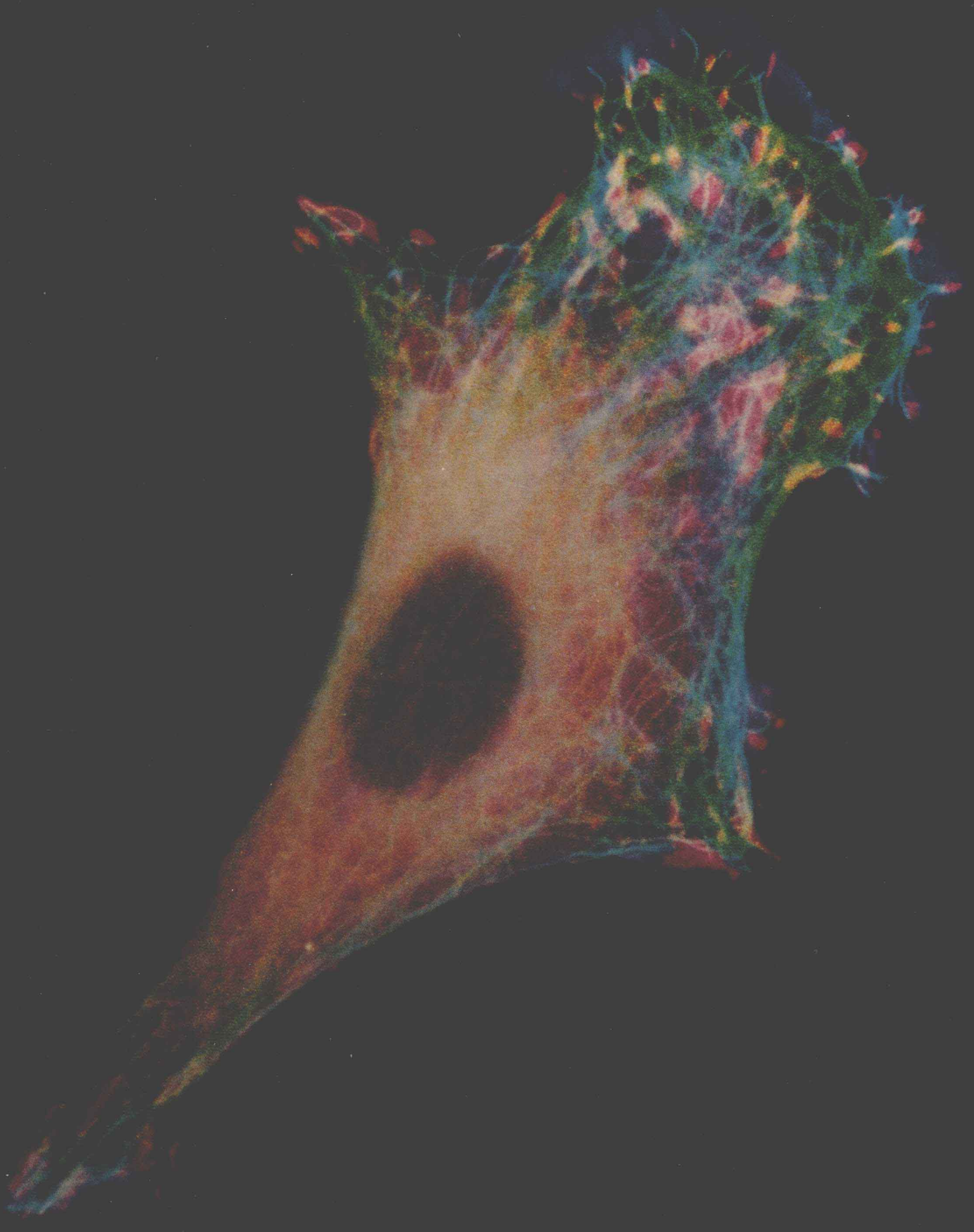
MOLECULAR CELL BIOLOGY



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MOLECULAR CELL BIOLOGY

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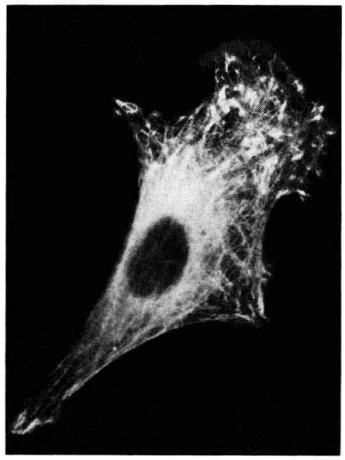

