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GOLDMAN'S
CECIL
MEDICINE

西氏内科学

第24版

内分泌与代谢疾病分册

LEE GOLDMAN
ANDREW I. SCHAFER

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Cecil

GOLDMAN'S CECIL MEDICINE

24TH EDITION

西氏内科学

（第24版）

内分泌与代谢疾病分册

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PREFACE

The 24TH Edition of *Goldman's Cecil Medicine* symbolizes a time of extraordinary advances in medicine and in technological innovations for the dissemination of information. This textbook and its associated electronic products incorporate the latest medical knowledge in formats that are designed to appeal to learners who prefer to access information in a variety of ways.

The contents of *Cecil* have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying normal physiology and pathophysiology of disease, now at the cellular and molecular as well as the organ level) and the *how* (now frequently based on Grade A evidence from randomized controlled trials). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert. Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient have diminished the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to counteract this tendency with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter. In addition to the information provided in the textbook, the Cecil website supplies expanded content and functionality. In many cases, the full articles referenced in each chapter can be accessed from the Cecil website. The website is also continuously updated to incorporate subsequent Grade A information, other evidence, and new discoveries.

The sections for each organ system begin with a chapter that summarizes an approach to patients with key symptoms, signs, or laboratory abnormalities associated with dysfunction of that organ system. As summarized in Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 100 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases but also for patients who may have undiagnosed abnormalities that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous editors of *Cecil Medicine* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, and Dennis Ausiello. As we welcome new associate editors—Wendy Levinson, Donald W. Landry, Anil Rustgi, and W. Michael Scheld—we also express our appreciation to Nicholas LaRusso and other associate editors from the previous editions on whose foundation we have built. Our returning associate editors—William P. Arend, James O. Armitage, David Clemmons, Jeffrey M. Drazen, and Robert C. Griggs—continue to make critical contributions to the selection of authors and the review and approval of all manuscripts. The editors, however, are fully responsible for the book as well as the integration among chapters.

The tradition of *Cecil Medicine* is that all chapters are written by distinguished experts in each field. We are also most grateful for the editorial assistance in New York of Theresa Considine and Silva Sergenian. These individuals and others in our offices have shown extraordinary dedication and equanimity in working with authors and editors to manage the unending flow of manuscripts, figures, and permissions. We also thank Faten Aberra, Reza Akari, Robert C. Brunham, Ivan Ciric, Seema Daulat, Gregory F. Erikson, Kevin Ghassemi, Jason H. Huang, Caron Jacobson, Lisa Kachnic, Bryan T. Kelly, Karen Krok, Heather Lehman, Keiron Leslie, Luis Marcos, Michael Overman, Eric Padron, Bianca Maria Piraccini, Don W. Powell, Katy Ralston, James M. Swain, Tania Thomas, Kirsten Tillisch, Ali Turabi, Mark Whiteford, and Y. Joseph Woo, who contributed to various chapters. At Elsevier, we are most indebted to Dolores Meloni and Linda McKinley, and also thank Cathy Carroll, Taylor Ball, Virginia Wilson, Linda Van Pelt, Suzanne Fannin, and Steve Stave, who have been critical to the planning and production process under the direction of Mary Gatsch. Many of the clinical photographs were supplied by Charles D. Forbes and William F. Jackson, authors of *Color Atlas and Text of Clinical Medicine*, Third Edition, published in 2003 by Elsevier Science Ltd. We thank them for graciously permitting us to include their pictures in our book. We have been exposed to remarkable physicians in our lifetimes and would like to acknowledge the mentorship and support of several of those who exemplify this paradigm—Robert H. Gifford, Lloyd H. Smith, Jr., Frank Gardner, and William Castle. Finally, we would like to thank the Goldman family—Jill, Jeff, Abigail, Mira, Daniel, and Robyn Goldman—and the Schafer family—Pauline, Eric, Pam, John, Evan, and Kate—for their understanding of the time and focus required to edit a book that attempts to sustain the tradition of our predecessors and to meet the needs of today's physician.

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APPROACH TO INBORN ERRORS OF METABOLISM

LOUIS J. ELSAS II

DEFINITION

Metabolism is a collective term for integrated biochemical processes that enables homeostasis for the organism by maintaining anabolic and catabolic flow of substrates to products. Inborn errors of metabolism refer to single gene disorders producing loss of function of a single protein that results in altered concentrations of linked metabolites in the reaction sequence.

HISTORY

In the early 20th century, Garrod recognized heritable blocks in normal human metabolic flow that conformed to mendelian mechanisms of inheritance. He first coined the term *inborn error of metabolism,* describing four diseases—alkaptonuria, albinism, cystinuria, and pentosuria. Garrod presumed that a patient expressing the full abnormality was homozygous for mutant alleles affecting a specific metabolic flow whereas the parents were heterozygous for this same inherited block but were clinically normal. The enzyme defect in alkaptonuria was not discovered until 50 years later, when homogentisic acid oxidase was found impaired in the liver and kidneys of patients with this disease. Twenty years ago, the gene for homogentisate 1,2-dioxygenase was cloned, and mutations causing altered function were defined.

Over the past two decades, advances in technology such as fast throughput, genome-wide DNA sequencing, tandem mass spectrometry, and bioinformatics have confirmed Garrod's postulate of chemical individuality and resulted in the discovery of more than 1321 catalogued inborn errors of metabolism, as well as vigorous research exploring normal and abnormal inherited variation in human metabolism for common conditions such as obesity and cancer. The implementation of public health–based newborn screening using these modern technologies defined the clinical power of genetics in presymptomatic prediction and prevention of more than 40 inborn errors.

PATHOBIOLOGY

Protein Diversity

Variations in human proteins do not usually produce disease. Heritable diversity in proteins within normal populations is required for optimal health (e.g., the ability of the immune system to produce γ-globulin in response to a wide range of antigenic epitopes). Nucleotide sequence variations in genes may produce different amino acid changes in the primary protein structure without producing a functional change. When no functional change occurs, the alteration is considered a *polymorphism.* The term *single nucleotide polymorphism* (SNP) is now used to define an individual's diversity after scanning the entire human genome. Continued research is trying to link genomic SNPs to regulatory RNA, messenger RNA, and protein and metabolic variations. Chromatographic separation of physiologic fluids followed by tandem mass spectrometry enables identification of the metabolomic effect of a given SNP on a wide range of molecules, including lipids, amino acids, phospholipids, and glycoproteins.

There are many molecular mechanisms producing normal protein diversity. Normal protein variation can occur through gene rearrangements, as exemplified by the formation of immunoglobins, which give rise to required variations in response to foreign antigens. Post-transcriptional, alternative splicing of RNA is another mechanism for protein variation. There are many examples of alternative splicing that provide organ specificity for protein isoforms. Post-translational modification of proteins produces diversity and is important in directing proteins to subcellular organelles, to the cell surface, or for secretion. Glycosylation of proteins directed to plasma membrane receptors is an example of this post-translational mechanism. As an example of the importance of these mechanisms, consider that humans have more than 250,000 functional proteins but less than 35,000 genes predicted from the human genome sequence. Added to this sequence diversity of proteins are recent biophysical observations that proteins undergo conformational plasticity that can alter their function.

TABLE 212-1 CLASSIFICATION OF PROTEIN FUNCTION BY LOCATION IN ORGANISM

Proteins act as follows:

1. Catalyze plasma membrane functions
   a. Substrate transport
   b. Cellular signaling (receptors)
2. Catalyze integrated metabolic pathways in the cytosol, lysosome, peroxisome, mitochondria, nucleus, and endoplasmic reticulum
3. Circulate in blood and provide and maintain various functions (clotting; metal, lipid, and vitamin transport; immunity; oxygen transport; regulation of proteases, hormones, and adhesion proteins)
4. Maintain structural integrity of organs and organelles (collagen, elastin, actin, dystrophin, and fibrillin)

TABLE 212-2 CLASSIC PATHOLOGIC MECHANISMS FOR INBORN ERRORS OF METABOLISM

1. Accumulation of substrates to toxic concentrations in a blocked catabolic reaction. *Examples:* maple syrup urine disease, galactosemia, glucose-galactose malabsorption, Fabry's disease, Gaucher's disease, urea cycle defects
2. Production of toxic byproducts through a normally minor pathway. *Examples:* tyrosinemia type I, adenosine deaminase deficiency
3. Deficiency of an end product in an anabolic pathway. *Examples:* albinism, orotic aciduria, scurvy, plasminogen deficiency
4. Loss of regulation resulting in overproduction of intermediates to toxic levels. *Examples:* congenital adrenal hyperplasia, acute intermittent porphyria, familial hypercholesterolemia

Mutations

The relatively rare circumstance in which a change in a protein impairs function is called a *mutation,* and it may produce an inborn error of metabolism. Naturally occurring mutations that produce pathology also provide insight into the functional role of normal proteins in human metabolism. Inborn errors of metabolism are classified here in accordance with the organ, cell, and subcellular location of normal protein function (Table 212-1) and the abnormal mechanisms that interfere with normal metabolic flow as a result of impaired proteins (Table 212-2).

