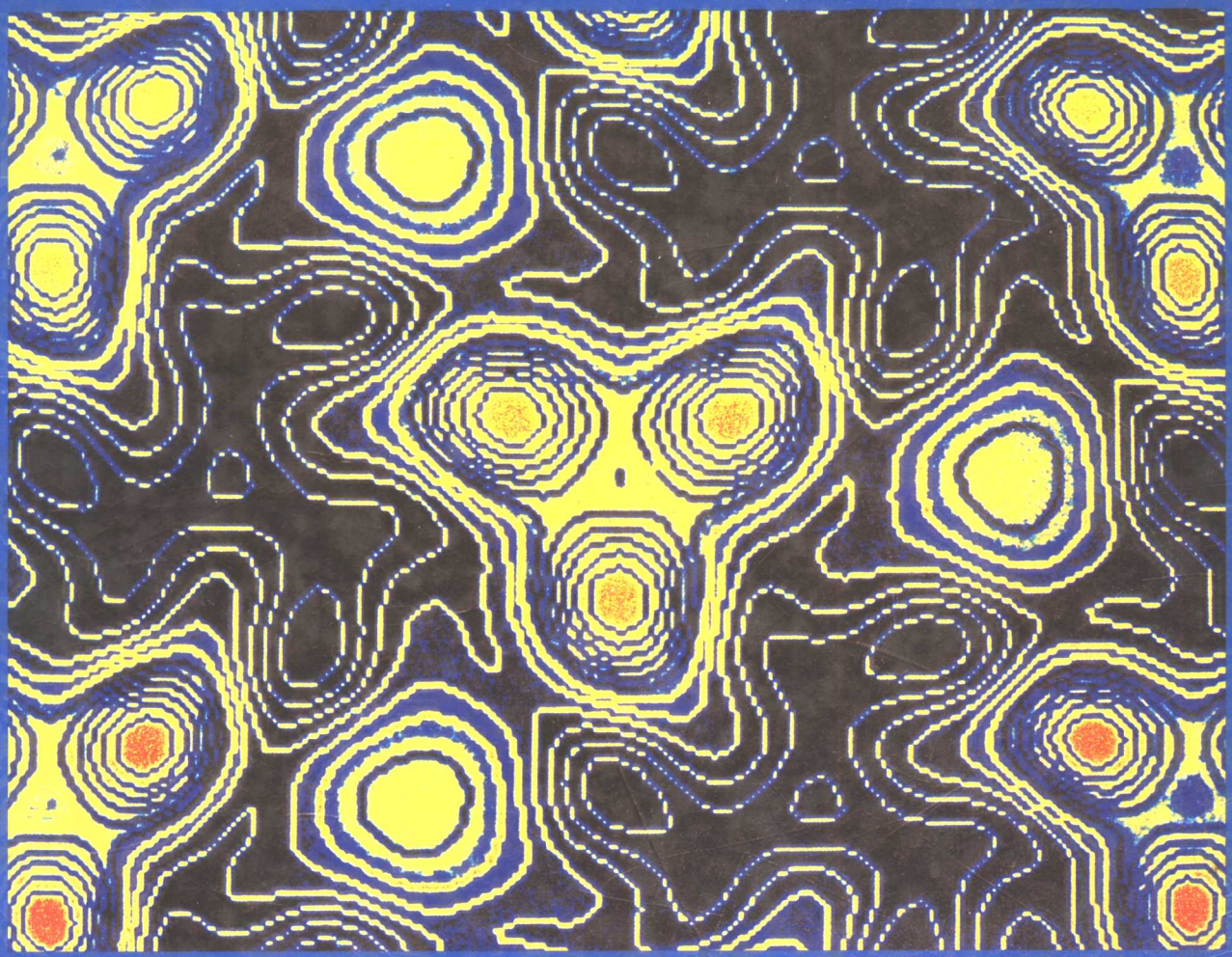

CELL BIOLOGY

Neal O. Thorpe

One of the layers of the cell wall of *Escherichia coli* viewed by the electron microscope and by computerized image processing techniques.

CELL BIOLOGY

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Preface

The introduction of a new text in cell biology needs little defense, for no single literary source can do justice to the cell. Several textbooks are now available on the subject, each with its own coverage and character. In addition, there are thousands of monographs dealing with various aspects of cell structure and function. In writing this text I have sought to condense a very complex and diversified field into a book that is easy to read and clearly focused. The central theme is the structure and function of the cell and its organelles.

Students of cell biology often have quite diverse academic backgrounds. Certainly introductory courses in biology and chemistry are prerequisite to a study of the cell, but beyond that some students may have little organic chemistry and others may be well grounded in both organic chemistry and biochemistry. This text is designed to speak to a heterogeneous audience, partly by the way in which material is presented and partly because of the introduction of marginal comments. Students with a minimum of organic chemistry or biochemistry will find in appropriate marginal locations structures and comments that will enable them to follow discussions that have a molecular or biochemical emphasis. Students with stronger chemical backgrounds will discover the value of these comments for recall. In addition, marginal comments are used to provide information to enrich a discussion or as a running glossary, especially when the information would interrupt the flow of the topic if thrust into the heart of the material.

