations. That is what science is all about, of course.

References. Each chapter, including the Appendix, has its own group of references, arranged by author within several broad subject-matter categories. The references consist mostly of reviews, but textbooks and reports of individual pieces of work are also listed. The credits in the figure legends should be considered an additional source of references.

When individual research papers are cited, it is either because they were specifically mentioned in the text, or because they can be recommended as classic presentations of a piece of work, or just because they are not adequately discussed in the reviews that are also listed.

In reading individual research papers, it helps to keep in mind that most are constructed with a format that includes: (1) a *summary* or *abstract*, giving the high points of the work; (2) an *introduction*, designed to describe the problem and its relationship to other work in the field; (3) a *materials and methods* section, giving experimental details; (4) a *results* section, containing the outcome of the experiments without much elaboration; and (5) a *discussion* section, in which the meaning of the results is presented, often with speculation about how the results bear on associated problems and what experiments along the same lines are planned for future work.

You may find the following approach to be a useful way for you to get the most out of a research paper without becoming confused by details: Try reading the introduction first, to define the problem; then the summary or abstract to get the outcome; then the discussion to gain the investigators' opinion about the significance of the work. The results section can serve as a reference to get more details about specific aspects of the experiments if you are interested. The materials and methods section is of little use to most students.

Suggestions for Further Study. To facilitate further study, and particularly as an aide in finding papers too recent to be included in the references, the major periodicals that review work on cell biology are listed here, grouped roughly according to their level of difficulty.

Generally easy:
- *American Scientist.*
- *BioScience.*
- *Hospital Practice.* Don't be misled by the name—excellent reviews of cell biology appear regularly.
- *New Scientist.* A news magazine.
- *Perspectives in Biology and Medicine.* Strong on history and philosophy.
- *The Sciences.*
- *Science News.*
- *Scientific American.* Always excellent.

Usually of moderate difficulty:
- *Essays in Biochemistry.* Published yearly.
- *The Harvey Lectures.* Collected and published yearly.
- *MTP International Review of Science.* Several volumes a year, each on one topic.
- *Nature.* Contains reviews plus brief original reports. The "News and Views" section of each weekly issue is an excellent way to keep up.
- *Nobel Lectures.* Collected and translated by the Elsevier Publishing Co. The lectures on "physiology or medicine" appear annually in *Science.*
- *Proceedings of the Royal Society (London).* The annual "Croonian lecture" and occasional review are highly recommended. The *Philosophical Transactions of the Royal Society* also publishes reviews.
- *Science.* Journal of the American Society for the Advancement of Science. Nice reviews plus a weekly section on scientific advances called "Research News."
- *Science Progress (Oxford).* The reviews are uniformly readable.
- *Society of General Physiologists. Society for General Microbiology. Society for Experimental Biology.* Each publishes an annual symposium volume with generally readable reviews.
- *Trends in Biochemical Sciences.* Several short, usually excellent reviews in each monthly issue.

Often more difficult:

Advances in . . . . Many of these. See especially volumes on *Genetics* and on *Morphogenesis*.

Annual Review of . . . . See especially the volumes on biochemistry, on genetics, and on microbology. The volumes on physiology, on plant physiology, and on neuroscience, should also be useful.

Bacteriological Reviews.

Biochimica et Biophysica Acta. Publishes multiple volumes each year, including a volume of reviews on biomembranes, one on bioenergetics, and one on cancer.

Biological Reviews (*Cambridge*).

Biomedicine. Their reviews stress cancer.

Biomembranes.

Cell. Frequent reviews.

Ciba Foundation Symposia. Each volume a separate topic.

Cold Spring Harbor Symposium on Quantitative Biology. Published yearly, each on a single topic.

CRC Critical Reviews in Biochemistry, and a companion volume in microbiology.

Current Topics in . . . *Bioenergetics; Cellular Regulation; Developmental Biology; Membranes and Transport;* and others.

Federation Proceedings. Publishes symposia sponsored by the Federation of American Societies for Experimental Biology.

International Journal of Biochemistry. Frequent short reviews.

International Review of Cytology. Published several times a year. Excellent reviews on all aspects of cell biology.

Life Sciences. Most issues carry one or more "Minireviews."

New England Journal of Medicine. Frequent short reviews on biological subjects.

Physiological Reviews.