Current diagnosis and therapy for inborn errors focus on relatively rare mutations in single genes that have major effects on disrupting metabolic flow. Current and future research will provide predictive tools for identifying variations in the genome and metabolome that produce sensitivity to the environment with onset of common illnesses of adults and an opportunity to intervene and prevent them. This concept is called *personalized medicine.*

The correlation of genes that are transcribed and translated approaches only 20% of the genome in any cell or organ. Network perturbation models for essential metabolic pathways are being defined, particularly in the context of drug-induced adverse events, where heritable variations are diagnosed by personalized genomic microarrays before the drug is given and thereby prevent adverse reactions by avoidance. Microarrays for genomic variation in the cytochrome P-450 genes are now commercially available and will assist in predicting some sensitivities to drugs. Similarly, genome microarrays to predict genetic variation producing early-onset heart, liver, eye, lung, and nervous system diseases, including cancers, are in development.

Pathophysiology

One important clinical aspect in defining the genetic component of a metabolic disease is that one can predict, intervene in, and prevent irreversible pathology by a variety of stratagems before irreversible disease is expressed. In general, the severity of an inborn error of metabolism depends on the degree of protein impairment rendered by the genetic mutation and the trauma induced by the environment. A "leaky" mutation may not be expressed until adulthood, whereas a complete block in the same metabolic pathway is lethal in infancy. The age at onset and severity of disease are a result of complex interactions of the gene, environment, or other genes that modify the underlying genetic susceptibility. The pathophysiologic mechanisms outlined in Table 212-2 may occur individually or may combine to produce loss in homeostasis and a disease state. The clinical manifestations are usually

pleiotropic, which means that one blocked enzyme reaction produces multiple dysfunctions at the organ level. An example is galactosemia, which causes cataracts, ovarian failure, liver disease, and central nervous system dysfunction. The phenotype (clinical outcome) is also affected not only by the specific genetic block but also by alternative metabolic pathways that may remove toxic precursors or supply deficient products of a blocked reaction. Outcome may be adversely affected by an alternative pathway that produces a toxic analyte, and a pathophysiologic mechanism may differ among organs. In galactosemia, the accumulation of galactose can produce excess intracellular galactitol through an alternative pathway catalyzed by aldose reductase and, consequently, cell death of optic lens fibers as a result of the osmotic effect of intracellular galactitol. Accumulation of galactitol causes cataracts, whereas accumulation of galactose 1-phosphate produces hepatic cell death, ovarian failure, and cerebellar dysfunction.

ERRORS IN PROTEINS THAT CAUSE DISEASES

Plasma Membrane Transporter Protein Mutations

Defects of Glucose Transporters

Many disorders are produced by mutant proteins that impair the transport of nutrients into and out of cells (Table 212-3). *Familial glucose-galactose malabsorption syndrome* exemplifies defective transporter proteins and results in the accumulation of nontransported glucose in the intestinal lumen with refractory diarrhea secondary to its osmotic effects. Direct evidence for genetic control of intestinal glucose transport in humans was obtained by in vitro studies of jejunal biopsy material from families in which the affected members expressed refractory diarrhea on ingesting D-galactose or D-glucose but not fructose. Pedigree analysis conformed to autosomal recessive inheritance. These data predicted a gene that coded for a stereospecific, sodium- and energy-dependent transporter protein in human jejunal (and proximal renal tubular) microvilli. Expression cloning of active glucose transport has now confirmed the presence of a family of glucose transporter genes, their deduced amino acid sequences, and specific codon changes producing the syndromes of familial glucose-galactose malabsorption and renal glycosuria. There are many inherited defects involving the plasma membrane transport of glucose that are caused by mutations of either active or facilitative glucose transport. Glucose transporters are a family of proteins whose definitions of function evolved after their cloning and molecular genetic analysis (Table 212-4). An insulin-responsive, facilitative glucose transporter (GLUT4) is not Na^+ dependent and is expressed primarily in insulin-responsive tissues (fat cells, skeletal muscle). More than one glucose transporter is expressed by most cells. The jejunal epithelial cell uses sodium-glucose cotransporter protein 1 (SGLT1) to concentrate glucose from its luminal surface into the cytosol, then effluxes glucose at its basal-lateral surfaces through GLUT2. GLUT2 is also involved in regulating the amount of glucose transported into β cells of the pancreas, a process that regulates glucose stimulation of insulin release. Indirect evidence suggests that mutations in the *GLUT2* gene are "sensitivity genes" involved in regulating insulin secretion.

Many other facilitative human glucose transporters have been identified by expressed sequence tags (EST) homology searches (GLUT 5, 6, 7, 8, 9, 10, 11, 12, 13). While GLUT5 and GLUT7 have functional assignments as a fructose transporter and as an exporter of glucose from the endoplasmic reticulum, respectively, the functions of these other glucose transporter isoforms are not clearly defined.

Plasma Membrane Receptor Protein Dysfunction

Parathyroid Hormone Resistance

Many diseases characterized by "hormone resistance" are caused by a family of proteins that function as receptors in the plasma membrane and as post-receptor transmitters of signals located in the cytosol and nucleus. The concept of failure to respond to hormone stimulation originated in the early 1940s with a description of *pseudohypoparathyroidism* (Chapter 253). Heritability of resistance to parathormone was suggested before the existence of parathormone receptors, hormone-sensitive adenylate cyclases, or guanine nucleotide-binding proteins was known.

TABLE 212-3 DISEASES CAUSED BY MUTATIONS IN PLASMA MEMBRANE TRANSPORTER PROTEINS

DISEASE	TISSUE AFFECTED	SUBSTRATE	MODE OF INHERITANCE	CLINICAL EXPRESSION
B_{12} malabsorption	Ileum	Vitamin B_{12}	Autosomal recessive	Pernicious anemia
Blue diaper syndrome	Gut	Tryptophan	Autosomal recessive	Hypercalcemia
Primary carnitine deficiency	Kidney + gut	Carnitine	Autosomal recessive	Hypoglycemia, hypotonia
Congenital chloridorrhea	Gut	Chloride	Autosomal recessive	Diarrhea, alkalosis
Cystic fibrosis	Apical epithelia	Chloride	Autosomal recessive	Lung, intestinal obstruction
Cystinuria	Kidney + gut	Cystine + lysine, arginine, ornithine	Autosomal recessive	Renal lithiasis (cystine)
Familial hypophosphatemic rickets	Kidney + gut	Phosphate	X-linked dominant	Rickets
Folate deficiency	Lymphocyte, erythrocyte	Methyltetrahydrofolate	Autosomal recessive	Aplastic anemia
Glucose-galactose malabsorption	Gut + kidney	Glucose and galactose	Autosomal recessive	Refractory diarrhea
Hartnup's syndrome	Gut + kidney	Neutral amino acids	Autosomal recessive (pellagra)	Nicotinic acid deficiency
Hereditary hypophosphatemic rickets	Kidney	Phosphate	Autosomal dominant	Growth restriction, rickets, phosphaturia
Hereditary renal hypouricemia	Kidney	Uric acid	Autosomal recessive	Urolithiasis (uric acid)
Hereditary spherocytosis	Erythrocyte	Sodium	Autosomal dominant or recessive	Hemolytic anemia
Hyperdibasic aminoaciduria (type I)	Kidney	Lysine, arginine, ornithine	Autosomal dominant	Symptoms of growth restriction?
Iminoglycinuria	Kidney + gut	Glycine, proline, hydroxyproline	Autosomal recessive	Benign? Pancreatitis
Isolated lysinuria	Kidney + gut	Lysine	Autosomal recessive	Growth failure, seizures
Lysinuric protein intolerance (type II)	Kidney, fibroblasts, hepatocytes, gut	Lysine	Autosomal recessive	Growth restriction, hyperammonemia, mental retardation
Methionine malabsorption	Gut	Methionine	Autosomal recessive?	Mental retardation, white hair, failure to thrive
Renal glycosuria	Kidney	Glucose	Autosomal recessive	Benign glycosuria
Renal tubular acidosis (type I)	Distal renal tubule	H^+ secretion, citrate, calcium	Autosomal dominant	Hypokalemia, growth restriction, nephrocalcinosis
Renal tubular acidosis (type II)	Proximal renal tubule	Bicarbonate	"Familial"	Hyperchloremic metabolic acidosis