The book is organized to examine the cell by starting with its environment, then moving to its surface components, and finally into its interior. Chapters dealing with cell components that are functionally related have been grouped into sections so that students can come to appreciate the way in which different cell structures and functions are interrelated and interdependent.

The first chapter surveys the field in a way that serves as a brief refresher course for all students, placing them on a common ground. Then that which is exterior to the plasma membrane—the cell environment and the cell wall—is discussed. These have a strong influence on the cell and in many instances are essential for its survival. The next section deals with the plasma membrane and the surface properties of antigenicity, reception, adhesion, and communication.

The cell interior is emphasized next, first by discussing organelles that have specialized biosynthetic and oxidative functions, the endoplasmic reticulum and microbodies. The mechanisms of transporting materials into

the cell in bulk form by endocytosis and the subsequent digestive activities of lysosomes are the subjects of the next section. Within the cell, materials are moved through a pathway that involves the Golgi complex, a fascinating function of the cell that is covered in a separate chapter. Energy transduction, the activities of mitochondria and chloroplasts, constitutes the next discussion. This is followed by a section that describes the manner in which information is compartmentalized and directed in the cell. A section on the molecular anatomy of form and movement completes the main narrative.

Within each chapter the topics are developed to move from rather low to high resolution, such as from the microscopic to the molecular. Where appropriate, this approach is integrated with a chronological development of the subject, taking the student from the technically simpler past into the more sophisticated present state of the art.

Even though the cell is a highly integrated structure, the study surrounding any given component has developed into its own area of research. Each area has a certain emphasis and uniqueness. These important scientific flavors have been retained throughout the book by, for example, providing a brief description of each research area from a historical perspective. Our present understanding of the parts of a cell draws from the roots of each field of research, a fact that is important to acknowledge. In most cases, the past has set the tone for the development of the field and for its current status. In general, I sought to move a topic in the direction and as far as experts in the field have taken it, thus maintaining the scientific atmosphere in which the study of a particular cell feature has emerged. Beyond that, I point out questions that are not yet answered and work that still must be done before topics can be discussed with a high level of confidence.

The material of each chapter is referenced with two basic objectives in mind. One is to acknowledge the sources of particularly important advances or to point to sources that may shed light on specialized areas that are not necessarily expanded in the text. A second is to indicate sources of information that were especially helpful to me and should be useful for student research and enrichment, as well. Each chapter ends with a list of books and articles that are excellent starting points for additional study.

The text contains an abundance of electron micrographs, diagrams, and tables. In every case, I have tried to select the best figure available to illustrate a point, and wherever practical I have employed an original rather than a newly constructed drawing. Investigators who have kindly provided prints that are reproduced in figures are acknowledged in the figure legends. All other credits for tables and line drawings based on published works are collected by chapter in a credit section at the end of the text. Figure legends are not merely labels. They are instructive and have important content to add to the narrative.

Since the study of the cell depends on a variety of methods, some explanation of the techniques employed and the kinds of information derived from them is found at the end of the text. This is not a thorough theoretical treatment of methods but merely a survey to help the student understand the experimental approaches used to solve particular problems. Throughout the text, marginal notes direct the student to a specific

method when it would be helpful, and the discussion of the method itself directs the student back to several examples of its use.

From the beginning to the end, the student will gain a feeling of the discipline of cell biology—a sense of its development and areas of current work and speculation. The subject of cell biology is extremely dynamic. To reflect this, I have avoided the use of dogmatic statements that might suggest that the final word is in. In many cases it simply is not, and it is good for the student to gain a sense of the drama of investigation and to catch a vision of opportunity to participate as a professional in the continuing development of the field. I have not avoided divergent points of view or interpretations of data or lines of speculation. These are all a part of the fabric of present-day cell biology. At the same time, I looked for and emphasized consensus, to give the subject a firm foundation.

To close these comments without thanking a number of people would be a serious omission, for many have influenced the writing of this text. First, to my colleague, John Holum, whose "Go—write!" was the shove I needed to leap into the chasm of textbook writing and who then frequently joined me down there with invaluable wisdom and encouragement, my heartfelt thanks. Then, to Jon Singer, who kindly provided an idyllic setting under the eucalyptus and Torrey pines where the writing was begun while snow and cold smothered the landscape of the Midwest, my deepest gratitude. The transfer from nearly illegible scrawl to typed perfection was efficiently executed by Tammi Trelstad, Carolyn Pratt, Kayla Polzin, and Judie Wester. To each, I offer my appreciation, as well as to Cathy Marlett for her beautifully drawn models. My departmental colleagues Ralph Sulerud, Robert Herforth, Roberta Lammers, and Erwin Mickelberg came to my rescue on many occasions when I stepped into puzzling scientific quagmires. Many thanks.

Scores of investigators from the four corners of the earth sent prints, advice, reviews, and permissions to help create a well-illustrated and scientifically accurate text. Their generosity was a heartening boost to the work, and to them I offer my sincere appreciation.

The combination of artistic talent and scientific understanding of John Balbalis is a treasure that has contributed greatly to the quality of this text. Ann Marie Renzi effectively applied her creative and artistic talents to the design of this text and Ruth Greif guided me through the intricacies of production with a wealth of skill and perseverance. Kathy Bendo significantly eased the effort in researching and procuring certain electron micrographs.