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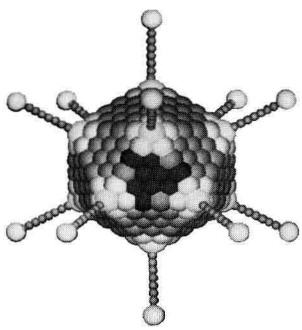

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MOLECULAR CELL BIOLOGY

To our families:
Jane, Chris, Bobby, and Jon
Pam, Heidi, Martin, and Stephanie
Alice and Teak

Preface

BIOLOGY today is scarcely recognizable as the subject that biologists knew and taught 10 years ago. A decade ago, gene structure and function in the simple cells of bacteria were known in considerable detail. But now we also know that a different set of molecular rules governs gene organization and expression in all eukaryotic cells, including those of humans. We are learning about the genes and regulatory proteins that control not only single metabolic steps but complicated developmental events such as the formation of a limb, a wing, or an eye. In addition to these advances in understanding the genetic machinery and its regulation, great progress has been made in the study of the structure and function of cell organelles and of specialized cell proteins. To comprehend fully what has been learned requires a reformulation of a body of related information formerly classified under the separate headings of genetics, biochemistry, and cell biology. *Molecular Cell Biology* aims to present the essential elements of this new biology.

Traditionally, the sciences of genetics, biochemistry, and cell biology—the three areas in which the greatest progress has been made in the last 25 to 30 years—used different experimental approaches and often different experimental material. Classical geneticists sought mutations in specific genes to begin identifying the gene products and characterizing their physiological functions. Biochemists tried to understand the actions of proteins, especially enzymes, from their sequences and three-dimensional structures. Cell biologists attempted to discover how specific proteins took part in the construction and operation of specialized cell structures. These subjects were taught as three courses, albeit with varying degrees of overlap.

A group of techniques collectively referred to as molecular genetics is mainly responsible for unifying the three disciplines. Not only do these techniques provide a powerful analytic force, but they also serve to unify all experimental biology in its language and concerns. With the tools of molecular genetics, genes for all types of proteins—enzymes, structural proteins, regulatory proteins—can be purified, sequenced, changed at will, reintroduced into individual cells of all kinds (even into the germ lines of organisms) and expressed there as proteins. Most of experimental biology now relies heavily on molecular genetics.

In addition to the outstanding advances in molecular genetics, comparable advances have been made in culturing the cells of vertebrates, invertebrates, and plants, including the cells that produce various individual monoclonal antibodies. The use of cell cultures has greatly unified and simplified experimental designs. Finally, very sophisticated instrumentation has become available. Powerful electron microscopes and advanced techniques in electron microscopy have greatly improved our understanding of cell substructure. Modern computers have arrived in time to store—and then to compare—rapidly accumulating information (such as protein and nucleic acid sequences), as well as to present graphic displays of molecular structures. Of equal importance, computers rapidly complete elaborate calculations so that x-ray crystallographic analysis (or other kinds of image analysis) can be performed in days instead of months or years.

Those who teach biology at the undergraduate or graduate level and in medical schools can convey this comprehensive and integrated experimental approach in the classroom only when they have access to appropriate teaching materials. Our book is intended to fill the need for such materials: We wrote it to solve our own problems as teachers. It was our purpose to teach a one-year course that integrates molecular biology with biochemistry, cell biology, and genetics and that applies this coherent insight to such fascinating problems as development, immunology, and cancer. We hope that the availability of this material in a unified form will stimulate the teaching of molecular cell biology as an integral subject and that such integrated courses will be offered to students as early as possible in their undergraduate education. Only then will students be truly able to grasp the findings of the new biology and its relation to the specialized areas of cell biology, genetics, and biochemistry.

We have aimed to provide a college textbook that is no more difficult than the basic textbooks encountered by undergraduate physics and chemistry students in their respective programs of study. That there will be complaints about the scope and depth of a textbook this large seems inevitable. But in addition to dividing the book into parts, we have clearly identified the parts of the chapters themselves, by means of descriptive subheadings. This organization will enable students and teachers to be selective in their reading. We recognize that some teachers of one-semester courses may wish to continue teaching molecular biology and cell biology as separate courses. The book is organized so that, in such situations, emphasis can easily be given to either the gene or the cell.