TABLE 212-4 HUMAN GLUCOSE TRANSPORTERS

PROTEIN	kD (AA)	mRNA SIZE (kb)	CHROMOSOMAL LOCALIZATION	EXPRESSION IN TISSUE AND CELLS	FUNCTION	DISORDER
FACILITATIVE GLUCOSE TRANSPORTERS						
GLUT1	55 (492)	2.8	1p35→p31.3	Blood-brain barrier, erythrocyte, fibroblast	Basal glucose transport across most cells, including the blood-brain barrier	Seizures with low cerebrospinal fluid and normal blood glucose
GLUT2	58 (524)	2.8 3.4 5.4	3q26.1→q26.3	Liver, kidney, intestine, β cell of the pancreas	Low-affinity glucose transport	Defective insulin secretion in diabetes
GLUT3	54 (496)	2.7 4.1	12p13.3	Neurons, fibroblasts, placenta, testes	Basal glucose transport, high affinity	?
GLUT4	55 (509)	2.8 3.5	17p13	Fat, skeletal muscle, heart	Insulin-stimulated glucose transport	Defective insulin-stimulated transport, NIDDM?
CONCENTRATIVE GLUCOSE TRANSPORTERS						
SLGT1	75 (664)	2.2 2.6 4.8	22q11→qter	Intestine, kidney (medulla)	Intestinal absorption, renal reabsorption, high affinity (2 Na: 1 glucose)	Glucose-galactose malabsorption
SLGT2	76 (672)	2.4 3.0 3.5 4.5	16p11.2	Kidney (cortex)	Low affinity, high capacity (1 Na: 1 glucose)	Renal glycosuria

AA = amino acids; NIDDM = non-insulin-dependent diabetes mellitus.

In *Albright's hereditary osteodystrophy,* or *pseudohypoparathyroidism* (Chapter 253), a heterogeneous group of mutations affect the gene for the parathormone receptor's guanine nucleotide-binding protein ($G_{s\alpha}$), which links the receptor to adenylate cyclase and stimulates cyclic adenosine monophosphate when the receptor is occupied by parathormone. The gene for $G_{s\alpha}$ is located on chromosome 20q13, and deletions and missense mutations that produce Albright's hereditary osteodystrophy have been defined. Somatic mutations in arginine 201 of the same gene turn the $G_{s\alpha}$ protein constitutively "on" and produce another disease, McCune-Albright-Sternberg syndrome. Cells are mosaic for the mutation, and the syndrome includes nonossifying bone tumors and premature puberty.

Growth Hormone Resistance

Diseases caused by defective transmembrane binding and signaling include *Laron dwarfism,* which results from growth hormone receptor (GHR) defects (Chapter 231). The phenotypic characteristics are *proportionate dwarfism,* hypoglycemia, craniofacial dysmorphology with a doll-like face, balding, frontal bossing, truncal obesity, and wrinkled skin. In this disorder, the growth hormone concentration in blood is elevated, peripheral tissue responses are decreased, and insulin-like growth factor I concentrations in blood are low. An autosomal recessive mode of inheritance has been defined. Dominant or polygenic symmetrical growth restriction may result from mutations in nuclear transproteins, hypothalamic pituitary trophic proteins, growth hormone, GHR, and postreceptor signaling. The *GHR* gene is found on chromosome 5p13-p12, and many different mutations in this gene account for disorders of stature.

Familial Hypercholesterolemia

Familial hypercholesterolemia defines a phenotype of autosomal dominant hypercholesterolemia and early-onset heart disease (Chapter 213). This disorder affects an estimated 1 in 500 individuals in the general population. An autosomal dominant mode of inheritance for early-onset adult heart disease is caused by many different mutations in the trafficking and function of low-density lipoprotein (LDL) cholesterol receptors. Dysfunction of LDL receptors results in a loss of the cell's ability to downregulate endogenous cholesterol synthesis and incorporate LDL cholesterol into cells. Increased intravascular accumulation of LDL cholesterol results in atherosclerosis and heart disease before the sixth decade of life (see Table 212-2).

Errors of Insulin Resistance

Leprechaunism

Leprechaunism has become a prototypical inborn error of severe insulin resistance and loss of cellular signal transduction through the insulin receptor. Affected infants have low birthweight, acanthosis nigricans, cystic changes in organs, and loss of glucose homeostasis. Affected patients have remarkably elevated plasma insulin concentrations greater than 500 mIU/mL. Specific impairment in iodine-125-labeled insulin binding is evident in cells cultured from patients, and a spectrum of mutations produces a variety of severe insulin-resistant syndromes (leprechaunism, Rabson-Mendenhall syndrome, and type A diabetes with acanthosis nigricans). Obligate heterozygotes (parents) of patients with leprechaunism have partially impaired insulin binding and glucose tolerance curves suggesting type 2 diabetes mellitus. The insulin receptor transduces its signal by phosphotransfer to the insulin receptor signal protein 1 (IRS-1), and a cascade of downstream phosphorylations occurs, leading to stimulation of glucose transport.

Impaired Cytosolic Enzymes

Inborn errors affecting proteins of the cytosolic compartment within a cell are the more "traditional" inborn errors of metabolism (Table 212-5). They impair the catalytic reactions of anabolic or catabolic pathways and are usually classified by the class of biochemical involved, such as impairment of glucose, lipid, fatty acid, amino acid, purine, organic acid, vitamin, or drug metabolism.

Phenylketonuria

Phenylalanine is essential for growth, and its anabolic products include tyrosine, thyroid hormone, adrenergic neurotransmitters, and melanin. *Phenylketonuria* (PKU) is caused by mutations in the gene encoding phenylalanine hydroxylase, the first enzyme in this anabolic flow that catalyzes tyrosine production. PKU may also occur if coenzymes are deficient in this reaction, such as dihydropteridine reductase or enzymes involved in biopterin biosynthesis.

Albinism

Albinism is an example of an inborn error in an anabolic pathway in which the pathophysiologic mechanism is related directly to the lack of an end product (see mechanism 3, Table 212-2). Tyrosine is converted by the action of a cytosolic tyrosinase first to dopa and then to dopamine. Dopamine can be converted either to the red-yellow pigment pheomelanin or to the black-brown pigment eumelanin. These reactions occur in the melanosomes produced in melanocytes and exported to keratinocytes. Color of skin is an inherited factor that depends on many genes (polygenic) and is a function of the intensity of the pigment in the skin and not the number of melanocytes, which is constant for all humans. Although skin color is a polygenic trait, single genes can have a profound effect on this color, as evidenced by the albino phenotype. In humans, *oculocutaneous albinism* (OCA) is inherited as an autosomal recessive trait. X-linked forms of *ocular albinism* also exist. Individuals with OCA are classified as tyrosinase negative or positive for tyrosine activity in hair bulbs. Tyrosinase-negative individuals form no pigment. The gene for tyrosinase has been localized to chromosome 11q14, and many mutations have been defined. A tyrosine-positive OCA has been associated

TABLE 212-5 SOME DISEASES CAUSED BY IMPAIRED CYTOSOLIC ENZYMES

DISORDER	ENZYME DEFECT	PHENOTYPE	INHERITANCE
CARBOHYDRATES			
Fructosuria	Fructokinase	Benign	Autosomal recessive
Hereditary fructose intolerance	Fructose 1-phosphate aldolase	Liver dysfunction, early death	Autosomal recessive
Galactosemia	Galactose 1-phosphate uridyltransferase	Liver dysfunction, cataracts, sepsis, mental retardation, death	Autosomal recessive
Hereditary fructose-1,6-*bis*-phosphate deficiency	Fructose-1,6-*bis*-phosphatase	Apnea, ketosis, lactic acidosis	Autosomal recessive
AMINO ACIDS			
Phenylketonuria	*p*-Hydroxyphenylalanine hydroxylase	Mental retardation (teratogenic)	Autosomal recessive
Tyrosinemia			
Type II	Tyrosine aminotransferase	Palmar bullae, corneal lesions	Autosomal recessive
Type I	Fumarylacetoacetate hydrolase	Succinyl acetone accumulation	Autosomal recessive
Homocystinuria	Cystathionine β-synthase	Marfanoid habitus, arterial thrombosis, lens dislocation, mental retardation	Autosomal recessive
Hyperornithinemia	Ornithine aminotransferase	Gyrate atrophy of the retina	Autosomal recessive
Lesch-Nyhan syndrome	Hypoxanthine phosphoribosyltransferase	Neurologic dysfunction with self-destructive tendency	X-linked

with an autosomal recessive gene located on chromosome 15q11-13 (the P gene), and X-linked ocular albinism is caused by *OCA1* gene mutations. Wide variation in the phenotypic expression of albinism, ranging from severe neurologic deficiency with ocular and sarcomatous skin cancers to mild cosmetic problems, has been reported. Therapy requires total body skin protection and eye avoidance of ultraviolet light.

