ESSENTIALS of HUMAN METABOLISM

· The Relationship of Biochemistry to Human Physiology and Disease

W. C. McMurray

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PREFACE

A young man with the overburdened expression characteristic of medical students approaching examinations came to the desk of a medical librarian and inquired wearily, "Have you anything light on obstetrics?" This book was written having in mind his preclinical counterpart seeking something less ponderous than the standard biochemistry texts for medical students.

My intent is to explain the metabolic processes and their regulation in the human body, emphasizing the relationship of biochemistry to human physiology and disease. Treatment of specific tissues and organs is considered as an integral part of metabolism, not as an addendum.

I have sought to explain the transformations of chemical components in the human body while largely omitting detailed analyses of the structures and properties of these components. By concentrating upon the broader outlines of metabolism, as viewed from the wrong end of the telescope, I have hopefully obliterated individual trees, which should render the metabolic forest more passable to the aspiring clinician. Since many problems in comprehension by the student arise from the terminology of the subject, I have endeavoured to limit the vocabulary to essentials and to define each new term (italicized) where it first appears in the text. The definitions for most of the common biochemical terms (which appear in bold type) are collected in the glossary section which begins the text.

Beginning with a description of simple molecular structures, Chapter 1 outlines the principles involved in construction of the giant polymers and membrane structures of cells. Chapter 2 surveys the general properties of enzymes and the genetic and physiologic factors that modify their activities. The major energy-transducing systems involved in biologic oxidations and active transport processes are summarized in Chapter 3. The next three chapters discuss carbohydrates, lipids, and nitrogen-containing compounds from the standpoint of individual organ systems—intestinal tract, liver, muscle, adipose tissue, brain, kidney, and red blood cells—indicating processes of digestion, absorption, transport, and homeostasis of major nutrients. Specialization of pathways of metabolism and control mechanisms of individual tissues, as well as pathologic aberrations of metabolic diseases affecting the tissues, are elaborated on. The final Chapter 7 provides an integrative approach to the biochemical interrelationships between organ systems, including examples of metabolic imbalances and adaptive responses in the body during starvation and obesity.

Our knowledge and understanding of human metabolism increase daily through the efforts of clinical and basic science investigators. Major advances come often in unexpected ways, by study of mammals and

vertebrates other than man, of insects and other invertebrate creatures, of yeasts, plants and microorganisms. We should be mindful and appreciative of the contributions to medical science made by these so-called "lesser species" of life. In focussing my attention upon man and his metabolism, in the interests of brevity I have omitted descriptions or attributions to individual workers and to the many forms of living organisms upon which our knowledge of life processes is founded. However, in paying tribute both to the investigators and the investigatees of biochemistry I must point out that this book is addressed primarily to an aspiring clinician rather than to a biochemist or an *Escherichia coli*.

Many of my associates have shown an interest in this book and have provided encouragement and advice about the presentation. In particular I would like to acknowledge with gratitude the contributions of two colleagues, Bill Magee and Valentina Donisch, who read the entire manuscript "stem to gudgeon" and spent a great deal of time and effort providing concrete suggestions for improvement. I am grateful to Ms. Doris Lesser for typing the manuscript, and to the staff of Harper and Row who have helped so much to fulfill the intent of the book.

W.C.McM.

CONTENTS

GLOSSARY

ACTIVE CENTER—that region of an enzyme molecule where the substrate combines and is activated to react during catalysis (syn. *catalytic site*)

ACTIVE TRANSPORT—the process whereby energy is utilized to carry a substance across a membrane, from a solution of lower to higher concentration (*i.e.*, against the concentration gradient of the substance)

ACYL CARRIER PROTEIN—a polypeptide whose prosthetic group, pantetheine, carries the intermediates of fatty acid biosynthesis in a thioester linkage during the reaction sequence catalysed by fatty acid synthetase

ADENOSINE TRIPHOSPHATE (ATP)—the nucleotide formed by joining the purine base, adenine, through ribose to three phosphate groups linked together. It is the principal mediator of energy-driven reactions in cells and is derived by phosphorylation of *adenosine diphosphate (ADP).*

ADENYLATE CYCLASE—an enzyme in the plasma membrane of cells, with a regulatory subunit on the outer surface whose interaction with appropriate extra cellular hormones will activate or suppress the catalytic subunit on the inner surface which converts ATP to intracellular cyclic AMP (syn. *adenyl cyclase*) (see also **Cyclic AMP**)

ALLOSTERIC MODIFIER—a substance which combines with a **regulatory enzyme** at one region *(allosteric site)* and modifies activity at the catalytic site; it may either enhance the activity *(positive modifier)* or inhibit it *(negative modifier)*

AMINO ACID—an organic compound with a hydrocarbon residue attached to an amino (NH_2) group and a carboxyl (COOH) group, that serves as the monomeric unit of the proteins

