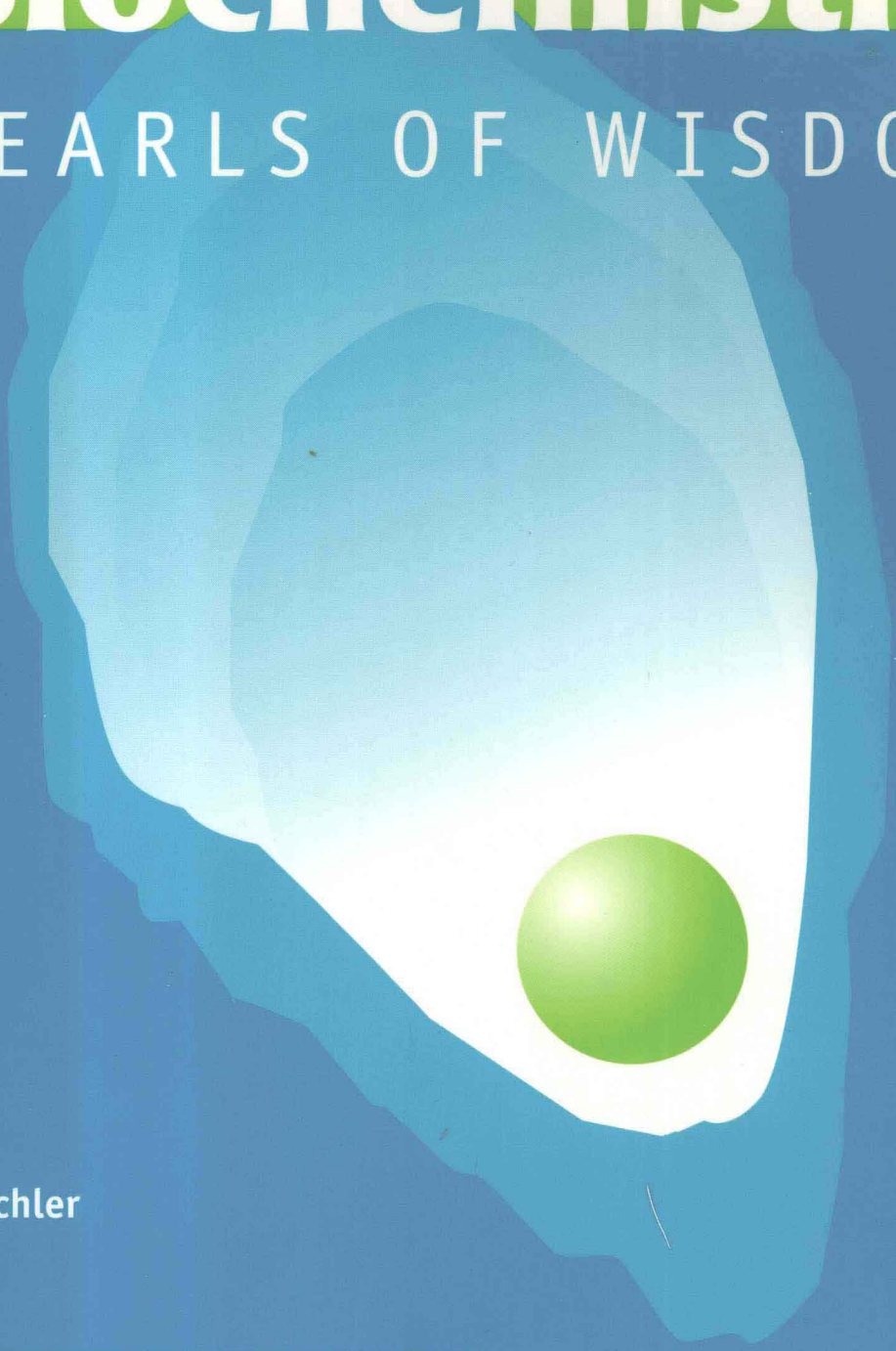
Medical Biochemistry

PEARLS OF WISDOM



Duane C. Eichler

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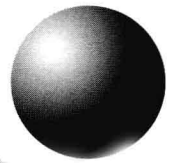

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Introduction

Medical Biochemistry Pearls of Wisdom is designed to help you prepare for your course, board, and recertification exams. *Pearls*' unique format differs from all other review and test preparation texts. What follows is a brief introduction to its purpose, format, limitations, and intended use.

The primary intent of *Pearls* is to serve as a study aid to improve performance on medical biochemistry examinations. With this goal in mind, the text is written in rapid-fire, question and answer format. You will receive immediate gratification with a correct answer. Misleading or confusing multiple-choice "foils" are not provided, thereby eliminating the risk of assimilating erroneous information that made an impression. Another advantage of this format is that you will either know or not know the answer to a given question. This results in active learning, rather than the passive review of studying multiple choice questions.

Questions themselves often contain a pearl reinforced in association with the question and answer. Additional information not requested in the question may be included in the answer. The same information is often sought in several different questions. Emphasis has been placed on evoking both trivia and key facts that are easily overlooked, are quickly forgotten, and yet somehow always seem to appear on exams.

It may happen that upon reading an answer you may think: "Why is that?" or, "Are you sure?" If this happens to you, go check! Truly assimilating these disparate facts into a framework of knowledge absolutely requires further reading in the surrounding concepts. Information learned as a response to seeking an answer to a particular question is much better retained than information that is passively read. Take advantage of this. Use *Pearls* with your preferred source texts nearby and open, or, if you are reviewing without your texts handy, mark questions for further investigation.

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Pearls is also designed to be re-used several times to allow, dare we use the word, memorization. If you are a pessimist, we suggest putting a check mark next to a question every time it is missed. If you are an optimist, place a check mark when the question is answered correctly once; skip all questions with check marks thereafter. Utilize whatever scheme you prefer.