Errors of the Urea Cycle (Cytosol and Mitochondrial Interaction)

Inborn errors of the urea cycle are represented by defects in the integration of anabolic and catabolic pathways and the distribution of catalytic proteins between mitochondria and cytosol. The role of the urea cycle is to convert ammonia, a byproduct of protein breakdown, to urea and to synthesize arginine and ornithine. Reactions to complete this anabolic cycle require mitochondrial enzymes, cytosolic enzymes, and mitochondrial transporter proteins. Inherited disorders affecting the function of these proteins are known. Individuals with defects in any of the enzymes have varying degrees of hyperammonemia caused by protein ingestion or a nutritional state in which muscle is catabolized. With the exception of the gene for ornithine transcarbamylase found on the short arm of chromosome X, the other proteins are encoded on autosomes, and defects are inherited as autosomal recessive traits. Many principles of diagnosis and therapy for inborn errors of metabolism are exemplified by disorders of the urea cycle.

Errors in Mitochondrial Proteins

A group of inborn errors of metabolism are caused by mutations in both mitochondrial and nuclear genes that encode mitochondrial proteins. Collectively, they are considered disorders of organic acid metabolism (Table 212-6). Branched-chain α-ketoacid dehydrogenase is a multienzyme complex located on the matrix side of the mitochondrial inner membrane in all tissues. When any of these proteins is impaired, the autosomal recessive disorder *maple syrup urine disease* may result. In addition to nuclear-encoded genes, 13 proteins of mitochondrial complexes involved in oxidative phosphorylation are encoded in the mitochondrial DNA genome. Only complex II is encoded entirely by the nuclear genome. A wide range of disorders affecting the eye, brain, and muscle are caused by mutations in mitochondrial DNA that impair oxidative phosphorylation. The inheritance pattern of disorders encoded by the mitochondrial genome is distinguished from disorders caused by mutations in nuclear DNA by being transmitted through an affected mother to all of her offspring. Males do not transmit mitochondrial mutations to their offspring, hence the term *maternal inheritance.* Because there are about 10,000 mitochondrial genomes per cell, variation in disease expression is caused by differences in the ratio of mutant to normal mitochondrial genomes *(heteroplasmy)* and the environment.

Lysosomal Disorders

Another group of inborn errors of metabolism are collectively categorized as *lysosomal disorders* (Chapter 215) to indicate the subcellular localization of these enzymes that function in this acidic environment. Most of these enzymes are involved in the breakdown of endocytosed membrane components, and when defective, their nondegraded substrates accumulate in the lysosomes and macrophages of affected organs. Enzyme replacement therapy and substrate deprivation therapy are available interventions for some of these disorders.

TABLE 212-6 ORGANIC ACIDEMIAS: DISORDERS OF METABOLISM BY MITOCHONDRIAL PROTEINS

DISORDER	ENZYME DEFECT	INHERITANCE
Isovaleric acidemia	Isovaleryl-CoA dehydrogenase	Autosomal recessive
Methylcrotonic aciduria	3-Methylcrotonyl-CoA carboxylase	Autosomal recessive
Glutaconic aciduria	3-Methylglutaconyl-CoA hydratase	Autosomal recessive
Glutaric aciduria (1)	3-Hydroxy-3-methylglutaryl-CoA lyase	Autosomal recessive
Mevalonic aciduria	Mevalonate kinase	Autosomal recessive
Thiolase deficiency	2-Methylacetoacetyl-CoA thiolase	Autosomal recessive
Isobutyric aciduria	3-Hydroxyisobutyryl-CoA deacylase	Autosomal recessive
Propionic aciduria	Propionyl-CoA carboxylase	Autosomal recessive
Methylmalonic aciduria	Methylmalonyl-CoA mutase	Autosomal recessive
Lactic acidosis	Pyruvate carboxylase Pyruvate dehydrogenase	Autosomal recessive
Acyl-CoA dehydrogenase deficiencies	Short-, medium-, and long-chain fatty acyl-CoA dehydrogenase	Autosomal recessive
Branched-chain α-ketoacidemia	Branched-chain α-ketoacid dehydrogenase	Autosomal recessive
Glutaric acidemia type II	Electron transfer factor deficiency	Autosomal recessive
Leber's optic atrophy	Mitochondrial oxidative phosphorylation complexes	Maternal
Myoclonic epilepsy and ragged red fibers	Mitochondrial oxidative phosphorylation complexes	Maternal
Leigh's disease	Mitochondrial oxidative phosphorylation complexes	Maternal

I-Cell Disease

I-cell disease is an inborn error of post-translational processing of proteins directed to the lysosome. Clarification of this pathophysiology led to an understanding of the mechanisms by which lysosomal enzymes are trafficked

and polarized through phosphorylation to remain in the acidic lysosomes. Patients with I-cell disease have inherited defects in the recognition markers required to direct enzymes to the endocytic receptor of the plasma membrane and to their capture in the acidic milieu of the lysosome. Patients lack all cellular lysosomal enzymes. Instead, empty lysosomes look like inclusion bodies ("I cell"). The misdirected lysosomal enzymes are secreted and are present in excess in plasma but are missing from cells. These extracellular enzymes were found to lack mannose 6-phosphate residues, and this observation led to an understanding of the post-translational mechanisms by which enzymes are directed to the lysosome and recaptured into endosomes by adding phosphorylated mannose to their protein structure. Individuals with I-cell disease lack this phosphotransferase activity.

Disorders of Mucopolysaccharides and Gangliosides

Inborn errors affecting single enzymes in the degradative pathway for mucopolysaccharides and gangliosides helped define the steps required for the breakdown of these complex macromolecules. Disorders of mucopolysaccharide metabolism include Hurler's syndrome; Scheie's syndrome; Hunter's syndrome; Sanfilippo's syndrome types A, B, C, and D; Morquio's syndrome types A and B; and Sly's syndrome (Chapter 268). Disorders of ganglioside metabolism include Fabry's disease, Gaucher's disease, Niemann-Pick disease (Chapter 215), Tay-Sachs disease, I-cell disease, fucosidosis, mannosidosis, sialidosis, and aspartylglycosaminuria.

Peroxisomal Diseases

Another group of inborn errors of metabolism defined by altered organelle function are *peroxisomal diseases* (Table 212-7). Peroxisomes are radiodense organelles, 0.5 to 1 nm in diameter, bounded by a single trilaminar membrane. Anabolic and catabolic reactions occur in this organelle. Primary pathways synthesize plasmalogens (unique fatty acids containing vinyl ethers), cholesterol, and bile acids. Other biosynthetic reactions include gluconeogenesis from amino acids and the formation of oxalic acid by the action of alanine-glyoxylate aminotransferase. Catabolic reactions include breakdown of hydrogen peroxide by peroxisomal catalase, a traditional protein of the peroxisome; polyamine oxidation; purine breakdown; ethanol oxidation; hydroxylation of phytanic acid; and degradation of pipecolic acid. A major function of the peroxisome is β-oxidation of very-long-chain fatty acids (>24 carbons). Diagnosis of these disorders entails finding an excess of very-long-chain fatty acids but reduced plasmalogen in blood.