AMINOTRANSFERASE—one of a group of enzymes that catalyzes removal of the amino group from an amino acid to produce the α-keto acid and then reversibly transfers the $-NH_2$ to a second α-keto acid to yield a new amino acid (syn. *transaminase*)

AMPHIPATHIC PROPERTY—the characteristic of a molecule possessing two regions of opposing solubility such that one end of the molecule dissolves readily in water **(hydrophilic),** while the other end does not **(hydrophobic)**

ANABOLIC HORMONE—an endocrine substance whose metabolic effects upon the target tissue are primarily to promote the biosynthesis of proteins, fats, or polysaccharides or to inhibit their degradation (ant. *catabolic hormone*)

ANABOLISM—biosynthetic transformations requiring energy input (*e.g.*, production of macromolecules from small precursors) (ant. *catabolism*)

ANTIBODY—a serum protein that is synthesized in response to the entry of a foreign substance **(antigen);** it combines selectively with the antigenic agent to neutralize its toxic or infectious effects (see also **Immunoprotein**)

ANTICODON—a sequence of three bases in transfer RNA that is complementary to the **codon** triplet of messenger RNA (see also **Codon, Transfer RNA**).

ANTIGEN—A substance, either free or combined at the surface of a bacterial or tissue cell, that elicits the formation of a specific **antibody** protein and combines avidly and selectively with the induced antibody (see also **Immunoprotein**)

ANTIMETABOLITE—a substance that bears a structural resemblance to a normal substrate or coenzyme thus competing with it in metabolism and antagonizing its actions

APOENZYME—the inactive protein portion remaining when an essential bound cofactor or prosthetic group is removed; it may regain catalytic activity when the prosthetic group is restored to form the holoenzyme (see also **Prosthetic group, Holoenzyme**)

BETA (β) OXIDATION—the enzymatic process in mitochondria whereby fatty acids are oxidatively degraded at the second carbon atom (β-position) from the carboxyl group, such that two-carbon fragments are successively released as acetyl CoA, with successive shortening of the fatty acid carbon chain

BILAYER—a bimolecular sheet formed by the associations of hydrophobic surfaces of two lipid monolayers to produce a sandwich two molecules thick with only the hydrophilic surfaces exposed on either outer side (see also **Monolayer**)

BILE PIGMENT—a breakdown product of hemoglobin (see **Bilirubin**)

BILE SALT—the salt form of a steroid acid, usually conjugated to an amino acid such as glycine; it is produced in liver by oxidation of cholesterol and secreted in the bile into the intestine to help emulsify fats and aid in their digestion and absorption

BILIRUBIN—a degradation product formed by opening the porphyrin ring derived from heme degradation, consisting of four pyrrole rings linked in a straight chain (syn. **bile pigment**)

BIOLOGIC HALF-LIFE—a measure of the time required for the body either to renew one-half of one of its normal components or to eliminate one-half of a foreign substance taken into the body

CARBOHYDRATE—a polyhydroxylic compound of carbon, hydrogen and oxygen; it may be a simple sugar (monosaccharide) or contain a few (oligosaccharide) or many (**polysaccharide**) sugar units joined together

CARNITINE—a carboxylic hydroxy acid related to choline found in high concentrations in muscle; it plays a role in transporting fatty acyl groups across the mitochondrial inner membrane

CATABOLIC HORMONE—an endocrine substance whose metabolic effects upon the target tissue are primarily to promote the degradation of proteins, fats, or polysaccharides or to inhibit their biosynthesis (ant. **anabolic hormone**)

CATABOLISM—degradative reactions releasing free energy and heat (*e.g.*, oxidation of organic compounds to carbon dioxide and water) (ant. **anabolism**)

CATECHOLAMINE—a family of aromatic substances with sympathomimetic activity, which possess an *o*-dihydroxybenzene (catechol) ring attached to an aliphatic amine portion

CHOLESTEROL—the major steroid derivative in the body; it exists as the free alcohol in cell membranes and as the fatty acid ester in blood plasma lipoproteins and serves as precursor of other important steroid derivatives, such as the sex hormones, bile salts, etc.

CHROMAFFIN GRANULE—a secretory vesicle containing high concentrations of catecholamines, particularly located in the adrenal medulla and sympathetic neurons

CHROMOSOME—one of the structures found in the nucleus of animal cells that contains the DNA of the genes, associated with histones and other proteins and with RNA

CHYLOMICRON—a small lipid droplet composed mainly of fat with small amounts of cholesterol and phospholipids and a thin coating of protein; it is synthesized in the intestinal mucosa cells from products of lipid digestion and released into the lymphatic vessels

CITRIC ACID CYCLE—the series of mitochondrial reactions whereby a two-carbon moiety (acetyl CoA) is completely oxidized by combining with oxaloacetic acid to form citric acid, the latter then being catabolized to 2 mols of CO_2, and regenerating the oxaloacetic acid (syn. *Krebs cycle; tricarboxylic acid cycle*)

CODON—a sequence of three bases (triplet) in messenger RNA which specifies the ordering of a particular amino acid through the complementary **anticodon** triplet

of its attached transfer RNA during protein synthesis. *Initiator* and *terminator codons* start and stop translation of the message.