The publisher and I welcome your comments, suggestions, and criticism. Great efforts have been made to verify these questions and answers. There will be answers we have provided that are at variance with the answer you would prefer. This is most often the result of differences between the original source and the source you have chosen to use. Please make us aware of any errata you find. We hope to make continuous improvements in future editions and would greatly appreciate any input with regard to format, organization, content, presentation, or about specific questions.

Study hard and good luck!

D.E.

DEDICATION

To my wife, Sandy Marie, whose love, support, and encouragement allowed me to advance confidently in the direction of my dreams; and to my father, Arthur O. Eichler, who instilled in me a need to ask questions and an enthusiasm for learning.

Contents

CHAPTER

1

Cell Structure and Function

Compartments and Function

What is the essential structural difference that distinguishes eukaryotic from prokaryotic cells?

In eukaryotic cells, membranes partition the cell into functionally distinct compartments. Compartmentation of function allows for the increased specialization and complexity of multicellular eukaryotic organisms.

What advantages does the partitioning by compartments offer to eukaryotic cells?

Compartments offer at least two obvious and important functions. The first is to maximize cellular efficiency by allowing different chemical reactions that require different environments (pH, ionic strength, etc.) to occur simultaneously in the cell, and to allow metabolic pathways involved in the synthesis and degradation of the same compound to be physically partitioned. Second, compartments can be used to enhance regulation. For example, the transfer of a metabolite from one compartment to another can be used as a key step in controlling the rate of that process.

What are the general features of cellular structure?

From the point of a simple overview, seven major compartments are common to most eukaryotic cells (Figure 1.1).

1. Cytosol
2. Mitochondria
3. Rough endoplasmic reticulum cisternae
4. Smooth endoplasmic reticulum cisternae
5. Lysosomes
6. Peroxisomes
7. Nucleus

Throughout any discussion of medical biochemistry, the relationship of a metabolic process to the organizational structure within the cell is important to recognize, and it will become apparent that metabolic patterns of eukaryotic cells are

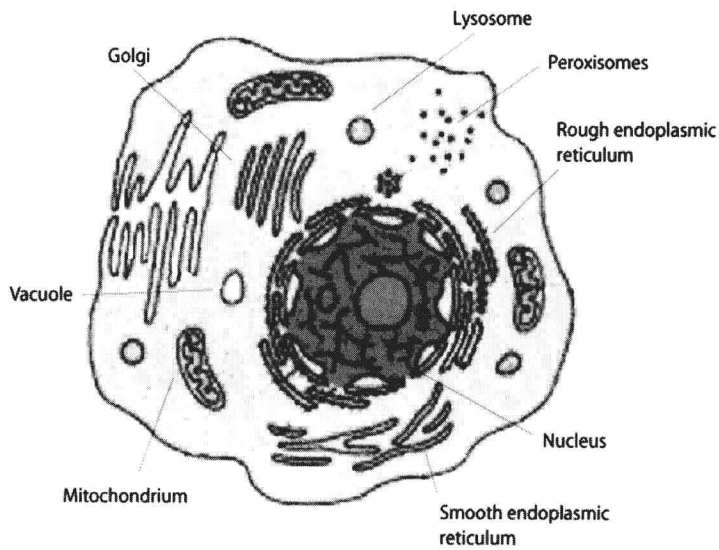

Figure 1.1 General features of cell structure. A schematic view represents the major structural compartments of a eukaryotic cell.

markedly affected by the presence of compartments. Glycolysis, the pentose phosphate shunt pathway, and fatty acid synthesis take place in the cytosol, whereas fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation are carried out in mitochondria. Some processes such as gluconeogenesis, urea synthesis, and even pyrimidine biosynthesis depend on the interplay of reactions that occur in two compartments: the cytosol and mitochondria.

What role does the cytoplasmic membrane play other than to act to partition the biological constituents of the cell from the immediate environment?

In the broadest sense, the cell surface occupies a key position in the economy of the cell as a mediator between the cell and the environment. Specifically, the cytoplasmic membrane acts as a shape constraint, as a selective permeable barrier (transport or at the anatomical scale, membranes and their selective function play a major role in the uptake of food material from the gut, the selective removal of wastes from the blood in the kidney, the blood–brain barrier, neuron transmission, etc.), as a site for receptors (hormones, etc.), and in important cell–cell interactions (contact inhibition, cell adhesion, etc.).

Why is the cytoplasmic membrane structure called a lipid bilayer?

This is due to the defined arrangement of phospholipids into a bilayer, with the polar phosphorous portion of the phospholipid on the outside and the apolar fat portion orienting inward. Within the apolar region, cholesterol molecules are found, whereas proteins, depending on their own bias, may distribute in a variety of places within this matrix. There are also sugar components, carbohydrates, that are primarily found on the outer surface attached to proteins or complex fats (Figure 1.2).

How do proteins that are associated with the cytoplasmic membrane differ?

Proteins that are major molecular constituents of membranes can be divided into two groups. Integral proteins are directly incorporated within the lipid bilayer, whereas peripheral proteins exhibit a looser association with mem-