An understanding of the importance of many reactions that occur in the peroxisome has come from identifying patients with either defects in individual biochemical pathways or lack of peroxisomes. The targeting signal for peroxisomal proteins may lie in their carboxyl-terminal end, and mutations in alanine-glyoxylate aminotransferase have resulted in mistargeting of this enzyme to mitochondria with consequent *familial hyperoxaluria.*

Errors In Nuclear Proteins

Several inborn errors are caused by abnormalities in proteins that function in the nucleus and are involved in gene expression or DNA repair (see class 2, Table 212-1). Patients expressing these inherited disorders carry a high risk for the development of cancer. Among these inborn errors of DNA repair are rare disorders, such as *xeroderma pigmentosum, Bloom's syndrome, ataxia-telangiectasia,* and *Fanconi's anemia;* diseases associated with early aging, such as *progeria, Cockayne's syndrome,* and *Werner's syndrome;* and more common adult-onset *nonpolyposis colon cancer.* Collectively, the disorders show increased sensitivity and delayed repair of DNA damaged as a result of ultraviolet, x-ray, or alkylating cross-link mechanisms. Disorders of nucleotide expansion of repeating elements such as -CGG- in the promoter region of the fragile-X protein (FMR1) result in cytosine methylation that turns off FMR1 protein expression with consequent dysregulation of the RNAs to which FMR1 binds.

Errors in Blood-Circulating Proteins

Many inborn errors involve proteins that circulate in blood (see class 3, Table 212-1). Stable circulating proteins in blood perform a variety of functions, including immunologic, hemostatic, regulatory, hormonal, and interorgan transport of trace metals, lipids, and other nutrients. Some inherited disorders affecting circulating proteins are tabulated in Table 212-8. Proteins involved in oxygen transport, coagulation, and immunity are detailed in other chapters, but the pathophysiologic mechanisms and genetic approaches of screening, diagnosis, and intervention to restore homeostasis and prevent an expected disease state make them appropriate to consider here as inborn errors of metabolism.

Abnormal Matrix Proteins

Abnormal matrix proteins produce inborn errors, such as Marfan syndrome (fibrillin), osteogenesis imperfecta (collagen type I) (Chapter 268), spondyloepiphyseal dysplasia (collagen type II), and Sachs' disease (collagen type III). These disorders exemplify class 4 of inborn errors of metabolism (see Table 212-1). The enzymes involved in post-translational processing of these proteins can also cause these syndromes. An example is Ehlers-Danlos syndrome (Chapter 268) type VI, in which procollagen lysyl hydroxylase

TABLE 212-7 INBORN ERRORS OF PEROXISOMES

NAME	GENE DEFECT	ABNORMAL ANALYTES
DISORDERS OF BIOGENESIS		
Zellweger's spectrum	*PEX* 1, 2, 3, 5, 6, 10, 12, 13, 14, 16, 19, 26 *DLP1*	Increased plasma very-long-chain fatty acids; bile acids intermediates, phytanic and pipecolic acids Decreased erythrocyte plasmalogen
Rhizomelic chondrodysplasia punctata, type I	*PEX* 7	Increased plasma phytanic acid Decreased erythrocyte plasmalogen
DISORDERS OF β-OXIDATION		
X-linked adrenoleukodystrophy Acyl CoA oxidase deficiency Methylacyl CoA racemase deficiency	*ABCD1* *ACOX1* *AMACR*	Increased plasma very-long-chain fatty acids Increased plasma very-long-chain fatty acids Increased plasma bile acid intermediates phytanic and pristanic acids
DISORDER OF PLASMALOGEN BIOSYNTHESIS		
Dihydroxyacetone phosphate acyltransferase deficiency	*GNPAT*	Decreased erythrocyte plasmalogen
DISORDER OF α-OXIDATION		
Refsum's disease	*PHYH*	Increased plasma phytanic acid only
DISORDER OF GLYOXALATE METABOLISM		
Hyperoxaluria, type I (alanine glyoxylate aminotransferase misplacement)	*AGXT*	Oxaluria

TABLE 212-8 SOME INBORN ERRORS OF PROTEINS THAT CIRCULATE IN BLOOD

FUNCTIONAL CLASS	PROTEIN	PHENOTYPE
Transport	Ceruloplasmin	Wilson's disease
	Albumin	Analbuminemia
	Hemoglobin	Hemoglobinopathies
	α-Lipoprotein	Analphalipoproteinemia
	β-Lipoprotein	Abetalipoproteinemia
	Transcobalamin II	Megaloblastic anemia
Hormones	Growth hormone	Pituitary dwarfism
	Insulin	Diabetes mellitus (insulin dependent)
	Somatomedin	Pituitary dwarfism
Coagulation	Factors I-XIII	Coagulopathies
	Kininogen	Kininogen deficiency
	Prekallikrein	Prekallikrein deficiency
Immune system	Complement components	Hypocomplementemias
	Immunoglobulins	Hypogammaglobulinemias
Inhibitors	α_1-Antitrypsin	Pulmonary emphysema and/or cirrhosis
	C1 esterase inhibitor	Angioneurotic edema
Drugs	Pseudocholinesterase	Prolonged paralysis after succinylcholine (Anectine) exposure

TABLE 212-9 APPROACHES TO TREATING INBORN ERRORS OF METABOLISM

Genetic counseling: prospective therapy
Diagnosis, recurrence risk assessment, informational transfer, support for resource allocation, identification of and intervention for "at-risk" relatives

Reproductive alternatives
Contraception, abstinence, artificial insemination, in vitro fertilization, risk taking with or without prenatal monitoring

Environmental engineering
Avoiding the offending agent
Supplemental physical, speech, occupational therapy

Metabolic management
Promote anabolism
Limit precursor of toxic substrate
Detoxify through alternative metabolic route
Provide feedback inhibitor
Provide supraphysiologic amounts of vitamin precursor

Molecular management
Provide gene expression and protein production
Provide stop codon read-through
Provide chaperone for misfolded protein

Protein and enzyme replacement
Infuse engineered enzyme
Provide clotting factors and peptide hormones
Transplantation
- Organ transplantation
- Bone marrow transplantation
- Stem cell transplantation (adult, hematopoietic, embryonic, nuclear transfer)

Genetic engineering
Somatic gene therapy
- Random insertion
- Homologous recombination (site specific)

Germline therapy

deficiency produces poorly hydroxylated lysyl residues in collagen. Inborn errors of matrix proteins are exemplified by disorders of collagen metabolism. More than 20 different genes dispersed on nine chromosomes are currently known to code for more than 13 different types of collagen. Abnormal proteins of matrix such as fibrillin 1 in the aorta may cause aberrant transforming growth factor-β signaling, inflammation, and consequent cystic medial necrosis with aortic dissection.

TREATMENT

Rx

Because the metabolic diseases considered in this chapter have in common causation by genes of large effect that disrupt normal homeostasis, we can consider a general approach to their treatment, as outlined in Table 212-9. The level at which therapy is rendered depends on the level of understanding of the pathophysiologic mechanisms producing disease and the interventional methods available.

Genetic Counseling

Genetic counseling is a unique and fundamental aspect of the management of inherited metabolic diseases and is used for all inherited diseases, even those whose mechanisms are not yet understood and for which no other treatment is available. Patients, their parents, and relatives usually ask questions such as the following: Why did this disease occur? Will this disease happen to me or my children? Can it be cured or prevented? Genetic counseling tries to answer these questions through processes involving probabilities derived from pedigree analysis. One cannot overemphasize the importance of an accurate family history, clinical diagnosis, and prognosis. A genetic discriminant is necessary for other family members before entering into formal genetic counseling. The genetic discriminant can be at the clinical, histologic, biochemical, or molecular level and must define whether an individual family member has or has not inherited the mutant allele or alleles. Transferring information about the burden of the phenotype, variation of clinical outcome including genotype-phenotype associations, and recurrence risks are important components of genetic counseling.

Environmental Engineering

Environmental engineering is the most commonly used approach to preventing disease in patients affected by inherited metabolic disease. Environmental factors (nutritional intake, exposure to toxins, sun, stress, climatic variation, and drug therapy) may produce a disease state in individuals who have inherited single genes or polygenic susceptibility to specific environmental stress. Newborn screening for galactose 1-phosphate uridyltransferase deficiency identifies infants susceptible to accumulation of galactose 1-phosphate, if they ingest human or cow milk. Restriction and replacement of lactose with sucrose save the lives of infants with galactosemia. Pharmacogenetic disorders exemplify the simple treatment of *avoidance* when the genetic susceptibility is identified. Health can be viewed as a continual adaptation between the genes and the environment. Environmental engineering is a form of genetic therapy in which individual genetic susceptibility is identified and the environment is altered to provide optimal health for the individual's unique genetic constitution. The frequency of diseases caused by genetic susceptibility to the environment varies from rare to 100%. *Scurvy* develops in all humans unless ascorbate is provided in the diet because we are unable to convert glucuronic acid to glucuronolactone and ascorbate. Humans and primates lost this anabolic pathway during evolution. By contrast, humans can usually synthesize tetrahydrobiopterin, a cofactor in many hydroxylase reactions, including phenylalanine hydroxylase. In some rare diseases (about 1 in 500,000) of increased blood phenylalanine and severe neurodegeneration, biopterin is not synthesized. Tetrahydrobiopterin can be provided to ameliorate this decreased product from the metabolic block.