COENZYME—an organic cofactor which functions in enzyme catalysis; it generally contains a **vitamin** as the reactive group

COENZYME A (CoA)—a nucleotide derivative containing the vitamin, pantothenic acid; its functional thiol (—SH) group forms thioesters with acyl groups of important metabolic intermediates *(e.g., acetyl-SCoA)*

COENZYME Q (CoQ)—a fat-soluble, substituted benzoquinone which functions as an electron carrier in the respiratory chain between flavoproteins and cytochromes

COFACTOR—a nonprotein substance which is required for the activity of an enzyme; it may be inorganic (*e.g.*, a metal ion) or organic (*e.g.*, a **coenzyme**)

COMPETITIVE INHIBITION—the action of an inhibitor which so closely resembles the substrate that it competes with it for binding sites at the enzyme's active center. (V_{max} is unaffected but K_m is increased in the presence of inhibitor.)

COMPLEMENTARY BASE-PAIRS—the specific pairs formed by hydrogen bonds between a purine base of one nucleic acid strand with a pyrimidine of another strand; adenine (A) always pairs with thymine (T) or uridine (U), guanine (G) with cytosine (C)

CONSTITUTIVE ENZYME—an enzyme whose concentration is fixed and not subject to stimulation (**induction**) or inhibition (**repression**) of its biosynthesis by regulatory agents

CORI CYCLE—the process in carbohydrate metabolism whereby lactic acid that is derived from muscle glycolysis is carried through the bloodstream and is recycled by liver gluconeogenesis to glucose which is returned in the bloodstream to the muscle (syn. *glucose-lactate cycle*)

COUPLING INHIBITOR—an agent that prevents the interaction of ADP with the energy-coupling steps in oxidative phosphorylation and, hence, blocks both ATP synthesis and respiration

COUPLING SITE—one of the oxidative reactions of the respiratory chain where there is a large release of free energy that is capable of being coupled to the formation of ATP from ADP and inorganic P (see also **Oxidative phosphorylation**)

CYCLIC AMP—a nucleotide that acts as the intracellular mediator in the target cells after their interaction with nonpenetrating hormones (syn. *adenosine 3',5'-cyclic phosphate;* **second messenger**)

CYTOCHROME—one of a class of heme-containing proteins, localized to the membranes of mitochondria and endoplasmic reticulum, whose iron atoms undergo cyclic reduction and oxidation during the sequential electron transfers of respiration

CYTOCHROME OXIDASE—the terminal carrier of the respiratory chain; it is the only cytochrome component capable of transferring electrons directly to oxygen (syn. *cytochrome a-a_3*)

DEHYDROGENATION—an oxidation reaction in which hydrogen atoms are abstracted from the substrate

DENATURATION OF PROTEINS—unravelling of the natural folded conformation of a polypeptide; it is generally accompanied by irreversible decrease of solubility and loss of biologic activity of the protein

DEOXYRIBONUCLEIC ACID (DNA)—the polymer formed of nucleotides containing deoxyribose (dAMP, dCMP, dGMP, dTMP); it is the chemical basis of the gene and is formed of two intertwined, complementary strands *(double helix)*

DEREPRESSION—removal or neutralization of action of a repressor molecule that blocks enzyme synthesis (see also **Induction, Repression**)

DYNAMIC STATE OF BODY CONSTITUENTS—the condition of turnover in tissue proteins and other components which may appear to exist in a static equilibrium in the absence of growth, but nonetheless are in a steady state of synthesis and degradation, undergoing continual exchanges with dietary substances (see also **Steady state**)

ELECTRON CARRIER—a compound which, by alternating between oxidized and reduced states, serves as an intermediary in the transfer of electrons from substrates to oxygen along the respiratory chain (see also **cytochrome**)

EMULSION—a fine, milky dispersion of one liquid in another liquid with which it is not capable of producing a solution

END-PRODUCT INHIBITION—a form of metabolite control in which the final products of a metabolic sequence exert **negative feedback** on the whole pathway by inhibiting a pacemaker regulatory enzyme, usually near the beginning of the sequence

ENDOPLASMIC RETICULUM—an interconnected network of flattened tubules in the cytoplasm. Regions with ribosomes attached to the cytoplasmic surfaces of the tubules are termed *rough endoplasmic reticulum* and are involved in the synthesis of proteins, especially those for secretion; regions lacking particles are termed *smooth endoplasmic reticulum* and play roles in the processing of secretory proteins and in drug detoxification.

