Review of Medical Physiology

William F. Ganong, MD

Twelfth Edition

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Preface

This book is designed to provide a concise summary of mammalian and, particularly, of human physiology which medical students and others can supplement with readings in current texts, monographs, and reviews. Pertinent aspects of general and comparative physiology are also included. Summaries of relevant anatomic considerations will be found in each section, but this book is written primarily for those who have some knowledge of anatomy, chemistry, and biochemistry.

Examples from clinical medicine are given where pertinent to illustrate physiologic points. Physicians desiring to use this book as a review will find short discussions of important symptoms produced by disordered function in several sections.

It has not been possible to be complete and concise without also being dogmatic. I believe, however, that the conclusions presented without a detailed discussion of the experimental data on which they are based are those supported by the bulk of the currently available evidence. Much of this evidence can be found in the papers cited in the credit lines of the illustrations. Further discussions of particular subjects and information on subjects not considered in detail in this book can be found in the references listed at the end of each section. Information about serial review publications that provide up-to-date discussions of various physiologic subjects is included in the note on general references in the appendix.

In the interest of brevity and clarity, I have in most instances omitted the names of the many investigators whose work made possible the view of physiology presented here. This is in no way intended to slight their contributions, but including their names and specific references to original papers would greatly increase the length of this book.

A number of new topics are considered for the first time in the twelfth edition. These include, for example, atrial natriuretic factor and the role of N_s and N_i proteins in the regulation of adenylate cyclase. Data obtained with new imaging techniques such as nuclear magnetic resonance and positron emission tomography have been expanded, and references to the clinical use of these techniques have been added. In addition, there have been many small changes and corrections throughout the book to keep it as accurate and up to date as possible. For those interested in self-study or preparing for examinations, a study guide will soon be published to accompany the twelfth edition.

I am greatly indebted to many individuals who helped with the preparation of this book. Those to whom I wish to extend special thanks for their help with the twelfth edition include Drs. John Baxter, Graeme Bell, John Exton, Seth Hootman, Jim Hudspeth, Floyd Rector, Jr., and Donald Reis. I am also indebted to my wife, who, as always, labored long hours typing corrections, and to Annette Lowe, who drew many of the illustrations. Many associates and friends provided unpublished illustrative materials, and numerous authors and publishers generously granted permission to reproduce illustrations from other books

and journals. I also wish to thank all the students and others who took the time to write to me offering helpful criticisms and suggestions. Such comments are always welcome, and I solicit additional corrections and criticisms, which may be addressed to me at

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Since this book was first published in 1963, the following translations have been published and are currently available: Portuguese (fourth edition), German (fourth edition), Italian (sixth edition), Spanish (ninth edition), Japanese (eighth edition), Indonesian (second edition), Greek, and French. Translations have also been published in Chinese, Czech, Polish, Serbo-Croatian, and Turkish but are no longer in print. A new translation into Serbo-Croatian is under way. The book has also appeared in various foreign English-language editions and has been recorded in English on tape for use by the blind. The tape recording of the eleventh edition (1983) is available from Recording for the Blind, Inc., 20 Roszel Road, Princeton, NJ 08540. The German edition is also being recorded on tape.

William F. Ganong

San Francisco
June, 1985

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Section I. Introduction

Physiologic Principles | 1

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include a gastrointestinal system to digest and absorb food; a respiratory system to take up O_2 and eliminate CO_2; a urinary system to remove wastes; a cardiovascular system to distribute food, O_2, and the products of metabolism; a reproductive system to perpetuate the species; and nervous and endocrine systems to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

FUNCTIONAL MORPHOLOGY OF THE CELL

Revolutionary advances in the understanding of cell structure and function have been made through the use of electron microscopy, x-ray diffraction, and the other techniques of modern cellular and molecular biology. The specialization of the cells in the various organs is very great, and no cell can be called "typi-