Medical Therapy

Nutritional management and chemoprevention involve correction of the metabolic imbalance and return of the patient to homeostasis through diet manipulation and drug therapy. Many of the diseases mentioned in this chapter are amenable to several concurrent therapeutic approaches listed in Table 212-9.

For example, in disorders of the urea cycle, protein intake is limited, and anabolism is encouraged to reduce accumulation of ammonia from either protein intake or catabolism of lean body mass. Arginine is supplemented to provide deficient product of the blocked reaction, and alternative pathways are induced for nitrogen excretion. The latter therapy is made possible by a ubiquitous enzyme, *N*-glycine-acylase, that forms adducts with benzoic acid and glycine to produce hippuric acid, which is excreted, thereby eliminating one nitrogen molecule. Phenylacetylglutamine transferase is also used by giving phenylacetate to produce and excrete two nitrogen molecules as phenylacetylglutamine. Orotic aciduria is caused by mutations in the bifunctional enzyme orotate phosphoribosyltransferase-orotidine-5′-monophosphate decarboxylase. The disease process, which includes severe anemia and immune deficiency, is caused by a deficient end product, uridine, and is treated by replacing 100 to 200 mg/kg/day of uridine, up to 1 g three times daily (orally). Feedback inhibition of pituitary adrenocorticotropic hormone production is important in treating congenital adrenal hypertrophy with replacement doses of hydrocortisone to prevent virilization from overproduction of testosterone.

Vitamin dependency disorders require supraphysiologic amounts of a specific vitamin as the precursor for an active cofactor required for holoenzyme function. Many vitamin-dependent metabolic disorders are known and include pyridoxine (vitamin B_6)–dependent homocystinuria (Chapter 216) and vitamin C–dependent Ehlers-Danlos syndrome type VI (Chapter 268). In vitamin B_6–dependent homocystinuria, mutant cystathionine β-synthase is stabilized to biologic degradation when saturated with pyridoxal phosphate. Others include vitamin B_{12}–dependent methylmalonic aciduria, thiamine-dependent maple syrup urine disease, biotin-dependent multiple carboxylase deficiency, and biopterin-dependent hyperphenylalaninemia. Some blocked metabolic reactions can be augmented by inducing transcription of their gene. Phenobarbital and several other drugs induce hepatic uridine diphosphate glucuronyl transferase gene expression and reduce the accumulation of unconjugated bilirubin in Gilbert's syndrome (Chapter 149). In tyrosinemia type I, the drug NTBC blocks the catabolic pathway by which tyrosine produces the toxin, succinylacetone, when fumarylacetoacetate hydrolase is defective, and successfully prevents hepatic and renal dysfunction.

If the specific protein or enzyme has been purified and engineered to function in its specified organ or subcellular organelle, it can be used to treat an inherited metabolic disease. One good example is glucocerebrosidase, the enzyme that is impaired in Gaucher's disease (Chapter 215). This enzyme has been purified in large quantities from the placenta and from recombinant mammalian cells. The secreted enzyme is biochemically engineered to contain the mannose recognition site for cellular uptake by macrophages into lysosomal compartments. It has been used successfully to prevent and reverse the hypersplenism, pancytopenia, and bone disease of type I Gaucher's disease (Chapter 215). Many proteins are now made through recombinant techniques to treat metabolic disease. Enzymes now include glucocerebrosidase, factor VIII for hemophilia type A, growth hormone for growth hormone deficiency, α-galactosidase to treat Fabry's disease, iduronidase for Hurler-Scheie syndrome, and acid maltase for Pompe's disease. Several other engineered proteins used to treat inherited metabolic disease include 1-deamino-8-D-arginine vasopressin to treat X-linked recessive diabetes insipidus and recombinant α_1-antitrypsin made stable by inactivating methionine-385 for the treatment of α_1-antitrypsin deficiency. Some enzymes, such as adenosine deaminase, have been modified with polyethylene glycol to reduce immunogenicity and

prolong their biologic half-life in blood. It is used to treat severe combined immunodeficiency. Chemoprevention is being developed for heritable cancers. Cyclooxygenase-2 inhibitors may prevent progression of colon polyps to adenocarcinoma, and estrogen receptor inhibitors may ameliorate some forms of breast cancer.

Treatment using chaperones and substrate reduction therapy represent novel approaches for lysosomal disorders in which substrate accumulation in brain cannot be reduced by intravenous therapy of bulky enzymes that do not cross the blood-brain barrier. Small molecules that inhibit ceramide glucosyltransferase reduce the rate of glucosylceramide accumulation in Gaucher's disease types II and III as well as glycosphingolipids that accumulate in the brain of patients with Niemann-Pick disease type C (Chapter 215). Rhodamine B inhibits glucosamine-glycans accumulation in mucopolysaccharidosis. Chaperones are used to protect misfolded enzymes that will otherwise be destroyed before reaching their lysosomal compartment. Structural analogues of substrates for genetically misfolded α-galactosidase (Fabry's disease) (Chapter 215) are in trial as chaperones for missense mutations. Future use of "read-through molecules" for mutations producing stop codons are in trial. For example, gentamicin will read through stop codons in *CFTR* (cystic fibrosis) and dystrophin (Duchenne muscular dystrophy) genes.

Surgical Therapy

Surgical intervention may be a useful adjunct for treating heritable disorders. Stabilization of hypoplastic cervical vertebrae may prevent quadriparesis or death in a variety of chondrodysplasias and mucopolysaccharidoses accompanied by hypoplasia of the odontoid process or atlantoaxial instability. In Marfan syndrome (Chapter 268), careful monitoring of aortic root diameter with surgical removal of the aorta and prosthesis may prevent lethal aortic dissection. Losartan therapy may prevent the inflammatory response to mutant fibrillin and mitigate the need for this surgery. Evaluation of polyps and early colectomy may prevent disseminated adenocarcinoma in families with the autosomal dominant forms of familial polyposis coli. Molecular diagnosis of mutations in the *APC* gene helps identify at-risk family members and reassure members who did not inherit the mutant allele. Preventing heritable cancer by surveillance and early surgical excision is therapeutic for medullary thyroid carcinoma, Wilms' tumors, and the neurofibromas of von Recklinghausen's disease. Other examples of the benefit of preventive surgery for inborn errors include splenectomy for hemolytic anemias associated with spherocytosis, pyloroplasty for pyloric stenosis, and mastectomy and oophorectomy for patients with *BRCA1* or *BRCA2* mutations.

Transplantation

Organ transplantation (Chapter 48) for metabolic disorders that are lethal and have no other available therapy may be life-saving. Liver transplantation is an option in the long-term treatment of patients with urea cycle defects. Stem cells from cord blood (Chapter 181) are being used to treat neurodegenerative disorders in early childhood. Cloned embryonic cells or stem cells that are still naïve to adult antigens and adult bone marrow are promising therapeutic agents in research. Adult stem cells from differentiated organs are proving useful in improving myocardial function after heart failure from infarction.

Several principles are required for successful treatment of an inherited metabolic disorder by organ transplantation: (1) the normal enzyme, protein, or function must be provided by the transplanted organ or adult stem cell; (2) the pathogenesis must be understood to decide whether the affected organ should be removed; and (3) the host must be immunologically tolerant to the gene product being introduced, in addition to the transplanted organ itself. These principles are particularly relevant when displacement bone marrow transplantation is used. In the latter, normal donor stem cells differentiate and provide their enzymes to the recipient's reticuloendothelial system. Diseases associated with accumulation of products in the central nervous system are not yet ameliorated by bone marrow transplantation, although accumulation in bone, liver, and spleen is reduced. In one group of metabolic diseases, stem cell bone marrow transplantation is performed to prevent leukemia caused by inherited syndromes that are associated with defective DNA repair, such as Fanconi's anemia, Bloom's syndrome, and ataxia-telangiectasia. Liver or kidney transplantation can reverse growth and developmental delay in type I glycogen storage disease, cystinosis, acute intermittent porphyria, type I tyrosinemia, Fabry's disease, oxalosis, and non-neuronotropic lysosomal storage diseases. Lung transplantation has been successful for cystic fibrosis and α_1-antitrypsin deficiency, and prophylactic aortic transplantation has prevented aortic dissection in patients with Marfan syndrome.