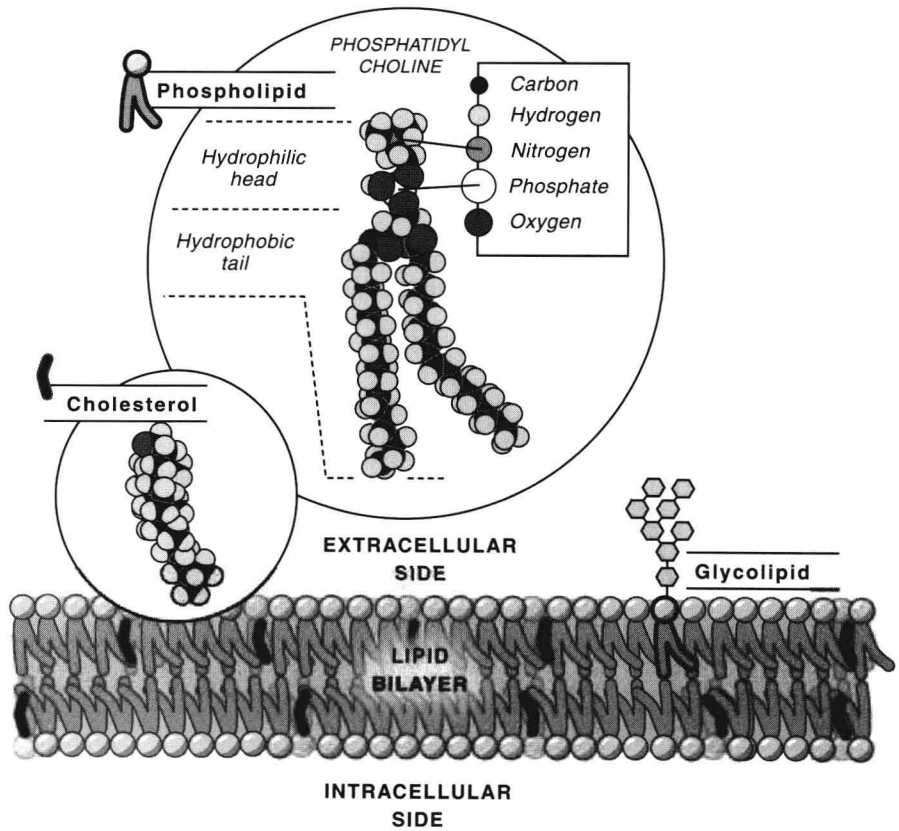

Figure 1.2 Plasma membrane lipid bilayer. The diagram illustrates the basic structural characteristics of the membrane lipid bilayer. The amphipathic phospholipids contain a hydrophilic head and hydrophobic tails. This membrane structure is quite stable because of the hydrophobic interaction of the hydrocarbon chains and attraction of polar groups to water on the outer surface.

brane surfaces. The loosely bound peripheral proteins can be easily extracted from cell membranes with salt solutions, whereas integral proteins can be extracted only by drastic methods that use detergents. Some integral proteins span the membrane one or more times from one side to the other. The extracellular portion of integral and peripheral membrane proteins is generally glycosylated. The intracellular portion of membrane proteins is bound to cytoskeletal components (Figure 1.3).

Do regions of the membrane differ in composition and structure?

There are regions of the cytoplasmic membrane enriched in cholesterol and sphingolipids. These are known as "lipid rafts," and these sites are responsible for cellular functions such as vesicular trafficking and signal transduction.

How do lipid rafts function?

A lipid raft is a precursor to a caveola, which is a structure that is predominant in tissue such as fibroblasts, adipocytes, endothelial cells, and muscle. A protein called caveolin binds to cholesterol in the lipid raft. There are at least three types of caveolins numbered 1, 2, and 3. Caveolae tend to concentrate signaling molecules such as Src-like tyrosine kinases, G protein, and nitric oxide synthase.

What are some of the functional properties of intracellular membranes?

An intracellular membrane system called the endoplasmic reticulum acts to partition the cytoplasm effectively into two phases separated by a single membrane surface. This relatively large area of membrane surface can be accommodated within a limited cytoplasmic volume. Surface-limited reactions can therefore be carried out with increased efficiency. Optimal concentrations and spatial interrelationships can be effectively maintained for enzyme systems attached to these intracellular membranes. This membrane system also provides a complex of interconnecting channels (cisternae) throughout the cell that can be used for the transport of material and a mechanism for separating newly synthesized molecules that belong in the cytosol from those that do not. Thus, the endoplasmic reticulum provides an important internal surface for enzyme systems as well as providing an internal channeling system to vector agents for the processing and transport of a defined class of proteins.

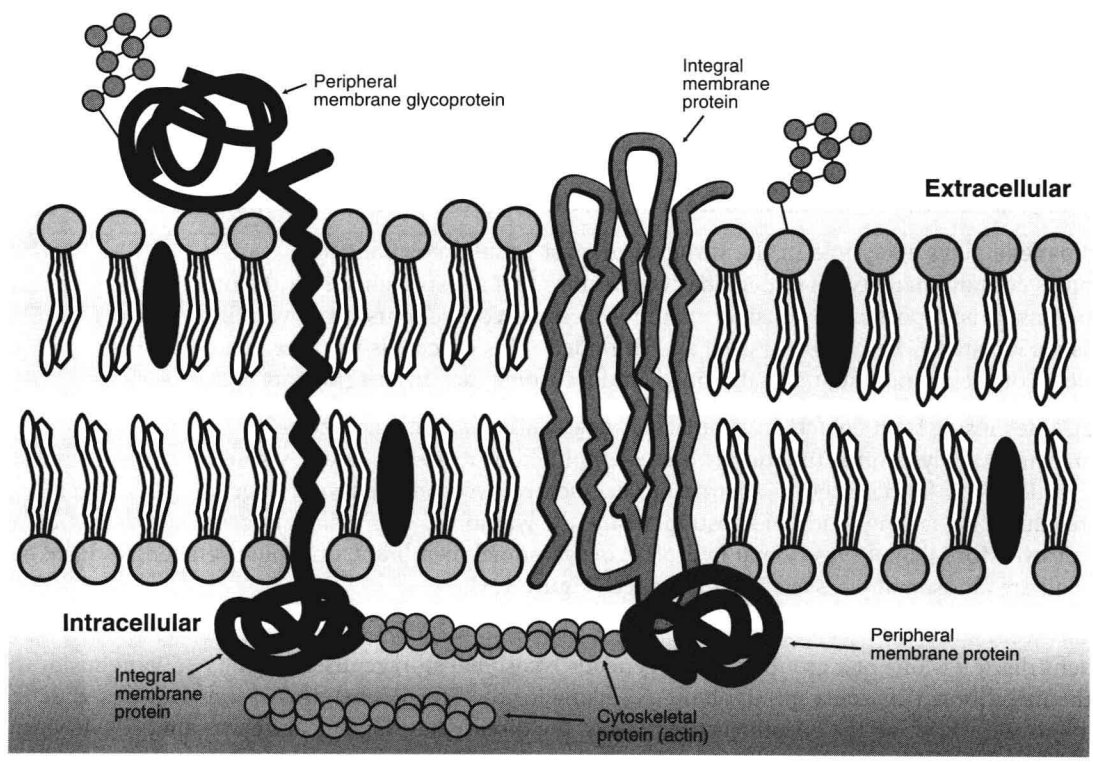

Figure 1.3 Plasma membrane components. The schematic illustrates the multiple types of proteins which bind or interact with the membrane lipid bilayer. Single or multiple transmembrane segments demonstrate integral membrane protein interactions, whereas peripheral membrane proteins bind to the membrane surface and/or integral membrane protein.