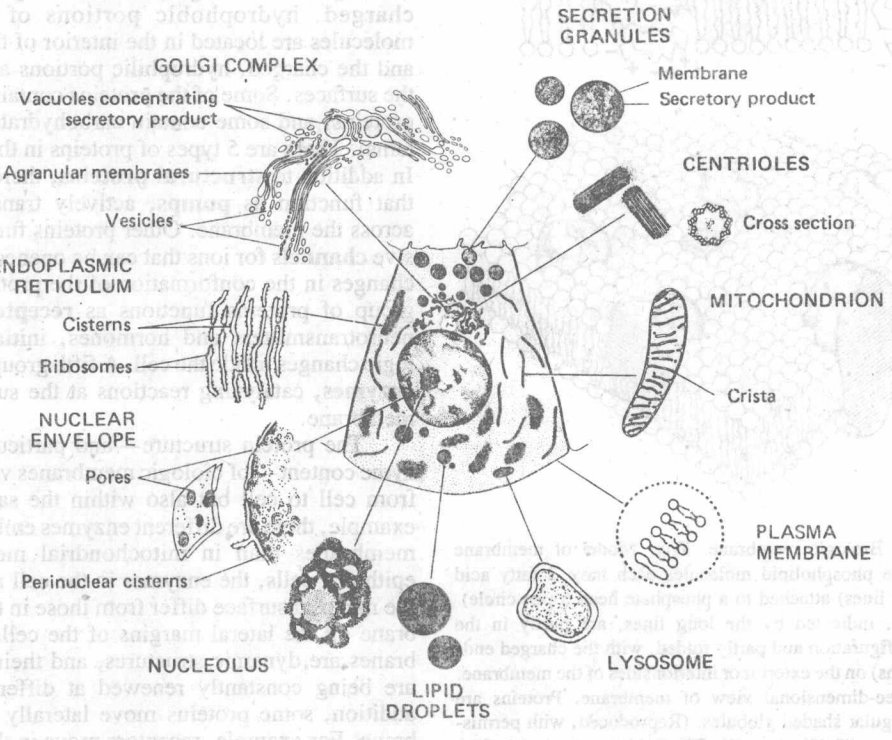

Figure 1–1. Ultrastructure of the common cell organelles and inclusions. The endoplasmic reticulum illustrated here is the granular type, with ribosomes attached to it. Some cells also contain tubes of membrane without ribosomes (agranular endoplasmic reticulum). The pores in the nuclear envelope are closed by a thin, homogeneous membrane. (Modified and reproduced, with permission, from Bloom W, Fawcett WD: *A Textbook of Histology,* 10th ed. Saunders, 1975.)

cal" of all cells in the body. However, a number of structures (**organelles**) are common to most cells. These structures are shown in Fig 1–1.

Cell Membrane

The membrane that surrounds the cell is a remarkable structure. It is not only semipermeable, allowing some substances to pass through it and excluding others, but its permeability can be varied. It is generally referred to as the **plasma membrane.** The nucleus is also surrounded by a membrane, and the organelles are surrounded by or made up of membrane.

Although the chemical structure of membranes and their properties vary considerably from one location to another, they have certain common features. They are generally about 7.5 nm (75 Angstrom units) thick. They are made up primarily of protein and lipids. The chemistry of proteins and lipids is discussed in Chapter 17. The major lipids are phospholipids such as phosphatidylcholine and phosphatidylethanolamine. The shape of the phospholipid molecule is roughly that of a clothespin (Fig 1–2). The head end of the molecule contains the phosphate portion, is positively charged, and is quite soluble in water (polar, **hydrophilic**). The tails are quite insoluble (nonpolar, **hydrophobic**). In the membrane, the hydrophilic ends are exposed to the aqueous environment that bathes the exterior of the cells and the aqueous cytoplasm; the hydrophobic ends meet in the water-poor interior of the membrane. However, there is a degree of asymmetry in the distribution of lipid in the membrane; in human red cells, for example, there is more phosphatidylethanolamine and phosphatidylserine in the inner lamella and more lecithin and sphingomyelin in the outer lamella. The significance of this asymmetry is unknown. In **prokaryotes** (cells like bacteria in which there is no nucleus), phospholipids are generally the only membrane lipids, but in **eukaryotes** (cells containing nuclei), cell membranes also contain cholesterol (in animals) or other steroids (in plants). The cholesterol/phospholipid ratio in the membrane is inversely proportionate to the fluidity of the membrane. Variations in the ratio lead to abnormalities of cell function. In healthy animals, the ratio is maintained at a nearly constant level by a variety of regulatory mechanisms.