I am most grateful to Fred Corey, who skillfully struck the delicate balance between encouragement, guidance, and keeping me on track.

Finally, to my family, who daily helped me back out of the chasm with patience, understanding, and encouragement. To them I cannot adequately express my indebtedness and gratitude and love.

Neal O. Thorpe

Contents

1

Cell Biology: A Preview

There is no "typical person." *Homo sapiens*, although a single genus and species, is made up of an assortment of individuals differing widely in regard to color, shape, size, mass, and behavior, to name but a few people properties.

Groups of people do exist, of course, in which the individuals are somewhat similar. We may say, for example, that a person is a typical Norwegian or Italian. But even if the statement is made with caution, it is likely to be disputed, especially by the individual in question, for there is within either group about as much variation as is found between groups. No two Norwegians are exactly alike, or at least no two would ever admit to this. The same is true for the members of any other group.

In the same sense, to refer to a "typical cell" would not be proper. Cells come as wildly assorted in size, form, and function as do people. This is, indeed, the basis for the heterogeneity of people. It is also the basis for the different kinds of tissues found in a single organism. A red blood cell in an elephant bears little resemblance to a striated muscle cell in the same animal and even less to a giant motor neuron running from the pachyderm's spinal column to the end of its trunk.

But groups of cells that possess similar traits are often found together. This is generally the case for a tissue, which is basically a group of cells with common structures and functions. It therefore is appropriate to speak of a typical liver parenchymal cell or nerve tissue cell. Were this not the case, a pathologist examining a biopsy specimen would have no basis for distinguishing between malignant and benign cells, in this sense, atypical and typical cells.

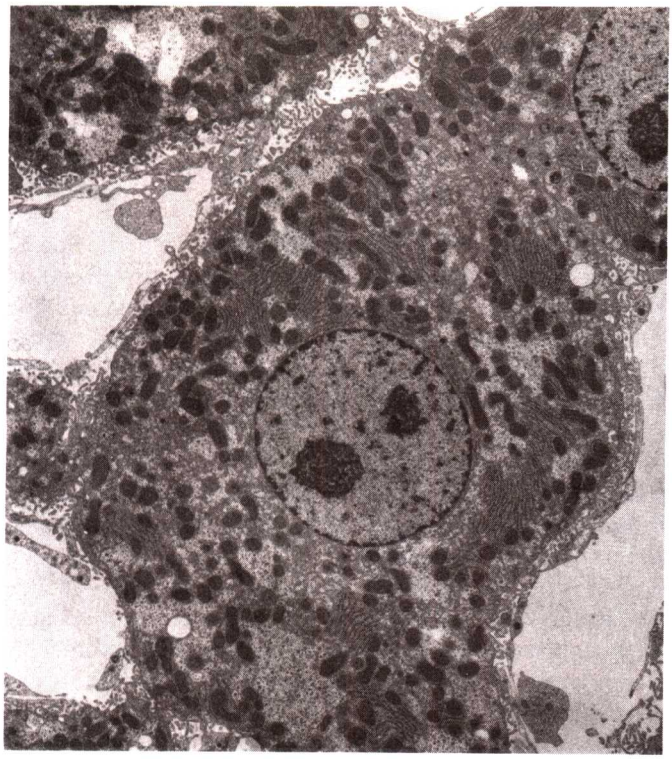
Fortunately, liver cells, or cells of any other type for that matter, are recognizable regardless of species. Thus, the difference between the livers of an elephant and a shrew lies not in the form or size of the constituent liver cells but rather in cell number. It would even be safe to say that there would be no microscopic difference between the liver cells of Norwegians and Italians. This law of likeness is something for which researchers are eternally grateful, for without it, mice and frogs could not take their place in experiments.

But except for this kind of likeness, cells display variations with respect to almost every conceivable property and structure. Hence, cells exist that are every color of the rainbow, with or without walls, with or without certain organelles, ranging in size from macroscopic to the edge of microscopic, and of shapes that challenge the most creative of imaginations.

There is no "typical" cell. This fact must be kept in mind when discussing cells in a course in cell biology. Nevertheless, we want to focus on structural and functional traits that are most typically evidenced by cells. In doing so, it is well to remember that variants, even in traits, are not infrequent in the cellular kingdom.

1.1 THE COMPOSITE CELL

When describing cells in a comprehensive sense, the best we can do is to speak of "composite" rather than typical cells. These are hypothetical cells, ideals, that embody the features of all cells. Such composite cells and electron micrographs from which models of this sort are derived are depicted in Figure 1.1. We use these composites to sketch very briefly,