Somatic Gene Therapy

Somatic cell gene therapy (Chapter 43) to treat patients with genetic disease continues in the arena of clinical research. Numerous laboratories throughout the world are actively designing strategies by which exogenous DNA can be incorporated into the genomic DNA of specific organs to provide a missing gene function and its protein product. Somatic gene therapy for many inherited metabolic diseases continues to be a goal of the future and awaits a nontoxic, stable vector with which to transfer normally transcribed genes.

SUGGESTED READINGS

Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet.* 2010;376:1417-1427. *Review of diet, tetrahydrobiopterin therapy, and possible future treatments.*

GeneTests and GeneClinics. http://www.genetests.org/cgi-bin. Accessed Nov. 30, 2010. *This newly merged website offers updated information for physicians and investigators on the availability of diagnostic tests and reviews of diagnosis and intervention for many inherited metabolic disorders.*

National Center for Biotechnology. http://www3.ncbi.nlm.nih.gov/Omim. *The database can be searched by disease name and contains updated information on the history, biochemistry, and molecular biology of all inherited disorders caused by mutations in single genes.*

Society for Inherited Metabolic Disorders. http://www.simd.org. Accessed Nov. 30, 2010. *This website has links to an international collection of websites dealing with diagnosis and treatment guidelines for inherited metabolic disorders. Includes patient support groups.*

213 DISORDERS OF LIPID METABOLISM

CLAY F. SEMENKOVICH

Despite considerable progress, morbidity and mortality from vascular diseases are substantial and are likely to increase, given the epidemic of lipid-associated diseases such as obesity and diabetes, as well as the export of Western habits to the developing world. Recently discovered mediators of lipid metabolism continue to provide new insight into the mechanisms causing abnormal levels of cholesterol and triglycerides, among the most common problems encountered by practicing physicians.

COMPONENTS OF LIPID TRANSPORT

Cholesterol and Triglycerides

Cholesterol is a critical constituent of eukaryotic cell membranes and the precursor for the synthesis of steroid hormones such as cortisol, vitamin D, progestins, estradiol, and testosterone. Triglycerides carry fatty acids, nutrients that are used preferentially by muscle tissue and are especially important as an energy source in the fasting state. Because both cholesterol and triglycerides are essentially insoluble in water, the lipid transport system evolved to transport fats from one site to another through an aqueous environment.

Lipoproteins

Cholesterol and triglycerides are transported in lipoproteins (Table 213-1), spherical particles that differ in size and composition, depending on their site of origin. Each particle is composed of a central core consisting of cholesteryl esters (the product of an esterification reaction between the polar cholesterol molecule and a fatty acid) and triglycerides, both nonpolar compounds. Free cholesterol, phospholipids, and apolipoproteins are found on the particle surface.

Chylomicrons and their remnants are the largest lipoproteins. Produced by the intestine, these particles carry fats that are absorbed from the diet. Their residence time in the circulation after a meal is short, on the order of minutes in healthy people. Chylomicrons are large and light; that is, their density is low. Because fat floats on water, particles with high fat and low protein content have lower density. Very low density lipoprotein (VLDL) is a triglyceride-rich particle produced by the liver. The removal of triglycerides from VLDL converts this particle to intermediate-density lipoprotein (IDL), which is subsequently metabolized to yield low-density lipoprotein (LDL, popularly known as "bad cholesterol"). A covalent modification of the apolipoprotein (apo) in LDL, apo B100, results in the formation of lipoprotein (a). High-density lipoprotein (HDL, or "good cholesterol") is formed in the blood as a byproduct of the metabolism of triglyceride-rich lipoproteins and the acquisition of esterified cholesterol from peripheral tissues.

Apolipoproteins

Apolipoproteins are amphipathic molecules capable of interacting with both the lipids of the lipoprotein core and the aqueous environment of the plasma. They function as biochemical keys, allowing lipoprotein particles access to specific sites for the delivery, acceptance, or modification of lipids. Major apolipoproteins, their chromosomal locations with sequence accession numbers, and functions are shown in Table 213-2. Serum measurements of apolipoproteins may have clinical utility. For example, increased levels of apo B and decreased levels of apo AI are associated with vascular disease. Apo B48, specific for gut-derived particles, derives its name from the fact that it

TABLE 213-1 LIPOPROTEIN CHARACTERISTICS

LIPOPROTEIN	APOLIPOPROTEIN CONTENT	MAJOR LIPIDS	SIZE (NM DIAMETER)	DENSITY (G/ML)
Chylomicrons, chylomicron remnants	Apo B48, apo E, apo AI, apo AII, apo AIV, apo CII, apo CIII	Triglycerides from diet	80-500	<<1.006
VLDL	Apo B100, apo E, apo CII, apo CIII	Triglycerides from liver	30-80	<1.006
IDL	Apo B100, apo E	Cholesteryl esters, triglycerides	25-35	1.006-1.019
LDL	Apo B100	Cholesteryl esters	18-25	1.019-1.063
HDL	Apo AI, apo AII, apo AV	Cholesteryl esters, phospholipids	5-12	1.063-1.210
Lp(a)	Apo B100, apo(a)	Cholesteryl esters	~30	1.055-1.085

Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); VLDL = very low density lipoprotein.

TABLE 213-2 MAJOR APOLIPOPROTEINS

APOLIPOPROTEIN	CHROMOSOMAL LOCATION, GENBANK SEQUENCE IDENTIFICATION	FUNCTIONS
Apo B100	2p24-p23, M14162	Structural component of atherogenic lipoproteins (VLDL, IDL, LDL), VLDL secretion, ligand for LDL receptor, elevated levels associated with vascular disease
Apo B48	Same as apo B100	Chylomicron secretion from intestine
Apo E	19q13.31, K00396	Ligand for binding of triglyceride-rich particles to LDL receptor and LRP, potential roles in Alzheimer's disease and neuronal injury
Apo AI	11q23-q24, X02162	Structural component of HDL, activates LCAT, elevated levels associated with protection from vascular disease
Apo AII	1q21-Q23, NM_001643	Genetically and biochemically associated with familial combined hyperlipidemia
Apo AIV	11q23-qter, NM_000482	Potential role in regulating food intake
Apo AV	11q23, AF202889	Required for normal lipolysis of triglyceride-rich lipoproteins
Apo CII	19q13.2, X00568	Activator of LPL
Apo CIII	11q23-qter, X01388	Inhibitor of LPL
Apo (a)	6q26-q27, X06290	Covalent bond with apo B100 forms Lp(a) and renders particle resistant to uptake by LDL receptor

Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); LPL = lipoprotein lipase; LRP = LDL receptor–related protein; VLDL = very low density lipoprotein.

TABLE 213-3 IMPORTANT RECEPTORS AND PROTEINS IN LIPID TRANSPORT

PROTEIN	CHROMOSOMAL LOCATION, GENBANK SEQUENCE IDENTIFICATION	FUNCTIONS
LDL receptor	19p13.3, AY114155	Clearance of apo B100 and apo E–containing lipoproteins, activity increased by statin drugs, deficiency causes familial hypercholesterolemia
LDL receptor–related protein (LRP)	12Q13-Q14, NM_000014	Clearance of apo E–containing lipoproteins
Scavenger receptor B1 (SR-B1)	12q24.32, Z22555	HDL receptor
Lipoprotein lipase (LPL)	8p22, NM_000237	Rate limiting for triglyceride metabolism, deficiency causes chylomicronemia syndrome
Lecithin-cholesterol acyltransferase (LCAT)	16q22.1, NM_000229	Esterifies cholesterol in HDL to increase HDL cholesterol levels, deficiency decreases HDL levels
Cholesteryl ester transfer protein (CETP)	16q13, NM_000078	Exchanges cholesteryl ester in HDL for triglycerides in apo B–containing lipoproteins, deficiency increases HDL levels
ABCA1	9q31, AJ12376	Transfers cholesterol in tissues to nascent HDL particles, deficiency causes Tangier disease
PCSK9	1p32.3, NC_000001.10	Degrades LDL receptor, deficiency decreases LDL levels

ABCA1 = ATP binding cassette A1; apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin-like/kexin type 9.

is about 48% of the size of apo B100. Apo B100 and apo B48 are products of the same gene, with B48 resulting from the post-transcriptional introduction of a premature stop codon in the apo B messenger RNA by apobec1, a cytidine deaminase. Genetic variants in apolipoproteins can be associated with well-defined clinical syndromes.