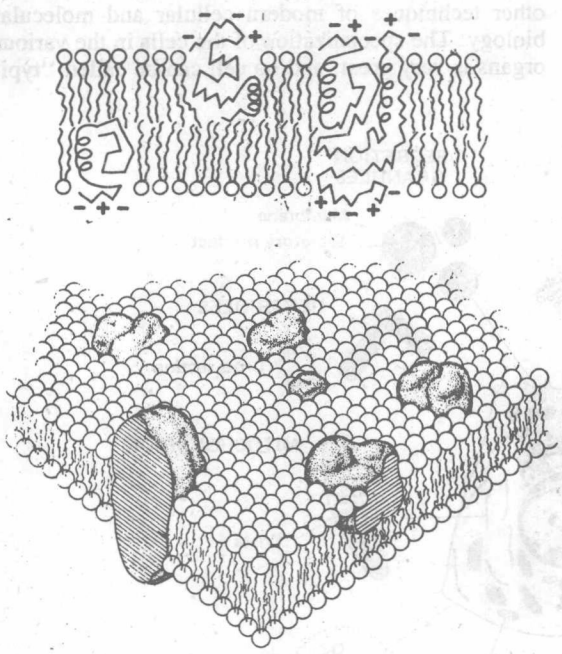

Figure 1–2. Biologic membrane. ***Top:*** Model of membrane structure. The phospholipid molecules each have 2 fatty acid chains (wavy lines) attached to a phosphate head (open circle). The proteins, indicated by the long lines, are partly in the α-helical configuration and partly folded, with the charged ends (+ and − signs) on the exterior or interior sides of the membrane. ***Bottom:*** Three-dimensional view of membrane. Proteins are shown as irregular shaded globules. (Reproduced, with permission, from Singer SJ, Nicolson GL: The fluid mosaic model of the structure of cell membranes. *Science* 1972;**175:**720. Copyright 1972 by the American Association for the Advancement of Science.)

There are many different proteins embedded in the membrane. They exist as separate globular units and stud the inside and outside of the membrane in a random array (Fig 1–2). Some are located in the inner surface of the membrane; some are located on the outer surface; and some extend through the membrane **(through and through proteins).** In general, the uncharged, hydrophobic portions of the protein molecules are located in the interior of the membrane and the charged, hydrophilic portions are located on the surfaces. Some of the proteins contain lipids (lipoproteins) and some contain carbohydrates (glycoproteins). There are 5 types of proteins in the membrane. In addition to **structural proteins,** there are proteins that function as **pumps,** actively transporting ions across the membrane. Other proteins function as passive **channels** for ions that can be opened or closed by changes in the conformation of the protein. A fourth group of proteins functions as **receptors** that bind neurotransmitters and hormones, initiating physiologic changes inside the cell. A fifth group functions as **enzymes,** catalyzing reactions at the surfaces of the membrane.

The protein structure—and particularly the enzyme content—of biologic membranes varies not only from cell to cell but also within the same cell. For example, there are different enzymes embedded in cell membranes than in mitochondrial membranes; in epithelial cells, the enzymes in the cell membrane on the mucosal surface differ from those in the cell membrane on the lateral margins of the cells. The membranes are dynamic structures, and their constituents are being constantly renewed at different rates. In addition, some proteins move laterally in the membrane. For example, receptors move in the membrane and aggregate at sites of endocytosis (see below). There is evidence that the lateral movement of components in the membrane is not random but is controlled

by intracellular mechanisms that probably involve microfilaments and microtubules (see below).

Underlying most cells is a thin, fuzzy layer plus some fibrils that collectively make up the **basement membrane** or, more properly, the **basal lamina.** The material that makes up the basal lamina has been shown to be made up of a collagen derivative plus 2 glycoproteins.