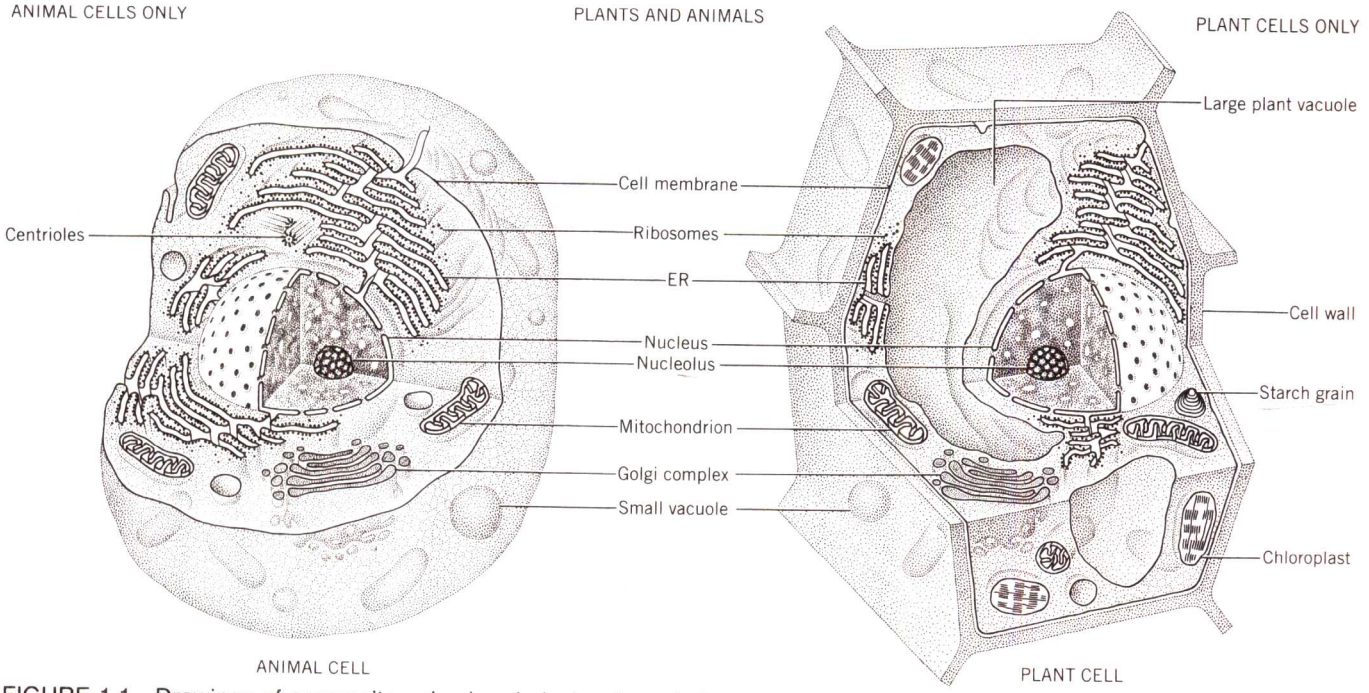


FIGURE 1.1 Drawings of composite animal and plant cells and electron micrographs illustrating some of the features depicted in the models. (Micrograph of animal cell courtesy of Dr. R. L. Wood; plant cell courtesy of Dr. Harry Horner.)

in preliminary form, the major structural and functional features of their components.

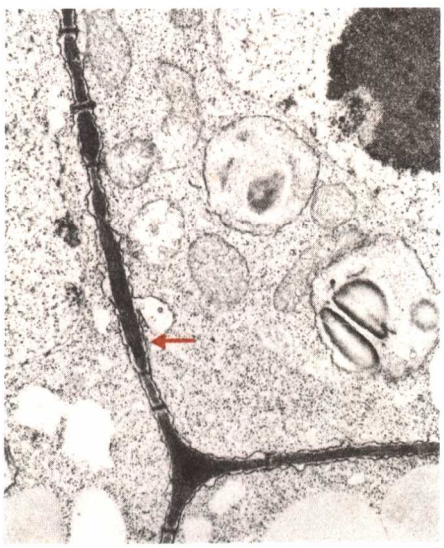
1.2 OUTSIDE THE PLASMA MEMBRANE

The Extracellular Environment

Cells of some sort inhabit virtually every niche in the biosphere. Some, therefore, are found in water, both fresh and salt, at its surface and at great depths. Some are found in air, in moist places, dry places, and hot and cold places. Others are found within masses of plant or animal tissue, where the environment may range from a fluid to a semisolid or solid matrix to that of neighboring cells. The environmental possibilities for cells are enormous.

The cell cannot ignore its environment. Its forces may desiccate it or squeeze it or impose strong osmotic pressures on its borders. Many characteristics of cells that we see displayed are there to cope with the difficult task of surviving in an adverse environment.

But the environment is not always harsh; in many cases it is beneficial. For example, it is by means of the environment that cells receive messages that influence their metabolism and provide for a stable cell economy. In addition, precisely controlled environmental conditions are absolutely essential for the proper differentiation of the cell.



The cell wall.

The Cell Wall

Walls surround certain kinds of cells. Bacteria, blue-green algae (cyanobacteria), fungi, higher algae, and plants are contained by walls. Walls are always exterior to the plasma membrane, where they serve both a protective and a structural, or support, function. They enable cells to survive in hypotonic environments without rupture, they prevent dehydration, and they provide plants with the opportunity for an aerial existence.