Progress in . . . *Biophysics and Molecular Biology; Molecular and Subcellular Biology; Nucleic Acid Research and Molecular Biology;* etc.

Quarterly Review of Biology.

Quarterly Reviews of Biophysics. Sometimes too mathematical.

Reviews of Physiology, Biochemistry, and Pharmacology.

Sub-Cellular Biochemistry.

Periodicals in the first and second categories should be understandable even before the text is read. Periodicals in the third group should probably be consulted only for further detail, after the relevant parts of the text have been mastered.

Contents

1

The Cellular Basis of Life

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

E. B. WILSON, 1925[1]

1-1 CELL THEORY

The foundations of cell biology were formed in the seventeenth century, with two of the most important advances of that period coming from the Englishman Robert Hooke (1635–1703) and the Dutch inventor and scientist Antony van Leeuwenhoek (1632–1723).

In 1665, Hooke published a collection of essays under the title *Micrographia*. One essay described cork as a honeycomb of chambers, or "cells." The chambers are now recognized to be the rigid remains of

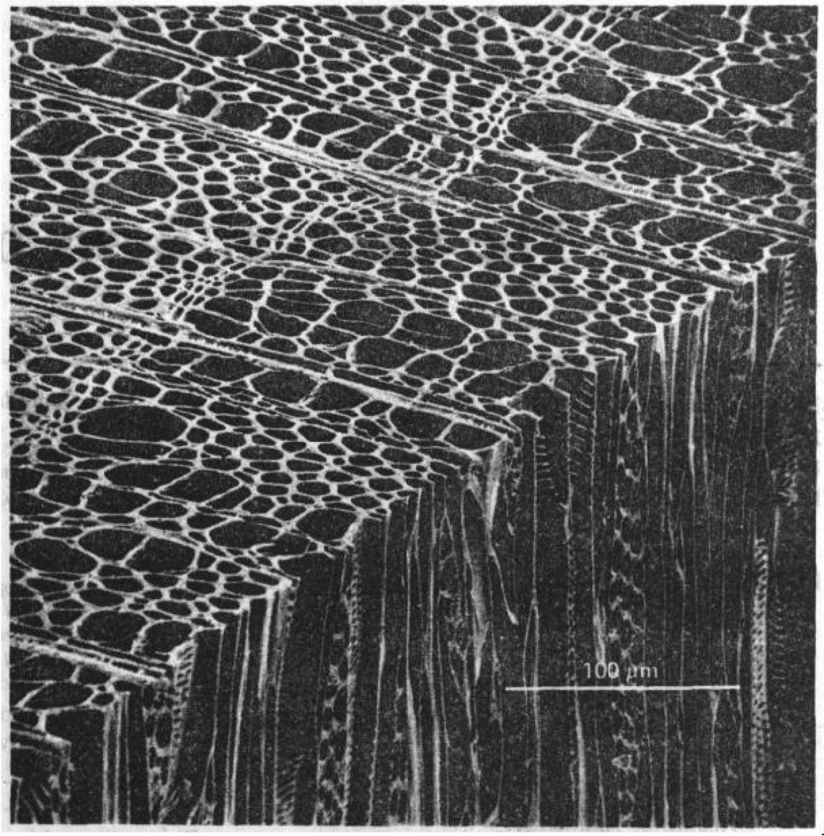
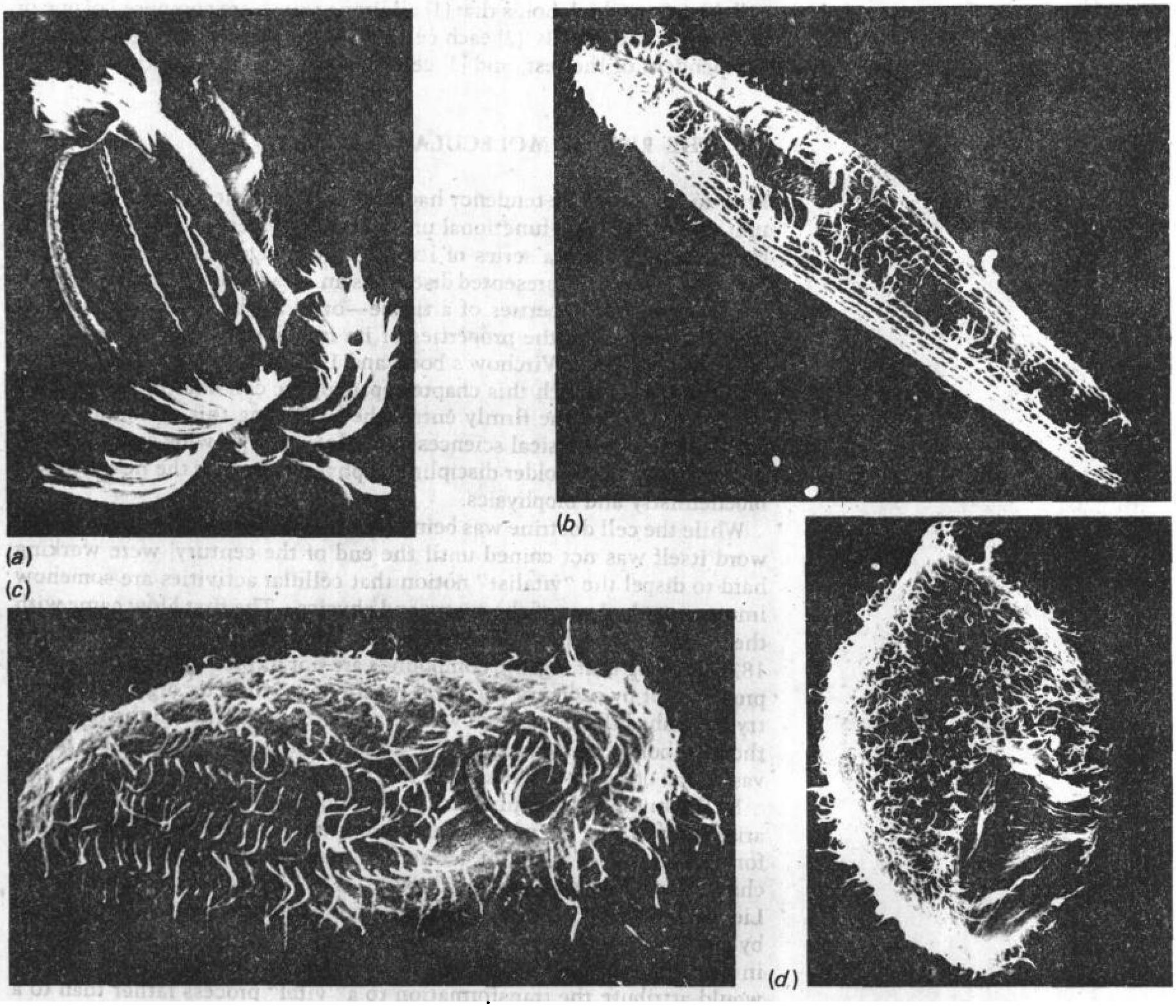