Intercellular Connections

Two types of junctions form between the cells that make up tissues: junctions that fasten the cells to one another and to surrounding tissues, and junctions that permit transfer of ions and other molecules from one cell to another. The junctions that tie cells together and endow tissues with strength and stability are **tight junctions** and **desmosomes** (Fig 1–3). Desmosomes are subdivided into **belt desmosomes, spot desmosomes,** and **hemidesmosomes.** The junctions by which molecules are transferred are **gap junctions.**

Tight junctions characteristically surround the apical margins of the cells in epithelia such as the intestinal mucosa, the walls of the renal tubules, and the choroid plexus. They are made up of ridges —half from one cell and half from the other—that adhere so strongly at cell junctions that they almost obliterate the space between the cells. The ridges were thought to be made up of protein, but recent evidence suggests that instead they may be long tubes made up of membrane lipids. In addition to tying the cells together, tight junctions form a barrier to the movement of ions and other solutes from one side of the epithelium to the other. Some epithelia are more "leaky" to solutes than others, but the tight junctions in all of them play an important role in their physiologic function.

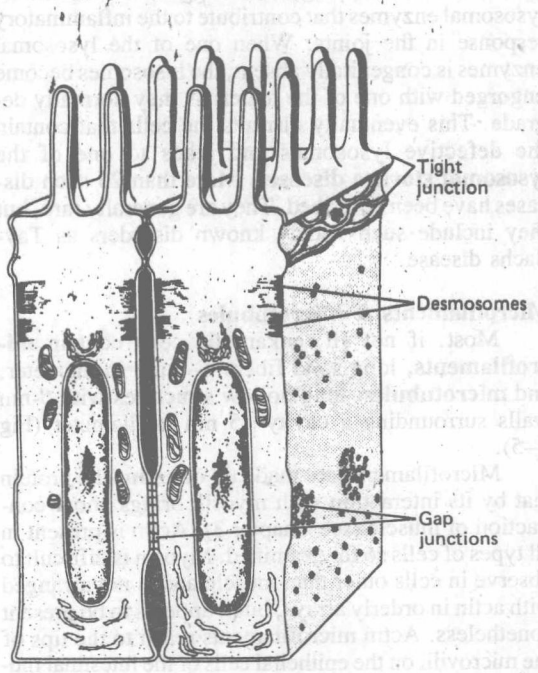

Figure 1–3. Intercellular junctions in the mucosa of the small intestine. The various types of desmosomes are not shown in detail. (Reproduced, with permission, from Weinstein RS, McNutt SN: Cell junctions. *N Engl J Med* 1972;**286:**521.)

Belt desmosomes and spot desmosomes are characterized by apposed thickenings of the membranes of 2 adjacent cells. Attached to the thickened area in each cell are cytoplasmic fibrils, some running parallel to the membrane and others radiating away from it. Between the 2 membrane thickenings, there is filamentous material in the intercellular space. Belt desmosomes, also known as **intermediate zones,** form bands that link epithelial cells just below and parallel to their tight junctions. The intracellular filaments associated with these junctions contain the protein **actin** (see below and Chapter 3) and are capable of contraction. However, the function of their contractions is unknown. The spot desmosomes are small, buttonlike points of attachment between the membranes of adjacent cells that are not limited to their apical regions. They have been likened to spot welds or rivets that hold tissues together. At spot desmosomes, the intercellular space is actually widened to 30 nm from its normal width of about 25 nm, and the filamentous material between the thickenings of the membranes of the 2 cells forms a dense central line called the **central stratum.** The cytoplasmic fibers associated with spot desmosomes are thicker than those associated with belt desmosomes and are not contractile. **Hemidesmosomes** anchor epithelial cells to the underlying connective tissue.

At gap junctions, the intercellular space narrows from 25 nm to 3 nm, and hexagonal arrays of protein units called **connexons** in the membrane of each cell are lined up with one another. Each connexon is made up of 6 subunits surrounding a channel that, when lined up with the channel in the corresponding connexon in the adjacent cell, permits substances to pass between the cells without entering the extracellular fluid. The diameter of the channel is normally about 2 nm, which permits the passage of sugars, amino acids, and other solutes with molecular weights up to about 800. Gap junctions thus permit the rapid propagation of electrical activity from cell to cell (see Chapter 4) and the exchange of various chemical messengers. However, the diameter of each channel is regulated by intracellular Ca^{2+}, and an increase in Ca^{2+} causes the subunits to slide together, closing the channel. Consequently, an increase in Ca^{2+} in an individual cell uncouples it from its neighbors.