Although cell walls possess many functions in common, the walls of cells of different types are far from identical in structure. There are major differences both in their composition and in their ultrastructural makeup. However, a common theme runs throughout the ultrastructure of walls: they contain high molecular weight linear polymers that are cross-linked to give three-dimensional structures that are extremely resistant to rupture and distortion. At the same time, these rigid barriers can be mobilized to respond to the growth and reproductive requirements of the cell. They are thus dynamic structures that have primarily a static role.

1.3 EXTERIOR MEMBRANES AND SURFACE COMPONENTS

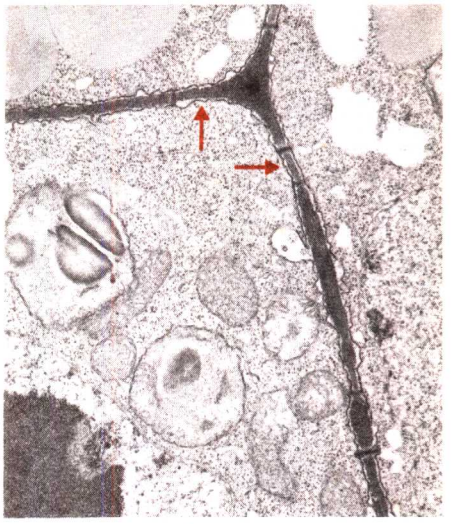
The Plasma Membrane

In spite of the structural and functional diversity of cells emphasized at the beginning of this chapter, *all cells possess a plasma membrane*. It is the bag that holds together the contents. Walls cannot serve this function

because they are too porous. *The plasma membrane is therefore the one common feature of all cells.*

The plasma membrane is a complex of lipids and proteins, often covered by carbohydrates, that is stabilized in its bilayer structure because of a molecular abhorrence for water and an affinity for self-type molecules. The membrane's content of amphipathic molecules makes this structure possible. In fact, membranes form spontaneously because of their unique chemical makeup.

The membrane functions as a selective barrier completely surrounding its contents. It is solely responsible for maintaining a difference in composition between the inside and the outside of the cell. Any defect in the membrane that neutralizes this difference spells a cellular struggle or death. Of all organelles, the plasma membrane is perhaps the most crucial to the second by second homeostasis of the cell. The mature human red blood cell serves as an example of this, for although devoid of all other internal organelles, it possesses a plasma membrane.



The plasma membrane.

The Cell Surface

In cells without walls, the cell surface is the plasma membrane. It is a dynamic mosaic of proteins, lipids, and carbohydrates.

Different components of the surface and patterns of components function as receptor sites for a variety of extracellular molecules that bring messages to the cell interior. By this means cells respond to their environments, are triggered to carry out various physiological activities, are stimulated to differentiate, and are controlled.

A specialized group of receptors is primarily concerned with intercellular adhesion. Surfaces interact to varying degrees, either directly or across short spaces, to maintain the integrity of multicellular systems.

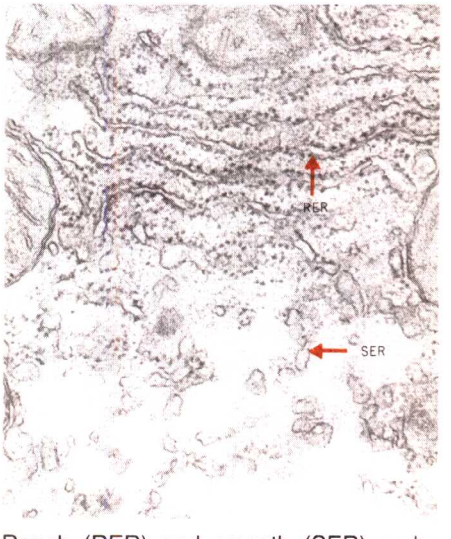
1.4 INTERIOR MEMBRANES: SPECIALIZED BIOSYNTHESIS AND OXIDATION

The Endoplasmic Reticulum

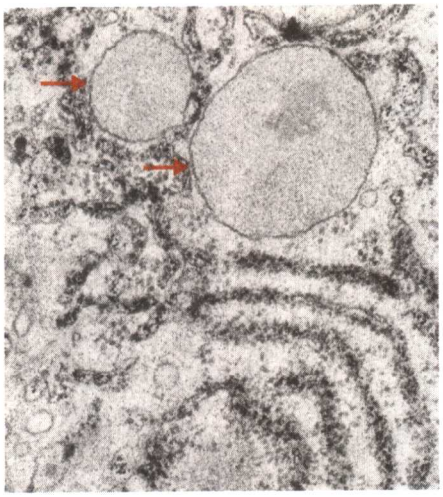
Within the cell interior there is a network of membranes referred to as the endoplasmic reticulum. The forms in which the endoplasmic reticulum exists, and the amount present, are usually related to the function of the cell.

A cell that synthesizes large amounts of protein generally possesses an abundance of endoplasmic reticulum with ribosomes attached. Ribosomes, in turn, are nucleoprotein particles on which the reactions of protein synthesis take place. This type of endoplasmic reticulum is called rough endoplasmic reticulum (RER).

A cell that specializes in the synthesis of steroids has endoplasmic reticulum without attached ribosomes. This form is called smooth endoplasmic reticulum (SER). This type of membranous system not only lacks the attached ribosomes of rough endoplasmic reticulum but tends to have a vesicular rather than a layered conformation.