Whichever path students and teachers choose to follow, we believe that the focus of teaching an experimental science such as biology should be the experiments themselves. We have devoted much space to presentations of experiments. Scientists make advances by phrasing the unknown as an experimental question, designing an experiment to answer the question, and assembling the experimental results to produce a coherent answer. Students who see how biological progress is intimately connected to experimentation will be more likely to keep pace with the progress of biology in the future and perhaps even to contribute to it.

Most students today begin an undergraduate major in biology with an introductory course in general biology and at least one course in chemistry. Such students need a clear explanation of how basic biochemical and biological principles relate to the central developing areas of molecular cell biology. This focus is provided in Part I of the book. Chapter 1 presents some of the key ideas in the history of modern biology. Chapters 2 and 3 deal with the fundamentals of biochemical structure, function, and energetics. Chapter 4 presents cellular polymer synthesis, including the flow of genetic information from DNA to RNA to protein. Then, Chapter 5 covers the basic principles of cell structure and function. Students who are well prepared probably will not need to restudy most of the material in the first five Chapters. All students should read Chapters 6 and 7, for these present the new (now standard) cell and molecular techniques that are changing the face of experimental biology. These chapters will enable students to follow the experiments described in the remainder of the book.

With the foundations established, we go on to describe research results and conclusions drawn from work in molecular and cell biology.

In Part II (Chapters 8 and 9) we stress RNA biosynthesis and gene expression before we discuss gene structure and chromosomal organization (Chapters 10 and 11). We use this order of presentation because the diversity of organisms, while surely encoded in DNA, is brought to reality by the programmed expression of genes during the differentiations of each organism. Thus, we concentrate on genes as transcription units and deal extensively with how genes are controlled (Chapter 12) as well as how they are replicated and repaired (Chapter 13).

In Part III we turn to the ways in which proteins—the ultimate gene products—work together to make a living cell. Instructing the new biology student in the names and shapes of the parts of a cell can by itself be a satisfying experience because of the wealth of pictorial detail available. But it is the integration of the structural detail with molecular function that gives meaning to cell activity, and many aspects of this integration have been brought to an advanced level within the last few years. We show how many fundamental properties of cells are explained by properties of specific membrane proteins (Chapter 14). These activities include the regulated entry and exit of molecules into and out of cells (Chapter 15), transmission of signals between cells (Chapter 16), the characteristics of nerve cells and electrical properties of membranes (Chapter 17), cellular movements and cell shape (Chapters 18, 19), and the generation and use of ATP (Chapter 20). We consider how a cell is assembled from its component nucleic acids, proteins, carbohydrates, and lipids, and, in particular, how proteins are "targeted" to their appropriate destination in the cell (Chapter 21). Special attention is given to organelles and cells that illustrate phenomena of general significance in many organisms—the contraction of muscle (Chapter 18), beating of flagella (Chapter 19), regulation of carbohydrate metabolism (Chapter 20), and the propagation of nerve impulses (Chapter 17).

Advances in molecular cell biology have led to significant discoveries about such changes in cell function and behavior as the development of higher organisms, the immunologic response, cancer, and cell evolution. These are discussed in Part IV of the book. Chapter 22 discusses the classical and modern experimental work that has led to the view that development is an organized train of cellular changes. Although much remains to be learned, development doubtless depends upon the expression of "the right gene in the right place at the right time." Chapter 23 makes the point that cancer, which is caused by alterations of normal cell growth control and tissue architecture, likely arises as a disorganization of the structure or function of relatively few genes. Chapter 24 is devoted to the cells of the immune system because they employ a very special mechanism of change during their differentiation: The DNA encoding antibodies is rearranged to form a virtually unlimited and constantly changing set of proteins that protects animals from the ever present threat of microbial infection. Finally all the variations that we see and study in cells are part of a continuum of ongoing evolutionary changes that began about 3.5 billion years ago. Molecular cell biology has taught us to look at the earliest stages of evolution in a new way, and so we close the book with Chapter 25, which examines those new insights.

Over the past seven years, from the earliest planning stages to completion, this book has occupied a significant portion of our energies. During this period we have often exchanged views and read each others' work, so that our book is truly a joint responsibility and a joint product.

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To our friends and associates in our laboratories and, most of all, to our families we apologize for the long absences and the vacant stares that frequently came in the wake of long hours of working on the book. If our efforts are successful in helping to unify the teaching of molecular cell biology we will be deeply grateful.

Jim Darnell
Harvey Lodish
David Baltimore

April 1986

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