ENERGY OF ACTIVATION—a measure of the energy required to raise a molecule to the excited transition state in order to permit a reaction to proceed

ENZYME—a protein molecule which combines selectively with and acts specifically upon another molecule, the **substrate**, to catalyze the conversion of substrate into particular **product** molecules

ENZYME INHIBITOR—a substance that selectively interacts either to block or to modify the conformation of the active center of an enzyme, thereby slowing or preventing its catalytic action upon the substrate

ENZYME-SUBSTRATE COMPLEX—the transient, activated intermediate formed when the substrate is bound in the active center of an enzyme during catalysis

EPINEPHRINE—a hormone produced by the adrenal medulla which produces effects on target tissues by raising cyclic AMP concentrations in the cells, which promotes glycogenolysis in muscle and liver, raising blood glucose levels, and activates lipolysis in adipose tissue, raising blood fatty acid levels. (see **Catecholamine**) (syn. *adrenaline*)

ESSENTIAL AMINO ACIDS—those which are not synthesized at all or rapidly enough in the body and, hence, must be provided in the diet. (For man they are *arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine.*)

ESSENTIAL FATTY ACIDS—those polyunsaturated long-chain acids which may not be synthesized in the body and, therefore, are essential in the diet. (They include *linoleic acid* (C18:2), *linolenic acid* (C18:3), *arachidonic acid* (C20:4.)

EXCITATION OF NEURONS AND MUSCLE—the alteration of membrane permeability in response to external stimuli that produces a change of the membrane potential due to movements of cations (K^+ and Na^+) across the cell membrane (syn. *depolarization*)

FATTY ACID—an aliphatic carboxylic acid, usually with a single carboxyl group attached to a long, straight hydrocarbon chain, with an even number of carbons

between 14 and 24 and a variable number of double bonds from 0 to 6 in the carbon chain

FATTY ACID SYNTHETASE—the multienzyme system that catalyzes the stepwise condensation of one molecule of acetyl CoA and seven molecules of malonyl CoA and the reduction of intermediates with NADPH to produce palmitoyl CoA

FLAVOPROTEIN—a protein which contains a riboflavin coenzyme (FMN or FAD) as its prosthetic group

FREE ENERGY (F)—the energy that is available to perform work as a system proceeds toward equilibrium. A process will occur spontaneously in nature only if its free energy change ($\triangle F$) is less than zero (syn. *Gibb's free energy* [*G*]).

GENE—the unit hereditary factor; it is the segment of a DNA molecule that specifies one polypeptide chain (syn. *cistron*)

GENOTYPE—the entire genetic constitution of an individual

GLOBULIN—one of the group of proteins in blood plasma that is precipitated by half saturation with ammonium sulfate. The various globulin proteins differ in their lipid and carbohydrate components and may be separated by ultracentrifugation and electrophoresis.

GLUCAGON—a polypeptide hormone secreted by the α-cells in the pancreatic islet tissue. It specifically activates the formation of cyclic AMP in liver cells, thus raising the blood glucose by stimulating liver glycogenolysis and gluconeogenesis.

GLUCOCORTICOID—any of the steroid hormones produced by the adrenal cortex which promote the synthesis of glucose by gluconeogenesis and, hence, elevate the concentration of liver glycogen and blood sugar

GLUCONEOGENESIS—biosynthesis of glucose from *lactate*, *pyruvate*, or *oxaloacetate* or from noncarbohydrates which give rise to these compounds or to other intermediates of glycolysis

GLUCOSE—an aldehyde-containing, six-carbon sugar (aldohexose), which is the most important and abundant monosaccharide in body fluids and is the monomer of the storage polysaccharide, glycogen, in the tissues

GLUTAMIC ACID—the five-carbon dicarboxylic amino acid, α-aminoglutaric acid. It is derived in metabolism by aminotransfer or reductive amination of the citric acid cycle intermediate, α-ketoglutaric acid.

GLYCOGEN—the storage carbohydrate of liver, muscle, and other body tissues; it is a highly branched polysaccharide of glucose monomers

GLYCOGEN SYNTHETASE—the enzyme that catalyzes the elongation of the linear chains of glycogen by sequential addition of glucose units from UDP glucose to the terminal 4-hydroxyl groups of growing polysaccharide chains

GLYCOGENESIS—the synthesis of glycogen by polymerization of glucose monomers

GLYCOGENOLYSIS—the splitting of the glycogen polymer chain to yield free glucose or glucose phosphate esters

GLYCOGENOSIS—one of a group of inborn errors of metabolism which exhibit the common characteristic of excessive storage of glycogen, though the tissues affected and structures of the polysaccharides may vary (syn. *glycogen storage disease*)

GLYCOLIPID—a fatty substance containing one or more sugars or carbohydrate derivatives; it will usually also contain the long-chain base, sphingosine (see also **sphingolipid**)

GLYCOLYSIS—the breakdown of hexose sugars, such as glucose, to three-carbon acids, such as *pyruvate* and *lactate*, yielding energy as ATP. In the absence of oxygen, lactate is the predominant carbon product (*anaerobic* glycolysis).