Is there a significant functional difference between the smooth and rough endoplasmic reticulum other than appearance?

The rough endoplasmic reticulum refers to the granular appearance of this membrane structure. This granular surface is due to numerous ribosomes associated with the membrane surface. These ribosomes are actively translating mRNA in the process of protein synthesis. The protein being synthesized is destined for export or to sorting to specific regions or compartments of the cell. The smooth endoplasmic reticulum is distinguished simply by the lack of ribosomes. Various important metabolic enzymes are associated with the smooth endoplasmic reticulum such as a group of enzymes that make up an electron transport system completely independent of the mitochondrion, and a key regulatory enzyme for cholesterol biosynthesis is also associated with the smooth endoplasmic reticulum.

What cellular structure plays a key role in the sorting and routing of cellular materials?

The Golgi apparatus or Golgi complex is the separation site of intracellular transport routes involved in the export of proteins from the endoplasmic reticulum. Here, components of the plasma membrane, secretory granules, and lysosomes are sorted and packaged into separate types of transport vesicles for delivery to their appropriate cellular destination. The Golgi stack has functional, as well as topologic, polarity. Vesicles with proteins enter the stack at its *cis* (entry) face and, at least in the case of plasma membrane and secretory proteins, depart at the opposite *trans* (exit) face. Thus, the cisternae at the *cis* and *trans* ends are biochemically distinct, differing in the kinds of proteins responsible for the entry and exit processes.

What organelle plays a key role in energy metabolism in the cell?

The essential functions of mitochondria are devoted to the energy needs of the cell. The respiratory assembly is an integral part of the inner mitochondrial membrane and cristae. Reactions of the TCA (Tricarboxylic acid) cycle and its interrelationship in energy production and oxidative phosphorylation are associated with the respiratory assembly. Specific protein carriers transport molecules such as ADP (Adenosine diphosphate) and long-chain fatty acids across the inner mitochondrial membrane.

What are the specific structural features of the mitochondrion, and what role do they play in the function of this organelle?

Cristae are produced by the folding of the inner mitochondrial membrane into a series of internal ridges. The respiratory assembly is an integral part of the inner mitochondrial membrane and cristae. Reactions of the TCA cycle and the oxidation of fatty acids occur in the matrix, which is the internal volume of the mitochondrion. The inner membrane is intrinsically impermeable to nearly all ions and most uncharged molecules. Therefore, specific protein carriers transport molecules such as ADP and long-chain fatty acids across the inner mitochondrial membrane. The outer membrane is quite permeable to most small molecules and ions.

Why is the mitochondrion considered, in a sense, to be "semiautonomous?"

Mitochondria contain their own DNA, RNA, and protein translational machinery. Thus, this organelle has the capacity to define and maintain some, but not all, of its own functions. Diseases that result from inherited defects in mitochondrial genes are therefore inherited from the mother, because the egg is the source of mitochondria.

What cellular organelle plays a key role in the turnover of most cellular components?

Lysosomes contain many types of degradative enzymes that are specialized for the orderly destruction of cellular components. It is important to consider that most cellular components turn over. In other words, biological compounds are constantly being synthesized and degraded. This process is finely regulated so that the proper "steady-state" level of each component is maintained, and lysosomes are an integral part of this process.

What class of diseases result from defects in a particular degradative lysosomal enzyme?

The importance of lysosomal function is best exemplified by a class of diseases known as "lysosomal storage diseases," which arise from defects in a particular degradative lysosomal enzyme. A genetic defect in a degradative enzyme results in an accumulation of substrate inside the lysosome. This results in cellular dysfunction and eventually in cell death. More than 48 lysosomal hydrolase or lysosomal membrane transport deficiencies have been described. Almost all are autosomal recessive in inheritance (Figure 1.4).

What is Tay-Sachs disease?

Tay-Sachs disease is one of a group of heterogeneous lysosomal storage diseases, the G_{M2} gangliosidoses, that results from the inability to degrade a sphingolipid, G_{M2} ganglioside. The biochemical lesion is a marked deficiency of hexosaminidase A. Although the enzyme is ubiquitous, the disease has its clinical impact almost solely on the brain, the predominant site of G_{M2} synthesis.

What organelle serves an essential purpose of metabolizing hydrogen peroxide?

Most eukaryotic cells of mammalian origin have a defined cellular organelle, peroxisomes (microbodies), that contain several enzymes that either produce or use hydrogen peroxide. The organelles are usually smaller than lysosomes and are spherical or oval in shape, with a granular matrix and in some cases a crystalline inclusion termed a *nucleoid*. Peroxisomes are the most numerous in liver and kidney cells. The matrix of all microbodies contains catalase, a heme protein that combines two molecules of H_2O_2 (hydrogen peroxide) to produce O_2 and H_2O, and peroxidases, which are also heme enzymes that combine H_2O_2 with a hydrogen donor substrate resulting in the oxidation of the donor and the formation of H_2O.

Catalase

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

Peroxidase

$$RH_2 + H_2O_2 \rightarrow R + 2H_2O$$

What disease results from a deficiency in the biogenesis of peroxisomes?

Although the peroxisomal membrane forms in Zellweger syndrome, there is a deficiency in the receptor that targets enzymes to the peroxisomes. As a result, peroxisomal function is compromised; thus, Zellweger syndrome presents with serious neurologic deficits during infancy, and afflicted children usually die during their first or second year. Because one role of the peroxisome involves the enzymatic machinery necessary for the degradation of very long-chain fatty acids via β-oxidation, accumulation of the very long-chain fatty acids (> C:20) is observed in these infants.