Rough (RER) and smooth (SER) endoplasmic reticula.



Peroxisomes.

Microbodies

Microbodies are membranous organelles that are often closely associated with the endoplasmic reticulum, as well as with mitochondria and chloroplasts. They are enzyme bags, noted for their unique content of oxidative enzymes that act on a wide variety of substrates.

Two classes of microbodies have been identified. The members of one class, called peroxisomes, contain catalases and oxidases. They are found in both plant and animal tissues. The others, called glyoxysomes, contain in addition to the enzymes above part or all of the enzymes of the glyoxylate cycle. Glyoxysomes are found in the endosperm of seeds, where they have a special function in germination.

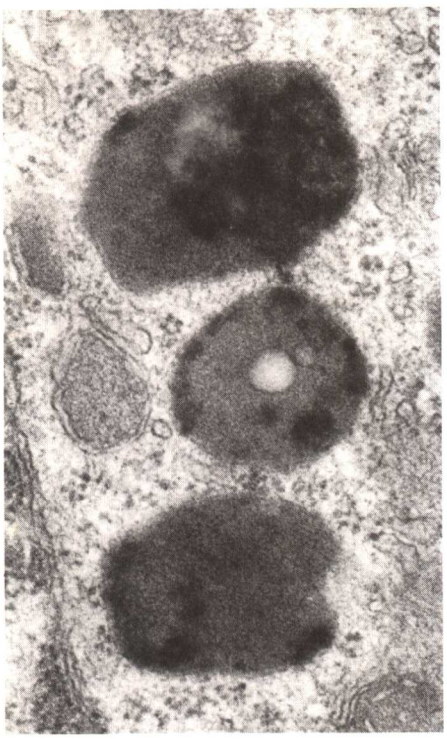
Whereas the role of the membranes of the endoplasmic reticulum is largely biosynthetic, the role of microbodies is to break down certain materials with a special set of enzymes.

1.5 BULK TRANSPORT AND INTRACELLULAR DIGESTION

Endocytosis

It has been known for some time that certain cells, such as amoebae and white blood cells, engulf extracellular materials and digest them intracellularly. It is now generally believed that most cells carry out some form of engulfment or endocytosis. During this process, the plasma membrane invaginates and brings into the cell interior either particles (via phagocytosis) or liquid (via pinocytosis).

Although the act of endocytosis is a continuum of cellular responses and movements, it can be considered to consist of several stages. The cell must sense a signal to begin the pursuit of an engulfable material. Then the material and the receptor sites on the endocytic cell interact. Finally, engulfment proceeds.



Lysosomes.

Lysosomes

The endocytic vacuole fuses with a lysosome, a membrane-bound collection of hydrolytic enzymes that can act on a large variety of substrates. The products released from this degradation are in turn made available to the cell as nutrients or vital building blocks for biosynthetic pathways.

Lysosomes may also act on other intracellular organelles and degrade them. This is apparently a mechanism to provide nutrients to the cell when they are not available from the outside. It is also a means of tissue mobilization such as that which takes place upon metamorphosis in the tadpole or tissue regression of the uterus after parturition.

Improperly functioning lysosomes often lead to "storage" diseases. Cells become saturated with materials they cannot break down, and the whole organism is adversely affected.

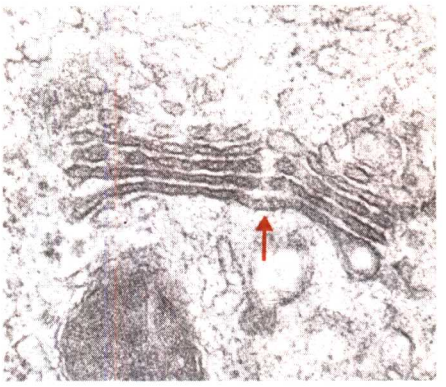
1.6 MODIFICATION AND EXPORT

The Secretory Pathway

The secretory pathway is a traffic route of transport through the cell interior. It begins on the ribosomes where secretory proteins are synthe-

sized. These are then moved through the cisternae of the endoplasmic reticulum and they eventually traverse the Golgi complex region. Here they are modified and leave the complex as secretory granules, packaged with membrane covers.

Secretory granules may be stored for some time before they are released from the cell, or the pathway may function more or less continuously to provide a constant efflux of products to the immediate cell environment. Eventually they are expelled by a type of reverse endocytosis mechanism.



The Golgi complex.

The Golgi Complex

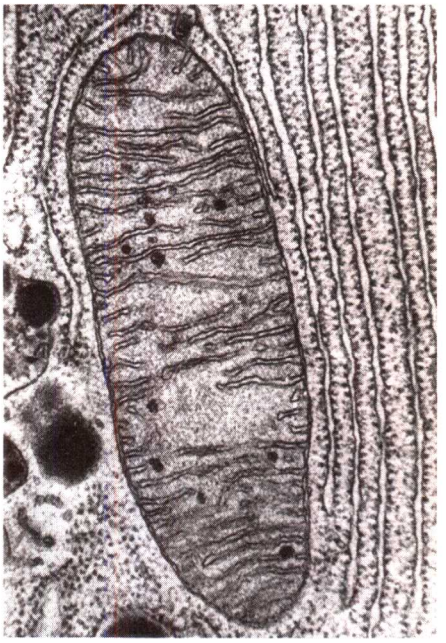
The Golgi complex is a system of membranes that ranges in structure from extremely amorphous, and hard to recognize, to highly organized, with a characteristic stacked arrangement of flattened sacs. It functions as a processing center for materials that are shipped to the cell exterior.