GLYCOLYTIC PATHWAY—the overall sequence whereby glucose is converted to pyruvate or lactate (see **Glycolysis**)

GLYCOPROTEIN—a polypeptide containing one or more sugars or carbohydrate derivatives as its prosthetic group; it frequently is a component of cell membranes, where the carbohydrate residues may act as antigenic determinants or other recognition sites on the exterior surface

GOLGI APPARATUS—a system of stacked, flattened tubules usually lying between the nucleus and plasma membrane whose cisternal spaces contain secretory proteins undergoing modification prior to being exported from the cell

HEME—the complex that is formed when ferrous iron is chelated in the center of the protophorphyrin ring; it is the prosthetic group of oxygen-carrying proteins (**hemoglobin**, *myoglobin*) and respiratory proteins (**cytochromes**).

HEMOGLOBIN—the pigmented protein of red blood cells; it reversibly binds oxygen to its heme prosthetic group and carries it from the lungs to the peripheral tissues

HIGH-ENERGY COMPOUND—a substance whose hydrolysis results in the release of a large amount of energy, *i.e.*, a negative free energy change of more than 5 kcal/mol under standard conditions

HISTONE—a strongly basic protein, rich in arginine and lysine residues, which forms a complex with DNA in the chromosomes of eucaryotic cells

HOLOENZYME—a conjugated protein that contains a prosthetic group which is necessary for the catalytic action of the enzyme (see also **Prosthetic group, Apoenzyme**)

HORMONE RECEPTOR—a protein molecule with a specific, high-affinity binding site for the hormone, located on the outer surface of a responsive target cell

HYDROPHILIC—a description for molecules or portions of molecules which are *polar* by nature and associate readily with water molecules (ant. **hydrophobic**)

HYDROPHOBIC—a description for molecules or portions of molecules which are *nonpolar* by nature and prefer to associate away from water molecules (ant. **hydrophilic**)

IMMUNOPROTEIN—a protein, usually found in the globulin fraction of blood plasma, that confers resistance to disease or eliminates another extrinsic molecule through a specific binding in response to an antigenic challenge (syn. *antibody, immunoglobulin*)

INBORN ERROR OF METABOLISM—an inherited disease in which a defect in a gene results in the failure to produce a normal catalytically active enzyme

INDUCIBLE ENZYME—an enzyme which is normally present in low amounts and will be induced to undergo accelerated biosynthesis by the increased concentration of a metabolite or hormone inducer molecule (syn. *adaptive enzyme*)

INDUCTION—the promotion of synthesis of an enzyme by a metabolite, the *inducer* molecule, which is often a substrate for the enzyme (syn. *derepression*)

INSULIN—a polypeptide hormone secreted by the β-cells in the pancreatic islet tissue which lowers the blood glucose by enhancing its uptake and utilization by tissues and by suppressing its synthesis in gluconeogenesis

IONOPHORE—a substance that forms a lipid-soluble complex with a specific ion and thus is capable of carrying the ion through the hydrophobic bilayer of biologic membranes

ISOELECTRIC POINT—the pH of the solution in which a protein will possess an equal number of positively and negatively charged groups, *i.e.*, no net charge

ISOENZYME—one of the variant forms in which an enzyme may be present in the same species; it will perform the same catalytic reaction as the other isoenzymes but

may be distinguished by its different kinetic properties and electrophoretic migration (syn. *isozyme*)

KETONE BODY—any of a group of products of the incomplete oxidation of fatty acids, namely, *acetoacetic acid, β-hydroxybutyric acid* or *acetone*

KINASE—an enzyme that catalyzes transfer of the terminal phosphate group from a nucleoside triphosphate (usually ATP) to an acceptor molecule (usually an alcohol), forming a phosphate ester (syn. *phosphotransferase*)

KREBS CYCLE (see **Citric acid cycle**)

KREBS-HENSELEIT CYCLE (see **Urea cycle**)

LIPASE—any of the group of esterase enzymes found in pancreatic secretion into the intestine, inside the fat cells, or at the cell membrane of liver and other tissues, that catalyze the hydrolysis of ester linkages between glycerol and the fatty acids of fats and phospholipids

LIPID—an organic compound of natural origin which is soluble in nonpolar reagents such as chloroform, ether, and alcohol (the so-called fat solvents) but is insoluble in water; it usually contains a long hydrocarbon chain or a sterol

LIPIDOSIS—one of a group of inborn errors of metabolism characterized by abnormal accumulations of lipids in the tissues

LIPOGENESIS—the synthesis of fats by condensation of acetyl CoA molecules and reduction to fatty acids and esterification of the latter to form the triacylglycerols

LIPOLYSIS—the hydrolytic decomposition of lipid, usually pertaining to fat hydrolysis into glycerol or partly acylated glycerol, plus free fatty acids.