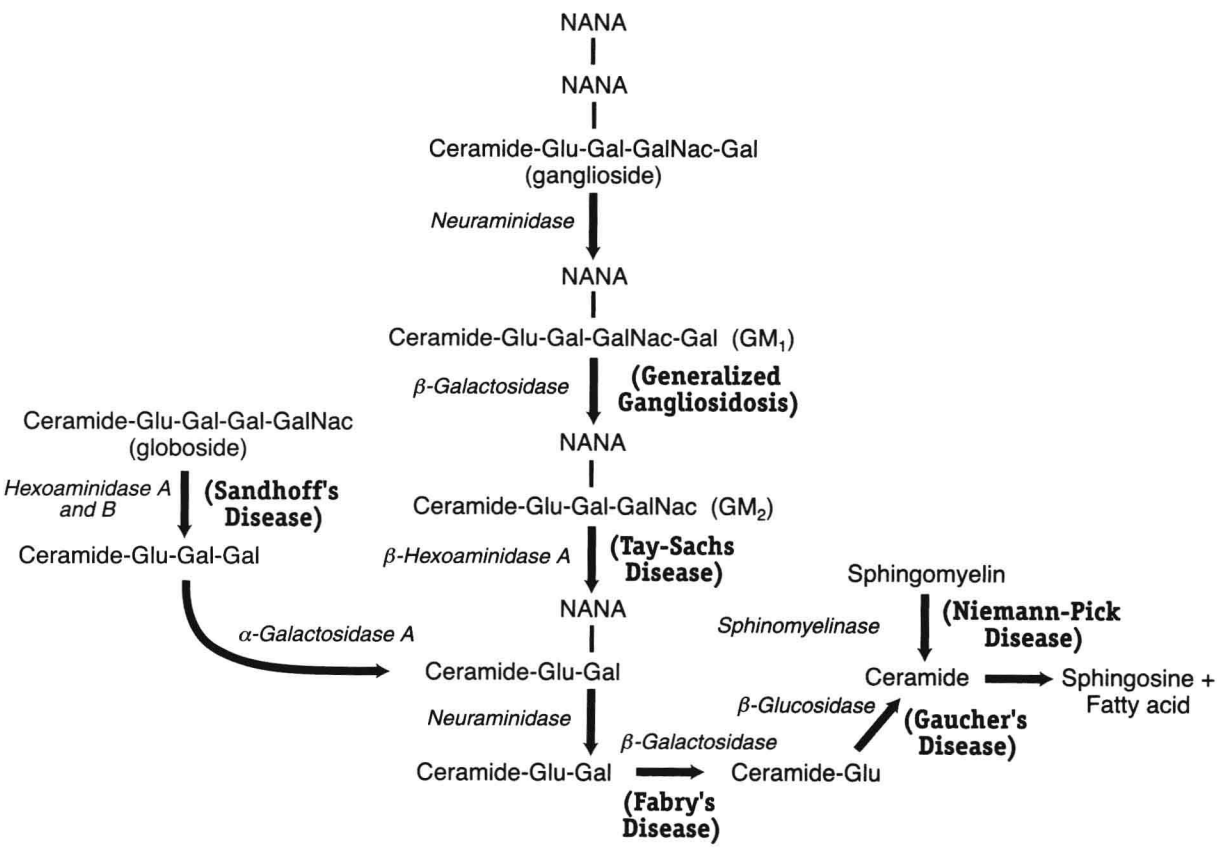

Figure 1.4 The ordered lysosomal catabolism of sphingolipids. Typically lysosomes of histocytes or macrophages of the reticuloendothelial system, located primarily in liver, spleen, and bone marrow, are responsible for the orderly degradation of sphingolipids. Sphingolipidoses caused by a genetically determined enzyme deficiency are indicated by parenthesis and bold print.

What other internal structures of the cell affect cellular function?

The cell contains a microtrabecular system that is essential for the coordinated activities of different parts of the cell. In this role, the cytoskeleton is a major factor in providing the nonhomogeneity of the cytoplasm that distinguishes a cell from an aqueous solution.

What are the basic components of the cytoskeleton?

The cytoskeleton consists of microtubules, intermediate filaments, and microfilaments. Biochemical studies, involving the extraction of cytoskeletal proteins from cells with detergents and salts, showed that each class of filaments has a unique protein organization. The basic component of microtubules is tubulin; intermediate filaments contain a number of substances, including keratin, desmin, and vimentin, whereas microfilaments are essentially composed of actin. The functions of these structures are greatly influenced by a number of other associated molecules.

What are the general functions of microfilaments in nonmuscle cells?

They form cross-linked bundles that provide mechanical support for various cellular structures and extensions. Together with myosin, microfilaments form the diverse contractile systems thought to be responsible for many cellular movements. Examples are microvilli, bundles of actin filaments that cover the exposed surfaces of many kinds of epithelial cells where cellular function requires a maximum surface for adsorption. Microspikes are composed of actin filaments and act as sensory devices or feelers by which cells explore their environment. The contractile ring consists of actin bundles with myosin, capable of contraction in cell division. Stress fibers are bundles of actin filaments that lie close to the cell surface and terminate at specialized regions of the plasma membrane known as adhesion plaques.

How do microtubules affect the shape and movement of cells?

Microtubules consist of a polymer of the protein tubulin that can be rapidly assembled and disassembled depending on the needs of the cell and are important in the formation of the mitotic apparatus spindle fibers, flagella, cilia, etc. As a result of rapid polymerization and depolymerization, thrusting out and retracting rigid tubular structures change the shape of a cell and are important in movement, aligning internal structures, and in producing localized changes in the surface of the cell.

What are intermediate filaments?