FIGURE 1-1 The Three-dimensional Structure of Wood. Scanning electron micrograph of magnolia shows the honeycomb of chambers left when wood is dry. A similar pattern in cork was described by Hooke as an array of "cells," although each chamber is actually the rigid remains of a dried "cell," as we now use that word. (Courtesy of B. A. Meylan, Physics and Engineering Lab., Dept. of Scientific and Industrial Research, New Zealand.)

dried cells (see Fig. 1-1). Hooke thought of the cells he observed as something similar to the veins and arteries of animals—they were filled with "juices" in living plants—but his microscope did not permit the observation of any intracellular structure, an observation that would have dispelled the notion that cells are merely partitioned channels for the passage of material.

Within a decade after the publication of Hooke's essays, Leeuwenhoek had succeeded in greatly improving the art of polishing lenses of short focal length and had used his lenses to describe a host of "little animals," many of which proved to be single cells (see Fig. 1-2). These little animals were probably protozoa. A typical size for these organisms would be 100 micrometers (100 μm), which is about the resolving power of the human eye.[2] In other words, when two objects get closer than 100 μm they begin to appear as one. Hence, it would take nothing more than a simple magnifying lens to make at least the larger protozoa visible.

Leeuwenhoek was later able to use his microscope to describe for the first time the existence of bacteria, the dimensions of which are typically only about 1 or 2 μm. This incredible feat means that he had an instrument theoretically capable of seeing not only whole animal cells but details of structures within the cells as well. However, in order to take advantage of that capacity, better ways of preparing tissues for microscopy were needed. By the end of the seventeenth century, considerable progress in that area had been made, so that microscopists were able to examine tissues as thin as 10 μm, stained in various ways to bring out different details. (See Appendix A-1, Microscopy.)