LIPOPROTEIN—a water-soluble combination of a lipid or a number of different lipids with a protein. (Combinations of lipids with protein which are fat-soluble are generally termed *proteolipids*.)

LIPOPROTEIN LIPASE—an esterase present in many tissues, especially liver and adipose tissue, that attacks the chylomicrons hydrolysing the triacylglycerols and, hence, clears the milky turbidity of blood plasma after a fatty meal (syn. *clearing factor*)

LYSOSOME—a membrane vesicle containing hydrolytic enzymes, which carries out intracellular digestive functions

MACROMOLECULE—a very large molecule with a polymeric structure, such as a **protein** or **nucleic acid**

MESSENGER RNA—the single-stranded ribonucleic acid molecule transcribed from the segment of DNA that codes for a protein molecule. It carries the genetic message from the nucleus to the ribosome and orders the amino acids into the correct sequence during protein synthesis.

METABOLIC ACIDOSIS—accumulation of abnormal quantities of organic acids *(lactate, acetoacetate)* that arise from excess tissue metabolism

METABOLIC ANTAGONISM—opposition to the actions of a substance by an analogue whose structure is similar enough to permit it to compete in metabolism (see also **antimetabolite**)

METABOLIC DEBT (OF MUSCLE)—the condition prevailing after prolonged activity of muscle, resulting in depletion of high-energy reserves which must be restored later when the muscle is at rest

METABOLISM—the chemical transformations of molecules, brought about in living organisms by the actions of enzymes, under the control of genes, hormones, energy state, and the end-products

METHYLTRANSFERASE—one of a group of enzymes that catalyzes the transfer of a methyl group from the activated methyl donor, S-adenosylmethionine, to a specific acceptor (syn. *transmethylase*)

MICELLE—a very fine, colloidal dispersion of molecules, usually as a parallel array, within a liquid phase which fails to form a true solution of the molecules

MICHAELIS-MENTEN CONSTANT (K_m)—the concentration of a substrate that results in one half of the maximal rate for an enzymatic reaction; it is a characteristic value for each enzyme-substrate combination and reflects the binding affinity

MICHAELIS-MENTEN EQUATION—the kinetic expression for the dependence of enzyme rate (v) upon substrate concentration [S]:

$$v = V_{max}\,[S]/[S] + K_m$$

where V_{max} is the maximal rate with saturating substrate concentration and K_m is the **Michaelis-Menten constant**

MICROFILAMENT—a fine threadlike contractile structure which is particularly abundant in the cytoplasm of motile cells and participates in cellular movements and changes of shape

MICROTUBULE—a hollow cylindrical structure which plays a role in maintaining the shape and rigidity of cells and forms the mitotic spindle during cell division

MITOCHONDRION—the double-membrane enveloped organelle of eucaryotic cells that is responsible for cellular respiration, oxidation of pyruvate and fatty acids, the citric acid cycle, and the aerobic generation of ATP by oxidative phosphorylation

MONOAMINE OXIDASE—a flavoprotein enzyme that catalyzes the oxidation of amines into their corresponding aldehydes plus ammonia

MONOLAYER—a monomolecular surface film produced by packing lipid molecules side-by-side at an interface between two liquids (*e.g.*, oil–water) or liquid and gas (*e.g.*, air–water)

MONOMER—the single unit of a polymeric molecule

MUTATION—chemical modification of a gene such that one or more of the bases in the DNA are deleted or altered or a new base is inserted, thus changing the base sequence of the genetic code, and hence the protein coded by the gene either is produced with an altered amino acid sequence or is not produced at all

MYELIN—a multilamellar system of membranes, particularly rich in sphingolipids, that forms a sheath around certain nerve fibers

Na^+, K^+-ATPase—an active transport system which uses the energy from hydrolysis of ATP to drive sodium ions outward across the plasma membrane, with an opposite migration of potassium ions into the cell

NEGATIVE FEEDBACK—an autoregulatory system whereby an increased concentration of an end-product of metabolism inhibits one of the enzymes in the sequence leading to its formation (see **End-product inhibition**)

NEUROTRANSMITTER—a chemical mediator that carries a nerve impulse across a synapse or nerve–muscle junction. Included in this group of agents are acetylcholine and a number of aromatic amine substances. (syn. *synaptic transmitter*)

NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD)—a coenzyme of oxidation-reduction reactions containing the vitamin, nicotinamide, as its functional group. The oxidized form (NAD^+) is reduced to form NADH by accepting two electrons as a hydride ion (H^-).

NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE (NADP)—This coenzyme differs from NAD in possessing an additional phosphate group. It has

analogous oxidized ($NADP^+$) and reduced (NADPH) forms but has a different specificity for dehydrogenases.