Intermediate filaments are tough, durable protein fibers that appear as straight or gently curving arrays in electron micrographs. They seem to be particularly prominent in those cells that have parts subject to stress, corresponding to their major function, which is to provide mechanical support for the cell. The types and composition of intermediate filaments vary between cell types, species, etc. The structure of intermediate filaments does not fluctuate between assembly and disassembly states such as microtubules and microfilaments. Unlike actin and tubulin, the assembly and disassembly of intermediate filament monomers are regulated by phosphorylation.

How do intermediate filaments differ from microfilaments?

Intermediate filaments consist of fibrous polypeptides that vary greatly in size (40,000 to 200,000 Da). They are generally defined by cellular extraction procedures and are the insoluble fibers left after high and low salt extraction with ionic detergents. Their structure and assembly are similar to collagen.

What structure is typically the most prominent organelle in eukaryotic cells?

The nucleus is the most prominent organelle in a wide variety of eukaryotic cells. The Greek word *karyon* means nucleus.

What essential role does the nucleus serve in affecting cellular function?

The nucleus has a vital role in directing protein synthesis through which it dominates and controls the structure and function of the cell.

What two membrane systems define the boundaries of the nuclear organelle?

The nuclear envelope partitions the nucleus from the cytoplasm and is composed of two separate membranes, each of which shows the characteristic trilaminar membrane structure. The inner nuclear membrane forms the limit of the nuclear contents and is separated by a space of 500 Å from the outer nuclear membrane. The width of this gap varies in different cells and is called the perinuclear space (cisternae).

How do large molecules enter and leave the nucleus?

Nuclear pores are involved in macromolecular transport between the nucleus and cytoplasm. A diaphragm with a dense collar (annulus) is part of the nuclear pore structure.

What are the general components of the nucleus?

The nucleus contains the bulk of cellular DNA, appreciable quantities of RNA, basic and acidic proteins of which a group of small basic proteins, called histones, are the most predominant species.

What relationship does the nucleolus have to nuclear function?

The nucleolus represents the aggregation of genes and specialized machinery involved in ribosomal RNA synthesis and maturation.

How does the structural organization of DNA in the nucleus relate to its ability to control cell function?

The nuclear organelle probably represents the highest form of structural organizational requirements. A human cell contains sufficient DNA to stretch 3 meters fully extended and is able to accommodate this DNA within roughly a 5-micron diameter space of the nucleus. Besides the enormous task of packaging this DNA (chromatin), the nucleus possesses the machinery to permit specific expression of regions (transcription) of this DNA for normal cell function. In addition, the nucleus contains the machinery for the maintenance (DNA repair) of the integrity of the genome, which is paramount to the survival and normal function of the cell. Finally, for those cells that are in active growth, machinery for replication of DNA and the mitotic process is also an integral part of the nucleus.

Chromatin Structure

What is chromatin?

Chromatin refers specifically to the complex of DNA and protein found in nuclei of eukaryotic cells.

What are the general features of chromatin in the nucleus of nondividing cells (interphase)?

Two forms of chromatin material can be identified in the interphase nucleus. Chromosomal material that returns to a dispersed condition of interphase chromatin is referred to as euchromatin. Chromatin material that remains in its condensed state is referred to as heterochromatin.

How does the packing of chromatin as either heterochromatin or euchromatin relate to transcriptional activity (gene expression)?

Heterochromatin is essentially transcriptionally inert and is not used to direct protein synthesis. On the other hand, euchromatin has regions that are active in RNA synthesis. This difference supports the role that the packaging of DNA can affect gene transcription. Any chromosome may have both heterochromatic and euchromatic regions. The centromeres and telomeres of chromosomes represent heterochromatic regions of chromosomes.

Is heterochromatin all the same?

Actually, two classes or types of heterochromatin appear to share the same characteristic condensed morphology and lack of transcriptional activity. Constitutive heterochromatin represents regions of densely staining material that is found essentially at the same position in both members of a homologous chromosome pair. Therefore, the location of constitutive heterochromatin is characteristic within a chromosome set. Facultative heterochromatin in mammalian tissue represents the inactivation of one of the X chromosomes in females by condensation into heterochromatin. Such condensed chromosomes are known as sex chromosome bodies, or Barr bodies. The formation of sex heterochromatin takes place at an early stage of embryogenesis, after which all of the somatic daughter cells derived from the cell with inactive sex chromosome contain one X chromosome that appears euchromatic and one that is heterochromatic.

What is the composition of chromatin?

Chromatin is a working definition, and its composition can vary based on the way that it is extracted. Nevertheless, some general features persist. The relative proportion of the components of chromatin varies according to tissue, organism, and method of preparation. However, a group of proteins called histones always makes up the greatest amount of the chromosomal proteins (Table 1.1).

What are the histones?

Histones are relatively small proteins, mostly a little more than 100 amino acids in length. They are rich in the amino acids lysine and arginine. There are five classes of histones in the typical eukaryotic cell that are distinguished based on their relative content of lysine and arginine residues. The evolutionary conservation of sequence supports a structural role for histones involving comparable interactions with DNA and playing essentially the same role in all tissues and in all eukaryotic organisms (Table 1.2).

Table 1.1	Composition of Chromatin

Component	Percent
DNA	100
Histories	114
Non-histories	33
RNA	7

Table 1.2	Types of Histones			
Type	**Lys/Arg**	**Number of Ratio**	**Mass Amino Acids**	**Location (kDa)**
H1	20	215	21	linker
H2A	1.25	129	14.5	core
H2B	2.5	125	13.8	core
H3	0.72	135	15.3	core
H4	0.79	102	11.3	core

What structural role do histones play in the packing of eukaryotic DNA?

Despite the great variety and complexity of eukaryotic chromosomes, there exists a remarkable uniform structure for the structural relationship between histones and DNA. This structure is called a nucleosome.

What is the structure of the nucleosome?

Histones are complexed to the DNA in a very defined repeating pattern called the nucleosome. This basic unit of chromatin structure is roughly spherical particle of about 100 Å in diameter, which contains approximately 146 bp of coiled DNA wrapped around an intranucleosome core of two each of the four histones: H2A, H2B, H3, and H4 (Figure 1.5).