With these improved microscopes and preparation techniques, R. J. H. Dutrochet was able to conclude by 1824 that all animal and plant tissues are actually aggregates of cells of various kinds, and that growth results from an increase in either the size or the number of cells, or both. Though he recognized that intact cells can be separated from each other, he did not realize that each is capable of its own independent existence including, in most cases, the ability to reproduce itself.

FIGURE 1-2 Leeuwenhoek's "Little Animals"—as he never saw them. These scanning electron micrographs are of protozoa. Each is a single cell. (*a*) *Uronychia* sp., 100 μm long. (*b*) *Blepharisma* sp., about 140 μm. (*c*) *Tetrahymena pyriformis W.* about 25 μm. (*d*) *Turaniella* sp., 250 μm. [Courtesy of E. B. Small and G. Antipa. (*a*) and (*b*) from E. Small, D. Marszalek, and G. Antipa, *Trans. Am. Micros. Soc.*, **90**: 283 (1971).]

The next few decades saw a rapid increase in the understanding and appreciation of cells. In 1838–1839 the German biologists M. J. Schleiden and Theodor Schwann argued convincingly that each cell is capable of maintaining an independent existence, an idea that had a profound influence on the scientific community. Schleiden and Schwann were followed by Rudolf Virchow, who in 1858 published his classical textbook *Cellular Pathology*, which supported the concepts suggested by Schleiden and Schwann and extended them to attribute every cell to a preexisting cell (*omnis cellula e cellula*—every cell from a cell). Virchow's ideas completed what has come to be known as the *cell theory* or *cell doctrine,* which holds that (1) all living things are composed of one or more units called cells, (2) each cell is capable of maintaining its vitality independent of the rest, and (3) cells can arise only from other cells.

1-2 THE RISE OF MOLECULAR BIOLOGY

Prior to Virchow, the tendency had been to regard the cell as a structural unit rather than as a functional unit of living systems. However, in his book, adapted from a series of lectures given at the Berlin Institute of Pathology, Virchow presented disease as an aberration in normal cellular processes. The properties of a tissue—or of a whole organism—must therefore be due to the properties of its individual cells. Between the 1858 publication of Virchow's book and 1925, when E. B. Wilson wrote the words with which this chapter opened, the cell doctrine as we now understand it became firmly entrenched. During this period also, the influence of the physical sciences on biology was growing ever stronger, complementing the older discipline of physiology with the new fields of biochemistry and biophysics.

While the cell doctrine was being formulated, biochemists (though the word itself was not coined until the end of the century) were working hard to dispel the "vitalist" notion that cellular activities are somehow immune to the laws of chemistry and physics. The first blow came with the laboratory synthesis of urea ($H_2N—CO—NH_2$) by Friedrich Wöhler in 1828, proving that organic compounds are not formed by any mysterious process, but by ordinary chemical reactions. Synthetic organic chemistry flourished thereafter, and with it came the first clues to the nature of the metabolic transformations by which a cell turns its foodstuffs into a vast array of quite different molecules.

By the middle of the nineteenth century, considerable controversy had arisen concerning the nature of one commonly observed metabolic transformation, that of alcoholic fermentation, a process in which glucose is changed to ethanol and carbon dioxide. The German chemist Justus von Liebig (1803–1873) maintained that alcoholic fermentation is catalyzed by nonliving "ferments," later called *enzymes,* that are naturally present in the juices being fermented. He was hotly opposed by those who would attribute the transformation to a "vital" process rather than to a chemical process.

In 1871 a Frenchman, Louis Pasteur (1822–1895), demonstrated that a living organism—yeast—is essential to alcoholic fermentation as it usually occurs. Although vitalists felt that Pasteur's observation proved their point, Eduard Buchner found in 1897 that it is not necessary for the yeast to be alive; extracts from yeast cells can still carry out alcoholic fermentation. The necessary enzymes are made out of simpler organic materials by the yeast cells; however, the function of enzymes does not depend on the vitality of the cells that make them. Thus Liebig's earlier contention that fermentation is a straightforward chemical process was vindicated, even though Liebig did not recognize the source of the enzymes responsible for it.

At the turn of the century, then, the identity and importance of the individual cell were recognized and serious efforts were being made to understand its function. Buchner's work established that individual