The chief function of the Golgi complex is to glycosylate proteins that are destined either for export or for incorporation into the plasma membrane. It also appears to modify membranes as they move along the secretory pathway. Thus it is a vital transformation center in the cell.

1.7 ENERGY TRANSDUCTION: MITOCHONDRIA AND CHLOROPLASTS

Mitochondria and chloroplasts are double membrane-bound organelles of adenosine triphosphate (ATP) production. Both plant and animal cells contain mitochondria, but chloroplasts are found only in photosynthetic cells, almost exclusively plants.

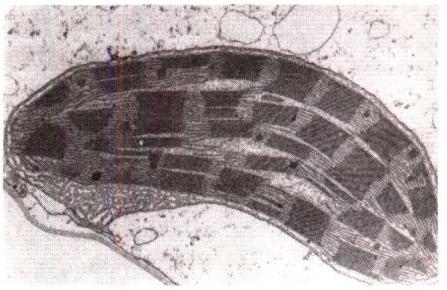
Mitochondria are present in high numbers with specially designed interiors in those cells that have high energy demands. A variety of metabolic pathways are conducted within mitochondria, including the reactions of the tricarboxylic acid cycle, the β-oxidation of fatty acids, and oxidative phosphorylation.



A mitochondrion.

Chloroplasts generate ATP and reduced coenzymes in higher plants. Once these two ingredients have been formed by molecular entrapment of radiant energy, carbon dioxide is fixed into organic compounds, a process that does not directly require light. Photophosphorylation, the production of ATP via radiant energy, is one of the most remarkable reactions to take place in the biosphere. It requires no nutrients, only a supply of electrons from the ubiquitous water molecule, and radiant energy. All living forms except for a small group of bacteria ultimately depend on this reaction.

Both mitochondria and chloroplasts contain their own genomes, but they are not sufficiently complete to allow these organelles an autonomous existence. Both organelles depend on the nuclear genome to become properly functional. Given this incentive, the rest of the cell obviously benefits enormously.



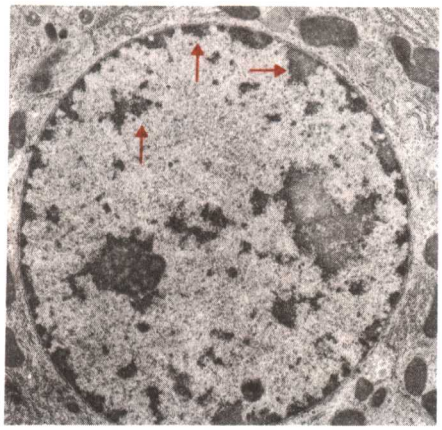
A chloroplast.

1.8 COMPARTMENTALIZATION AND INTRACELLULAR FLOW OF INFORMATION

Within the cell there is a dynamic pathway of information flow that originates in the genetic material and culminates in proteins. Although systems

have been discovered in recent years whereby portions of this pathway can be reversed it is for the most part a unidirectional flow that is crucial both to cellular reproduction and to the overall economy of the cell.

Chromosomes



Interphase chromosomes.

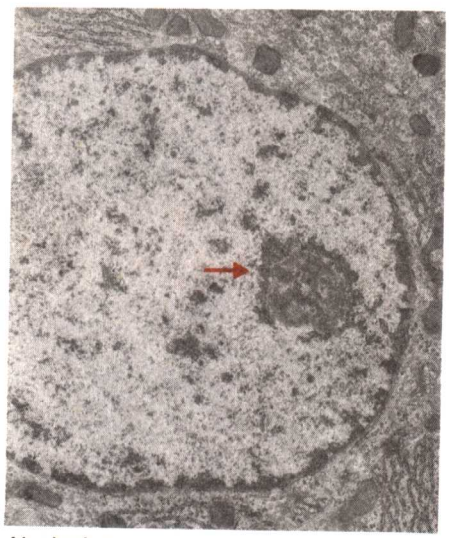
Chromosomes in eucaryotic cells are protein–deoxyribonucleic acid (DNA) complexes. They are the primary seat of the genetic information of the cell, with much smaller genetic roles played by mitochondria and chloroplasts.

Chromosome morphology is synchronized with the cell cyle. During interphase, chromosomes are not visible by light microscopy because they exist as extended fibers of a diameter beyond the resolving power of the light microscope. During late prophase, metaphase, and early anaphase, the same chromosomes are visible because they take on a highly coiled conformation. The function of the extended form as seen in interphase is that of permitting DNA replication and the manufacture of RNA from DNA templates. The function of the coiled form is to permit a reliable separation of chromosomes into daughter cells during mitosis or meiosis and to retain the genetic information in a nonexpressed state.