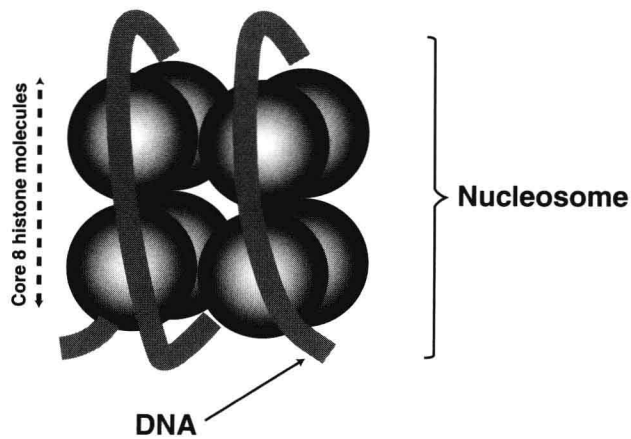

Figure 1.5 Structure of a nucleosome. The nucleosome is a nearly invariant structure in eukaryotes consisting of 146 bp of DNA, wrapped about an octamer of histone molecules.

How are nucleosomes organized?

The DNA between each nucleosome particle is called linker DNA, which represents approximately 54 base pairs. Histone 1, which is not part of the core particle, is involved in higher order chromatin structures. H1 binds the linker DNA and is believed to consolidate the nucleosome beads through head-to-tail interactions based on its asymmetric shape. This consolidation of the nucleosome beads and the coiling of the 100 Å fiber results in a higher order "solenoid" structure.

What are the higher order structures of chromatin?

The 100 Å fiber can compact further into a 200–300 Å fiber. This thick fiber is most stable and has been termed the *solenoid* structure. The 300 Å fiber is flexible and exhibits periodic discontinuities. This fiber appears to be arranged in loops that interact with a superstructure known as the nuclear matrix (or during metaphase the nuclear scaffold). These looped domains may act as structural units that also may relate to function. When chromatin is being transcribed by an RNA polymerase, the looped region is thought to uncoil into the 100 Å nucleosome units such that they would appear as "beads-on-a-string" (Figure 1.6).

Bioenergetics

What does the term *bioenergetics* mean?

Bioenergetics represents an area of thermodynamics that considers energy acquisition, exchange, and utilization in living systems.

For a given metabolic process, what determines the direction of the reaction?

Reactions may be reversible (near equilibrium) or irreversible (far from equilibrium), but the direction of the reaction to equilibrium is determined by thermodynamics and the free energy change, ΔG. The criterion for a favorable direction is that the free energy change is negative.

Why are free energy changes important to the consideration of metabolism?

The central role of free energy changes determines the favorable direction for a reaction. Thus, the metabolic pathway must be thermodynamically possible.

What is the biological significance of coupling reactions?

Unfavorable processes can be made thermodynamically favorable by coupling them to strongly favored reactions. Thus, coupling endergonic reactions to exergonic reactions is an important fundamental of metabolism and is used not only to drive the countless reactions of metabolism, but also to affect transport across membranes, transmit nerve impulses, contract muscles, and carry out other physical changes.

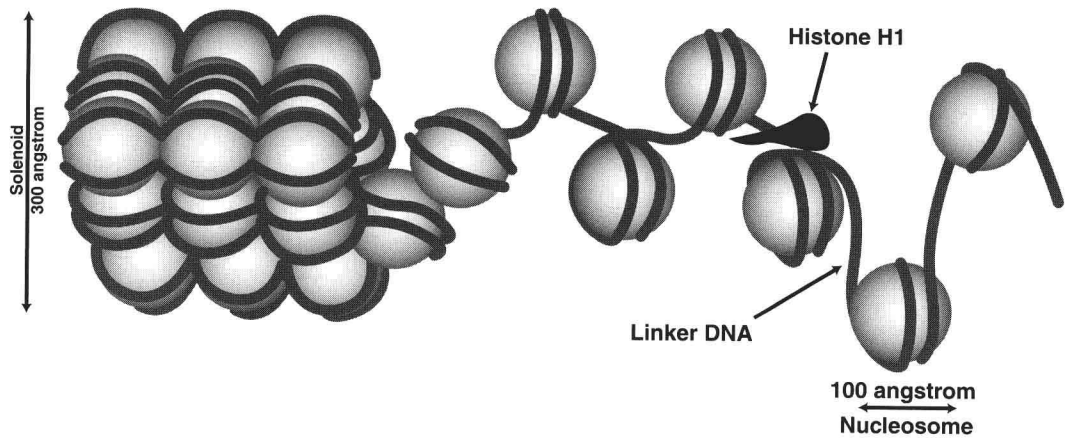

Figure 1.6 Chromatin packaging. The internucleosomal DNA, or linker DNA, is occupied by histone H1, which probably plays some role along with other proteins to condense and coil nucleosome units into a thicker fiber of approximately 300 Å (solenoid).

In coupling reactions, how does the cell use energy currency to drive the unfavorable coupled reaction?

The cell contains a variety of compounds that undergo reactions with large negative free energy changes. They include phosphate anhydrides (i.e., ATP, or Adenosine triphosphate), enol-phosphates (i.e., phosphoenol-pyruvate), some thioesters (i.e., acetyl-CoA), and compounds containing N-P bonds (i.e., creatine phosphate). Such compounds are thought of as energy currency in cells. By coupling these two reactions, the phosphorylation of glucose is now a favorable process.

ATP	$\rightleftharpoons$	ADP + Pi	$\Delta G^{0'}$ = -31 kJ/mol
Glucose + Pi	$\rightleftharpoons$	Glucose-6-phosphate	$\Delta G^{0'}$ = +14 kJ/mol
ATP + glucose	$\rightleftharpoons$	ADP + Glucose-6-phosphate	$\Delta G^{0'}$ = -17 kJ/mol

Can a change in the concentration of reactants affect the direction of a reaction?