Mitochondria

Although their morphology varies somewhat from cell to cell, each mitochondrion (Figs 1–1, 1–4) is in essence a sausage-shaped structure. It is made up of an outer membrane and an inner membrane that is folded to form shelves (**cristae**). The space between the 2 membranes is called the intracristal space, and the space inside the inner membrane is called the matrix space. The mitochondria are the power-generating units of the cell and are most plentiful and

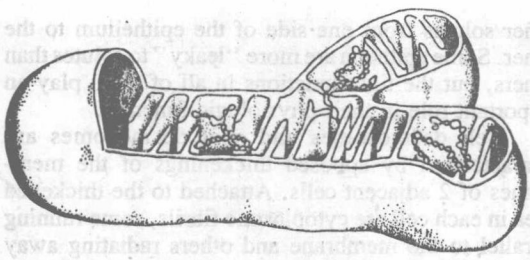

Figure 1–4. Cutaway drawing of a mitochondrion, showing the inner and outer membranes. The inner membrane is folded, forming shelves (cristae). The coiled structures represent possible arrangements of the mitochondrial DNA. Mitochondrial branching of the type shown here is not present in all cells. (Reproduced, with permission, from Nass MMK: Mitochondrial DNA: Advances, problems and goals. *Science* 1969;**165**:25. Copyright 1969 by the American Association for the Advancement of Science.)

best developed in parts of cells where energy-requiring processes take place. The chemical reactions occurring in them are discussed in detail in Chapter 17. The outer membrane of each mitochondrion is studded with the enzymes concerned with biologic oxidations, providing raw materials for the reactions occurring inside the mitochondrion. In the interior, the matrix space contains the water-soluble enzymes that convert the products of carbohydrate, protein, and fat metabolism to CO_2 and water via the citric acid cycle (see Chapter 17). In this process, electrons are transferred along the respiratory-enzyme chain and there is synthesis of the high-energy phosphate compound **adenosine triphosphate (ATP)** by the process of **oxidative phosphorylation.** ATP is the principal energy source for energy-requiring actions in plants and animals. The enzymes responsible for electron transfer and oxidative phosphorylation are embedded in the inner membrane, and they form characteristic repeating units visible under the electron microscope. Each unit is made up of a basepiece, a stalk, and a spherical headpiece. The basepieces contain the enzymes of the electron transfer chain, and the stalks and headpieces contain adenosine triphosphatase and other enzymes concerned with the synthesis and metabolism of ATP.

Mitochondrial DNA is discussed below.

Lysosomes

In the cytoplasm of the cell, there are large, somewhat irregular structures surrounded by membrane that may contain fragments of other cell structures. These organelles are the **lysosomes.** Some of the granules of the granulocytic white blood cells are lysosomes. Each lysosome contains a variety of enzymes (Table 1–1) that would cause the destruction of most cellular components if the enzymes were not separated from the rest of the cell by the membrane of the lysosome.

The lysosomes function as a form of digestive system for the cell. Exogenous substances such as bacteria that become engulfed by the cell end up in membrane-lined vacuoles. A vacuole of this type **(phagocytic vacuole)** may merge with a lysosome, permitting the contents of the vacuole and the lysosome to mix within a common membrane. Some of the products of the "digestion" of the engulfed material are absorbed through the walls of the vacuole, and the remnants are dumped from the cell (exocytosis; see below). The lysosomes also engulf worn-out components of the cell in which they are located, forming **autophagic vacuoles.** When a cell dies, lysosomal enzymes cause autolysis of the remnants. In vitamin A intoxication and certain other conditions, lysosomal enzymes are released to the exterior of the cell, with resultant breakdown of intercellular material. There is evidence that in gout, phagocytes ingest uric acid crystals, and that such ingestion triggers the release of lysosomal enzymes that contribute to the inflammatory response in the joints. When one of the lysosomal enzymes is congenitally absent, the lysosomes become engorged with one of the materials they normally degrade. This eventually disrupts the cells that contain the defective lysosomes and leads to one of the **lysosomal storage diseases.** More than 25 such diseases have been described. They are generally rare, but they include such widely known disorders as Tay-Sachs disease.