NITROGEN BALANCE—the nutritional state of an individual in relation to his protein metabolism; it is a measure of the differential between ingested and excreted nitrogen

NITROGEN-RING COMPOUNDS—a group of heterocyclic substances including *pyridine* (C_5H_5N), found in nicotinamide coenzymes; **pyrimidine** ($C_4H_4N_2$) and **purine** ($C_5H_4N_4$), found in the nucleic acids and nucleotides

NONCOMPETITIVE INHIBITION—the action of an inhibitor which interferes with groups involved with catalysis at the enzyme's active center without affecting substrate binding. (V_{max} is decreased but K_m is not altered in the presence of inhibitor.)

NONESSENTIAL AMINO ACIDS—those which may be synthesized in the body rapidly enough to meet the needs for protein synthesis. (In man they include *alanine, aspartate, asparagine, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine.*)

NOREPINEPHRINE—a neurotransmitter produced in sympathetic nerves and released in response to nerve stimulation; it produces similar metabolic effects on peripheral tissues to those evoked by epinephrine (see also **catecholamine**) (syn. *noradrenaline, 3,4-dihydroxyphenylethanolamine*)

NUCLEIC ACID—a polymer of nucleotides joined together by phosphodiester linkages (syn. *polynucleotide*) (see also **Deoxyribonucleic acid, Ribonucleic acid**)

NUCLEOLUS—the region inside the nucleus which contains much of the nuclear RNA and is involved in the synthesis of ribosomal RNA

NUCLEOPROTEIN—a complex formed between a nucleic acid and a protein, usually a basic protein such as a **histone**

NUCLEOSIDE—a compound consisting of a nitrogenous base (purine or pyrimidine) joined to a pentose sugar. (A **nucleotide** has one or more phosphate groups attached to the sugar of a nucleoside.)

NUCLEOTIDE—a compound consisting of a nitrogenous base (purine or pyrimidine) joined through a pentose sugar to one or more phosphate groups; it may function as a coenzyme or polymerize to form the **nucleic acids** (DNA and RNA)

NUCLEUS—the largest organelle in eucaryotic cells; it contains within its membrane the DNA of the genes bound to histones in the chromosomes and an RNA-rich structure, the nucleolus

ORGANIC ACID—a compound with a hydrocarbon residue attached to an acidic group (usually COOH = *carboxylic acid*)

ORNITHINE CYCLE (see **urea cycle**)

OXIDATIVE DEAMINATION—the removal of an amino group from a compound and its release as ammonia, accompanied by transfer of hydrogens from the compound to a coenzyme, NAD or FAD (ant. **reductive amination**)

OXIDATIVE PHOSPHORYLATION—the mitochondrial process whereby the energy released during the passage of electrons along the respiratory chain is partially conserved by the coupled synthesis of ATP from ADP and inorganic phosphate

OXIDATION-REDUCTION REACTION—a chemical process whereby one or more electrons are transferred from a substance being oxidized to a substance being reduced

PEPTIDASE—one of the group of hydrolytic enzymes that attacks the peptide linkages of the small peptide fragments which arise from digestion of proteins

PHENOTYPE—the characteristics of an organism that are the product of inherited factors interacting with the environment

PHOSPHAGEN—a compound that serves as a reservoir of high-energy phosphate for the regeneration of ATP from ADP *(e.g., phosphocreatine)*

PHOSPHATASE—an enzyme that catalyzes the hydrolytic cleavage of a phosphate ester to release inorganic phosphate (syn. *phosphohydrolase*)

PHOSPHATIDIC ACID—the phospholipid produced by acylation of α-glycerophosphate with 2 mols of fatty acyl CoA; it is the precursor of other phosphoglycerides and triacylglycerols

PHOSPHOGLUCONATE PATHWAY—the reaction sequence which oxidizes glucose-6-phosphate to produce NADPH and either pentose sugars or carbon dioxide (syns. *pentose phosphate pathway; hexose monophosphate shunt*)

PHOSPHOGLYCERIDE—a lipid containing glycerol esterified to a phosphate group and one or two fatty acyl groups (syn. *glycerophosphatide*)

PHOSPHOLIPID—one of the family of lipid substances containing phosphate and either glycerol or sphingosine linked to long-chain fatty acids (syn. *phosphatide*)

PHOSPHORYLASE—the enzyme that catalyzes the degradation of the linear chains of glycogen by addition of inorganic phosphate to cleave the glycosidic links sequentially from the terminal 4-hydroxyl ends yielding glucose-1-phosphate

PHOSPHORYLATION—the transfer of a phosphoryl ($-PO_3$) group from one compound to another (syn. *phosphoryl group transfer*).

PLASMA MEMBRANE—the outer, limiting envelope of animal cells; it consists of a bilayer of lipids with a similar amount of proteins either embedded in or attached to the bilayer

P:O RATIO—a measure of the stoichiometry of the phosphorylations coupled to electron flow in the respiratory chain; it is the quotient of moles of phosphate esterified to form ATP divided by the atoms of oxygen consumed during respiration.