Free energy changes for a reaction are affected by the concentration of components. The equation $\Delta G = \Delta G^{0'} + Rt ln\{[products]/[reactants]\}$ relates the free energy change to the equilibrium constant. Therefore, the relative ratio of reaction components can determine the direction of the reaction. For example,

Glucose-6-phosphate $\rightleftharpoons$ Fructose-6-phosphate $\quad \Delta G^{o'}$ = +1.7 kJ/mol

The reaction is favored in the direction of glucose-6-phosphate formation. However, in a cell, the concentration of fructose-6-phosphate can be very low because it can enter the glycolytic pathway through an irreversible step catalyzed by phosphofructokinase. As a result, the free energy change for this reaction $\Delta G = \Delta G^{0'} + Rt ln\{[F6P]/[G6P]\}$ depends not only on the standard free energy change but also on the relative ratio of reaction components. When F6P is very low relative to G6P, the free energy change for the reaction will favor formation of F6P despite the positive value for the standard free energy change. In this way, the direction of some metabolic reactions can be influenced by the availability of either substrate or products, and a reaction appears to be unfavorable as indicated by the standard free energy change can be driven by changing the ratio of product/reactant.

How is the energy content in food measured?

The energy content in food is generally described in terms of calories. Technically, however, the dietary term *calories* actually refers to kilocalories of heat energy released by combustion of that food in the body.

What is the caloric value of food?

The caloric value of protein is 4 calories per gram. Fat is 9 calories per gram. A carbohydrate is 4 calories per gram, and for comparison, alcohol is roughly 7 calories per gram. Based on these values and the amount and composition of the food, one can roughly calculate the caloric content of food.

What factors influence energy balance?

These are dietary constituents, frequency of eating, and amounts per feeding versus one's basal metabolism, resting energy as well as nonresting energy expenditure.

What are the metabolic consequences of chronic energy imbalance where energy uptake exceeds energy expenditure?

Obesity is a metabolic disorder that results from the chronic imbalance between energy uptake and energy expenditure. Excessive adiposity is associated with dyslipidemia, elevated serum free fatty acids, cholesterol, and triacylglycerols. In addition, obese individuals most often present with hyperglycemia and insulin resistance. As a consequence, there is a direct correlation with the increased risk of co-morbidities such as cardiovascular disease, type II diabetes, and hypertension, as well as cancer.

CHAPTER

2

Nucleic Acid Chemistry

Nucleotide Chemistry

What three common chemical components make up the structure of a nucleotide?

Nucleotides consist of three components: (1) a pyrimidine or purine base linked to a (2) sugar, either ribose or deoxyribose, and (3) phosphate esterified to a sugar (Figure 2.1).

How does the structure of the base moiety of nucleotides differ?

There are two types of purines, adenine (A) or guanine (G), and three types of pyrimidines, uracil (U) or cytosine (C) or thymine (T).

How are the atoms of the bases distinguished?

For purposes of nomenclature, the atoms of the rings in purine and pyrimidine bases are numbered (Figure 2.2).

Are there different types of sugars that can make up the sugar component of nucleotides?

There are two types: D-ribose or D-deoxyribose (Figure 2.3).

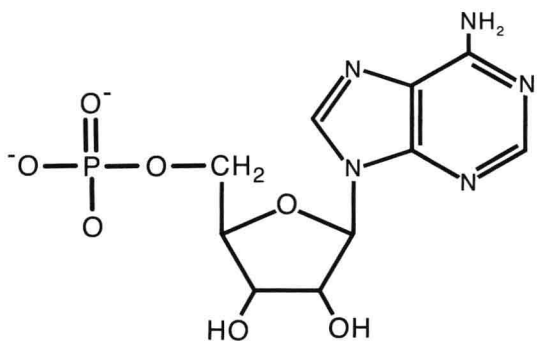

Figure 2.1 Structure of a nucleotide. The schematic illustrates the three components that make up a nucleotide; the base, which is either purine or pyrimidine, the sugar component which is either ribose or deoxyribose, and the phosphate group which is attached through an ester linkage to the sugar.

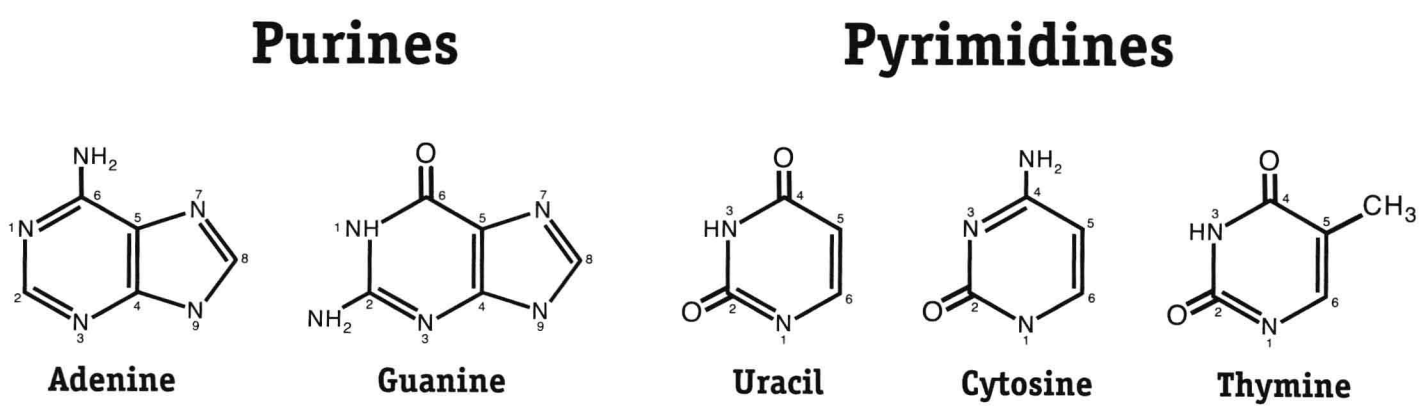

Figure 2.2 Numbering system for the atoms in purine and pyrimidine ring structures.