Table 1–1. Some of the enzymes found in lysosomes and the cell components that are their substrates.

Enzyme	Substrate
Ribonuclease	RNA
Deoxyribonuclease	DNA
Phosphatase	Phosphate esters
Glycosidases	Complex carbohydrates: glycosides and polysaccharides
Arylsulfatases	Sulfate esters
Collagenase	Proteins
Cathepsins	Proteins

Microfilaments & Microtubules

Most, if not all, eukaryotic cells contain **microfilaments,** long solid fibers 4–6 nm in diameter, and **microtubules,** long hollow structures with 5-nm walls surrounding a cavity 15 nm in diameter (Fig 1–5).

Microfilaments are made up of **actin,** the protein that by its interaction with myosin brings about contraction of muscle (see Chapter 3). Actin is present in all types of cells so far examined. Myosin is difficult to observe in cells other than muscle and is not arranged with actin in orderly arrays, but it appears to be present nonetheless. Actin microfilaments reach to the tips of the microvilli on the epithelial cells of the intestinal mucosa and bring about their contraction, probably via interaction with myosin filaments located at their bases. Microfilaments are also found in association with belt desmosomes (see above), in bundles under

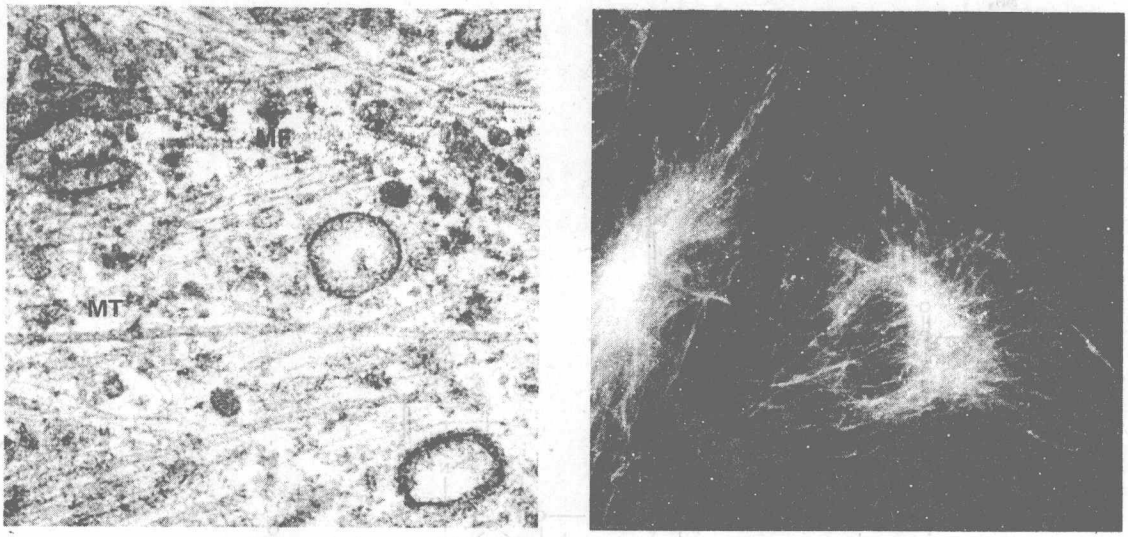

Figure 1–5. ***Left:*** Electron micrograph of the cytoplasm of a fibroblast, showing microfilaments (MF) and microtubules (MT). (Reproduced, with permission, from Junqueira LC, Carneiro J: *Basic Histology*, 4th ed. Lange, 1983.) ***Right:*** Distribution of microtubules in fibroblasts. The cells are treated with a fluorescently labeled antibody to tubulin, making microtubules visible as the light-colored structures. (Reproduced, with permission, from Connolly J et al: Immunofluorescent staining of cytoplasmic and spindle microtubules in mouse fibroblasts with antibody to τ protein. *Proc Natl Acad Sci USA* 1977;**74:**2437.)

the plasma membrane, and scattered in a seemingly random fashion in the cytoplasm.