Chromosomes are about half nucleic acid and half protein. The protein component is of two types: histone and nonhistone proteins. Histone proteins have an important structural role in the chromosome, whereas nonhistone proteins regulate the expression of genes by way of blocking or effecting the transcription of DNA.

A recent finding concerning chromosome ultrastructure is the presence of nucleosomes as elemental repeating units of the chromosome. The nucleosome is a histone–DNA complex that takes on the appearance of beads on a string when the chromosome fiber is extended. The fiber is shortened and thickened by a supercoiling of nucleosomes into a cylindrical solenoid.

The Nucleolus



Nucleolus.

For many decades light microscopy has revealed dense areas in nuclei called nucleoli. Electron microscopy, with its greater resolving power, has shown these regions to be granular and fibrous, generally in physical association with particular chromosomes in the cell. Some very interesting experimental approaches have now unveiled the mystery of these regions. They are sites where ribosome subunits are assembled before they are exported to the cytoplasm.

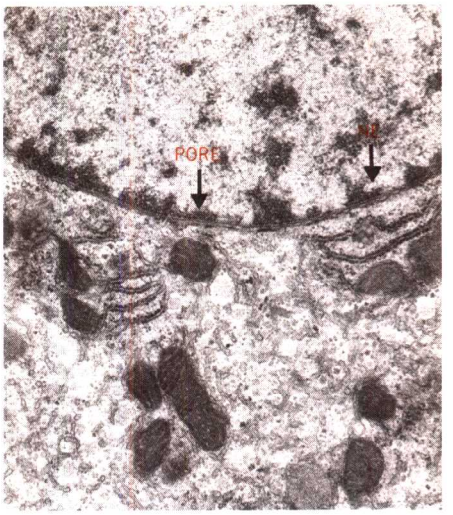
The nucleolus, therefore, is not an organelle in the usual sense. It is rather a depot area where manufacture, assembly, and transient storage of products occur.

The Nuclear Envelope

For ribosomes to get to the cytoplasm, their natural habitat in the cell, they must pass across a formidable double membrane barrier, the nuclear envelope. The nuclear envelope forms a continuous membrane shell around the chromosomes, structurally isolating the nuclear contents from the rest

of the cell and functionally permitting only a highly controlled movement of materials to and from the nucleus.

The control routes apparently involve pores that pockmark the surface of the nuclear envelope as seen by freeze-fracture electron microscopy. These are complex structures that permit the passage outward of messenger RNA (mRNA) and ribosome subunits and the passage inward of proteins essential for the replication and transcription of DNA and the assembly of ribosome subunits.



Nuclear envelope (NE) and pore.

The Nuclear Interior

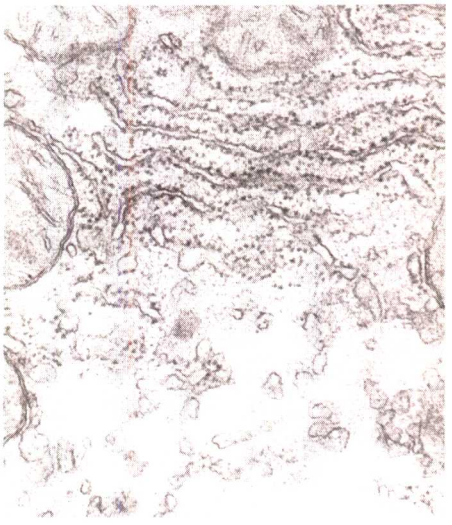
The interior of the nucleus contains, besides chromosomes and nucleoli, a structural network called the matrix. It consists of only a few major proteins that aggregate to provide a nuclear skeleton. This structure is thought to have roles in DNA replication, in transcription, and in the posttranscriptional processing and transport of RNA products.

Within the nucleus, between the larger structures, there resides a heterogeneous population of granules and fibrils. In the region of the nucleolus these are ribosome subunits in the process of assembly. In other regions these particles and fibrils are early forms of RNA, referred to as heterogeneous nuclear ribonucleoproteins. These are processed and modified before they are exported to the cytoplasm as finished messengers.

Ribosomes

When ribosome subunits leave the nucleus to take up residence either on the surface of endoplasmic reticulum or in a free unattached state, they are apparently completely formed. From the point of view of composition, ribosomes are approximately half protein and half RNA. From the point of view of structure, they consist of two subunits that are reversibly dissociated and associated into the intact particle. From the point of view of their molecular anatomy, they consist of approximately 55 different proteins and 3 or 4 different RNA molecules.

Ribosomes are the sites of proteins synthesis when an appropriate complex forms between the ribosome, mRNA, transfer RNA (tRNA), and a variety of other factors essential to the process.


Ribosomes.

1.9 THE MOLECULAR ANATOMY OF FORM AND MOVEMENT

Distributed throughout the cell at different stages in its life cycle are systems of microtubules and microfilaments.

Microtubules

Microtubules are the largest of the intracellular fibrils, with an outside diameter of approximately 24 nm. They are hollow structures, like tubes, with a wall made up of a repeating protein dimer called tubulin.

Microtubules are present as core structures in cilia and flagella as well as in basal bodies and centrioles. Cilia and flagella are generated by basal