POLYMER—a large molecule produced by linking single molecular units (**monomers**) into an elongated, linear chain.

POLYMERIZATION—the head and tail attachment of multiple single molecules (**monomers**) to form long chains (**polymers**): with sugars as monomers the polymers are termed **polysaccharides**; with amino acids, **polypeptides** or **proteins**; with nucleotides, **polynucleotides** or **nucleic acids**

POLYNUCLEOTIDE—a long chain or polymer of nucleotides (see also **Nucleic acid**)

POLYPEPTIDE—a long chain or polymer of amino acids (see also **Protein**)

POLYRIBOSOME—a number of ribosomes joined to a strand of messenger RNA (syn. *polysome*) (see also **Ribosome**)

POLYSACCHARIDE—a long chain or polymer of sugar molecules *(monosaccharides)*

PORPHYRIN—one of a class of compounds with four pyrrole rings joined in a flat cyclic structure by methyne bridges (syn. *cyclic tetrapyrrole*)

POSITIVE FEEDFORWARD—an autoregulatory system whereby a precursor of a metabolic sequence stimulates the activity of one of the enzymes responsible for its utilization (ant. **negative feedback**)

PRODUCT—the resultant substance arising from catalytic action of an enzyme upon its substrate

PROSTAGLANDIN—one of a family of 20-carbon hydroxy fatty acids with a cyclopentane ring in the center of the chain. The prostaglandins have variable effects upon metabolism in different tissues by modulation of cyclic AMP action.

PROSTHETIC GROUP—a nonprotein component attached to a protein which is generally essential for its biologic activity. (Removal of the prosthetic group leaves the *apoprotein.*)

PROTEASE—one of the family of hydrolytic enzymes that attacks certain peptide linkages of large polypeptides, *i.e.*, intact proteins

PROTEIN—a polymer of amino acids joined together by peptide (CO–NH) linkages (syn. *polypeptide*)

PROTEIN KINASE—an enzyme that catalyzes transfer of a phosphate group from ATP to the serine hydroxyl group of a protein acceptor

PROTEOLYSIS—the hydrolytic cleavage of proteins at certain peptide linkages to yield smaller polypeptide fragments and, when complete, free amino acids

PROTONMOTIVE FORCE—the electrochemical gradient of hydrogen ions that is generated across the mitochondrial inner membrane during respiration and is proposed by the chemiosmotic theory of energy coupling to provide the driving force for ATP formation or cation movements by oxidative phosphorylation

PURINE—a nine-membered heterocyclic ring system with imidazole condensed to a pyrimidine ring

PYRIMIDINE—a six-membered heterocyclic ring with two nitrogen atoms in the one and three positions (syn. *1,3-diazine ring*)

REDUCTION POTENTIAL (E'_o)—a measure of the affinity of a substance for electrons; under standard conditions it is the electromotive force in volts when reductant and oxidant forms of the substance are present in 1.0 mol concentrations

REDUCTIVE AMINATION—the addition of an ammonia molecule to an α-keto acid forming an α-amino acid at the expense of the reducing energy furnished by NADH or NADPH (ant. **oxidative deamination**)

REGULATORY ENZYME—an enzyme whose activity may be controlled by its interaction with an **allosteric modifier** or by *covalent modification* of the enzyme protein. It generally catalyzes an early step of a metabolic sequence.

RENAL REABSORPTION—the uptake of substances which have passed into the glomerular filtrate by active transport mechanisms of the kidney tubules for retention in the bloodstream

REPLICATION—the production of an identical copy of the double-stranded DNA molecule when the gene is duplicated during cell division

REPRESSION—the inhibition of the synthesis of an enzyme, often resulting from accumulation of a biosynthetic end-product of the pathway in which the enzyme participates

RESPIRATORY ACIDOSIS—a decrease in pH of body fluids occasioned by excessive retention of carbon dioxide in the body (syn. *hypercapnic acidosis*)

RESPIRATORY CHAIN—a series of flavoproteins, hemoproteins (cytochromes), and nonheme iron proteins in the mitochondrion which act to transfer electrons from substrates to oxygen

RESPIRATORY CONTROL—the condition pertaining to oxidative phosphorylation, when energy demands upon the mitochondrion are low and the rate of electron transfer through the respiratory chain is strictly dependent upon the ADP concentration (syn. *acceptor control*)

RESPIRATORY INHIBITOR—a compound which specifically blocks one of the electron transferring reactions involved with substrate oxidation or the respiratory chain

RIBONUCLEIC ACID (RNA)—the polymer formed of ribose-containing nucleotides (AMP, CMP, GMP, UMP); it performs key roles in the biosynthesis of proteins in the ribosomes of cells

RIBOSOME—an assembly of RNA and protein molecules which acts to join together the amino acids aligned by messenger RNA during protein synthesis. Several ribosomes joined to one messenger RNA strand are termed a *polyribosome* or *polysome*.