Microtubules are made up of 2 globular protein subunits, α and β tubulin. The subunits unite to form dimers (Fig 1–6), and the dimers aggregate to form long tubes made up of stacked rings, with each ring usually containing 13 subunits. The tubules also contain other proteins that facilitate their formation. The assembly of microtubules is facilitated by warmth and various other factors, and disassembly is facilitated by cold and other factors. Both processes occur simultaneously in vitro. Assembly is prevented by colchicine and vinblastine.

Microtubules have been called the skeleton of the cell, but because of their constant assembly and disassembly, they are a very dynamic skeleton. They are associated with cell movement, although the actual motion is probably brought about by microfilaments. They appear to provide the tracks along which secretory granules move to the cell membrane. They play key roles in nerve fiber outgrowth, axoplasmic transport (see Chapter 2), maintenance of cell shape, structure and function of cilia, and cell division.

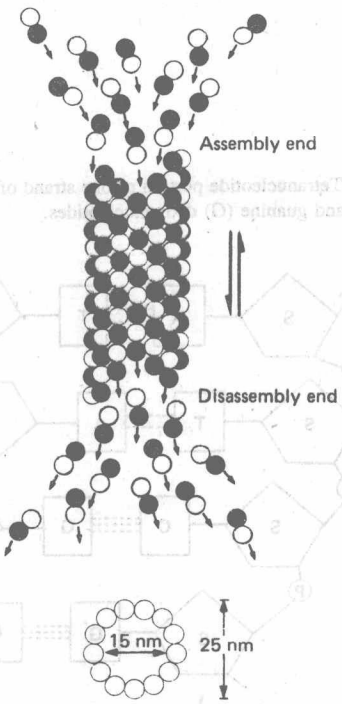

Figure 1–6. Assembly and disassembly of a microtubule by aggregation and disaggregation of dimers made up of α and β tubulin. (From Sloboda RD: The role of microtubules in cell structure and cell division. *Am Sci* 1980;**68:**290. Reprinted by permission of *American Scientist*, journal of Sigma Xi, the Scientific Research Society.)

Centrioles & Cilia

In the cytoplasm of most cells there are 2 short cylinders called **centrioles.** The centrioles are located near the nucleus, and they are arranged so that they are at right angles to each other. Microtubules in groups of 3 run longitudinally in the walls of the centriole (Fig 1–1). There are 9 of these triplets spaced at regular intervals around the circumference. **Cilia,** the hairlike motile processes that in multicellular animals extend from various types of epithelial cells, also have an

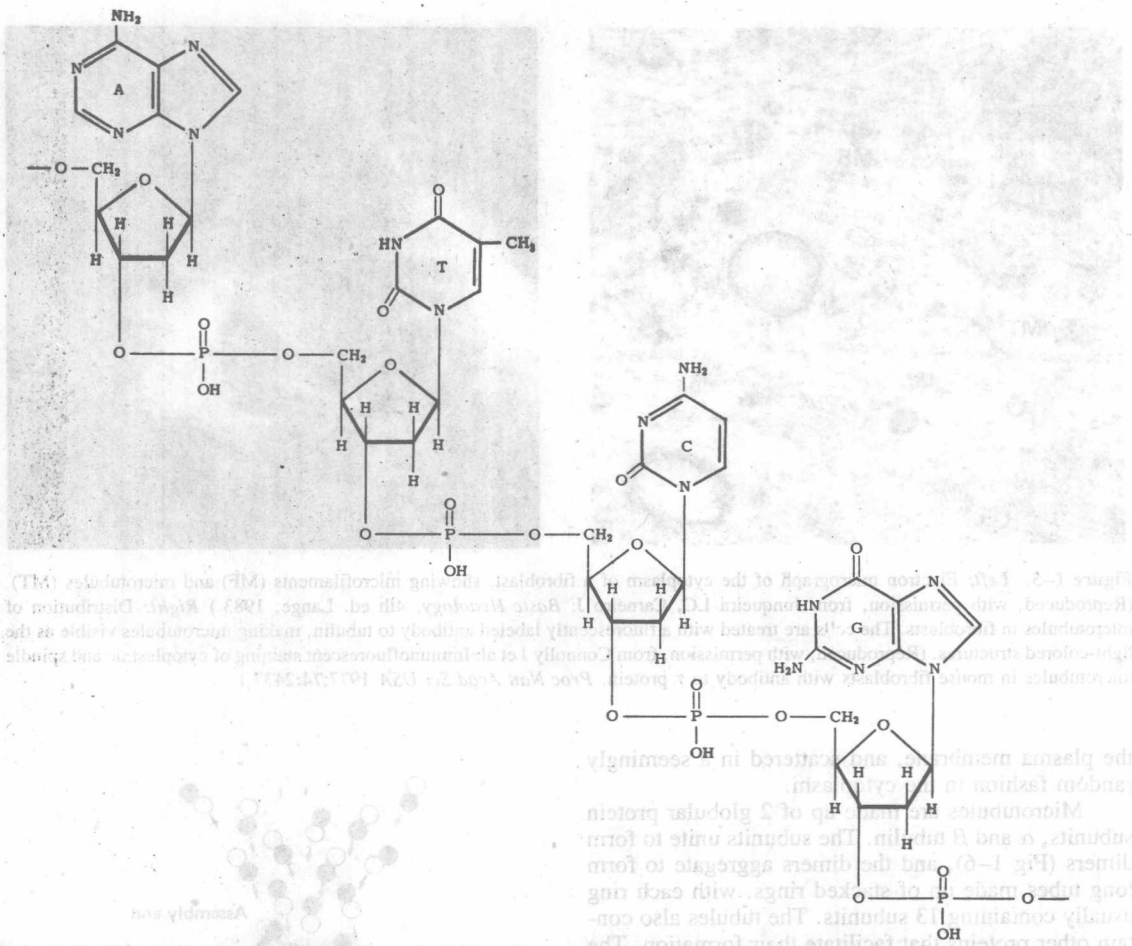

Figure 1–7. Tetranucleotide portion of one strand of deoxyribonucleic acid. The strand is composed of adenine (A), thymine (T), cytosine (C), and guanine (G) deoxynucleotides.

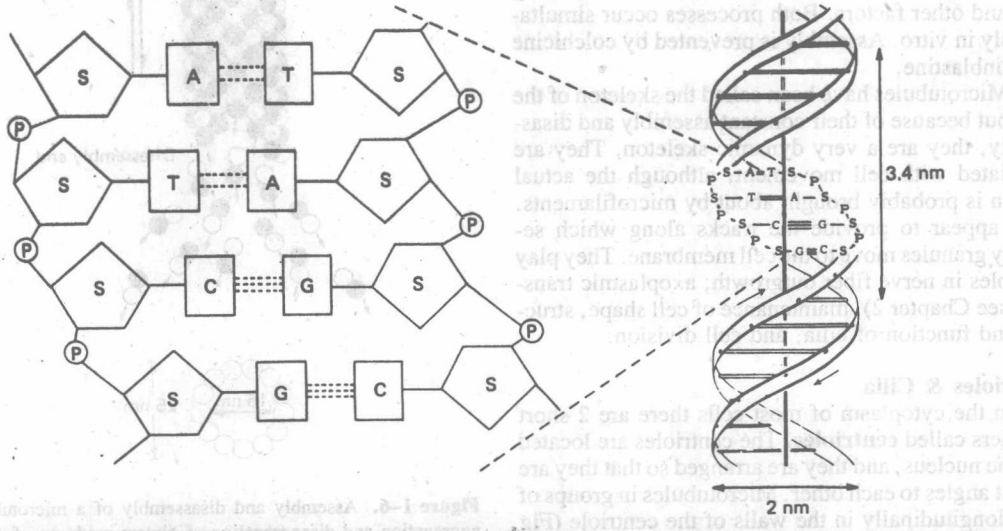

Figure 1–8. Diagram of the Watson and Crick model, slightly modified, of the double helical structure of DNA. On the left, the hydrogen bonding between the bases of the 2 nucleotide chains is shown. A, adenine; T, thymine; C, cytosine; G, guanine; S, deoxyribose; P, phosphate. (Reproduced, with permission, from Harper HA: *Review of Physiological Chemistry,* 15th ed. Lange, 1975.)