Receptors and Proteins

Several receptors and proteins required for normal lipid transport are listed in Table 213-3.

Low-Density Lipoprotein Receptor

The LDL receptor mediates the removal of LDL as well as some VLDL and IDL particles by binding to apo B100 and apo E. The most important site of LDL receptor expression is the liver, where its regulation is mediated by sterol regulatory element-binding proteins (SREBPs). SREBPs are found in inactive forms in the endoplasmic reticulum (ER). When cellular cholesterol levels rise after the delivery of cholesterol by the LDL receptor, increased ER sterol content causes cholesterol to bind to Scap, a protein that promotes the migration of SREBPs from the ER to the Golgi. In the Golgi, SREBPs undergo proteolytic conversion to active forms that move to the nucleus and stimulate the expression of genes involved in cholesterol synthesis. The binding of cholesterol to Scap induces a conformational change that causes it to bind to Insigs, ER anchor proteins. However, when intracellular cholesterol levels are high, the Scap/SREBP complex does not move to the Golgi, SREBPs are not processed, and cholesterol synthesis stops. When cholesterol levels are low, Scap is released from Insigs, the Scap/SREBP complex moves to the Golgi,

SREBPs are converted to active forms, and genes important for cholesterol synthesis and acquisition (such as the LDL receptor) are transcribed. Statin drugs effectively lower cholesterol. They inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol levels fall, Scap is free to shepherd SREBPs to the Golgi for activation, an active SREBP stimulates transcription of the LDL receptor gene, and increased levels of the LDL receptor protein on the surface of the hepatocyte bind and remove LDL particles from the circulation.

Low-Density Lipoprotein Receptor–Related Protein

The LDL receptor–related protein (LRP), also called the chylomicron remnant receptor, participates in the removal of intestine-derived lipoproteins by interacting with apo E. Chylomicron remnants carry apo B48, which is missing the LDL receptor binding domain, but these particles are also cleared by the LDL receptor through apo E binding.

Scavenger Receptor B1

Scavenger receptor B1 (SR-B1) is a protein expressed in liver that binds HDL. Unlike the LDL receptor that endocytoses LDL particles, SR-B1 does not appear to internalize HDL particles but instead facilitates the transfer of cholesteryl ester from HDL to the liver. Its genetic manipulation in mice has raised clinically relevant questions regarding the significance of elevated HDL levels. Inactivation of SR-B1 elevates HDL cholesterol levels but promotes atherosclerosis, presumably because of disruption of the transport of cholesterol from peripheral cells, where it can cause disease, to the liver, where it is excreted. These results suggest that it is not the level of HDL per se but the flux of cholesterol through HDL that affords protection from vascular disease.

Lipoprotein Lipase

Lipoprotein lipase (LPL) is rate limiting for the metabolism of triglyceride-rich lipoproteins and is required for the generation of HDL particles because HDL is absent from LPL-deficient mice. Deficient LPL activity thus provides a physiologic explanation for the common association between high triglyceride levels and low HDL cholesterol.

Lecithin-Cholesterol Acyltransferase

Another protein important in HDL metabolism is lecithin-cholesterol acyltransferase (LCAT). LCAT is associated with HDL in the circulation, where it esterifies free cholesterol to form cholesteryl esters that are easily stored in the nonpolar core of the lipoprotein. LCAT deficiency, a rare disorder, is characterized by low HDL as well as anemia and renal failure, clinical features probably related to disruption of the normal membrane function by the accumulation of excessive amounts of unesterified cholesterol.

Cholesteryl Ester Transfer Protein

Cholesteryl ester transfer protein (CETP) exchanges one molecule of cholesteryl ester in HDL for one molecule of triglyceride in apo B–containing particles such as VLDL. The resulting HDL particle is triglyceride enriched, enhancing its clearance (especially by an enzyme related to LPL, hepatic lipase) and lowering HDL. Inhibition of CETP activity increases HDL levels.

ATP Binding Cassette A1

ATP binding cassette A1 (ABCA1) is a cell membrane protein that mediates the transfer of cholesterol and phospholipids from cells to lipid-poor apo AI, a process that promotes HDL formation. ABCA1 in the liver contributes to the genesis of HDL, and overexpression of ABCA1 in macrophages may diminish atherosclerosis. Heterozygous ABCA1 deficiency is responsible for isolated low HDL cholesterol levels that occur in some kindreds (also known as familial hypoalphalipoproteinemia, based on an older term for HDL). Rare homozygotes for ABCA1 mutations have Tangier disease, characterized by the accumulation of cholesteryl esters in macrophages and resulting in distinctive features, including orange-yellow tonsils, neuropathy, and hepatosplenomegaly. HDL is very low to absent. Atherosclerosis is probably increased in these patients, but its extent may be moderated by concomitant low LDL levels.

Proprotein Convertase Subtilisin–Like/Kexin Type 9

Proprotein convertase subtilisin–like/kexin type 9 (PCSK9) is a secreted enzyme that promotes the degradation of the LDL receptor. Its overexpression decreases the LDL receptor, resulting in hyperlipidemia. PCSK9 deficiency in humans is associated with low LDL levels and less atherosclerosis. Pharmacologic inhibition of PCSK9 would be predicted to have similar effects.

EXOGENOUS LIPID METABOLISM

Animal products containing cholesterol and triglycerides are eaten regularly by most people. Dietary fats are broken down in the gut to free cholesterol and fatty acids, which are then transported across cell membranes into the enterocyte. There, they are re-esterified into cholesteryl ester and triglycerides and then packaged onto apo B48. These particles gain access to the plasma through the thoracic duct and acquire other apolipoproteins in part by transfer from HDL. These mature chylomicrons circulate to peripheral tissues. LPL, bound to the capillary endothelium in tissues such as adipose tissue and muscle, is activated by apo CII on chylomicrons, and fatty acids hydrolyzed from triglycerides by LPL are released and transported into adipose tissue for storage or into muscle for energy. This process also requires apo AV, an apolipoprotein transported in HDL that appears to facilitate the interaction between LPL and triglyceride-rich lipoproteins, as well as glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1), a recently discovered protein that forms a platform for triglyceride metabolism at the endothelium.

Progressive hydrolysis of triglyceride converts chylomicrons into chylomicron remnants, which are relatively enriched in cholesteryl esters. Chylomicron remnants are removed in the liver by species that bind apo E: LRP, the LDL receptor, and cell surface glycosaminoglycans. Chylomicrons are large, and it is unlikely that they contribute to atherosclerosis. Chylomicron remnants are enriched in cholesteryl esters, the major lipid component of the atherosclerotic lesion, and small enough to enter the subendothelial space, where they are taken up by macrophages. Remnants are atherogenic, consistent with the idea that the progression of atherosclerotic lesions can occur in the postprandial state, a potential contributor to morbidity that is not assessed by current practices, which focus on the measurement of fasting lipoproteins.

Chylomicrons are not soluble. Their presence causes the "tomato soup" appearance of blood drawn after a fatty meal. Because they are mostly triglycerides, they float to the top of serum that is refrigerated overnight, leaving a layer of "cream" on top of the sample. The detection of chylomicrons in fasting serum has clinical relevance because it indicates a risk for pancreatitis and other elements of the chylomicronemia syndrome.

ENDOGENOUS LIPID METABOLISM

Fats deposited in the liver are further metabolized into component lipid species, re-esterified as cholesteryl ester and triglycerides, and either stored in hepatocytes or exported as lipoproteins (Fig. 213-1). The liver produces the triglyceride-rich VLDL. Its rate of production appears to depend on the availability of triglycerides. Apo B100 is the major apolipoprotein of VLDL, but under normal conditions, regulation of the apo B gene does not appear to play an appreciable role in the control of VLDL synthesis. Production of the apo B100 protein depends on its cotranslational stabilization. As the message is translated into protein, the presence of triglyceride stabilizes the peptide and allows the continued addition of amino acids. In the absence of triglycerides, the apo B molecule is degraded. The transfer of triglycerides to the growing apo B peptide is mediated by microsomal transfer protein (MTP). Mutations in MTP cause abetalipoproteinemia, a rare disease characterized by the absence of circulating apo B. In the absence of apo B, the metabolism of fat-soluble vitamins (normally carried in lipoproteins) is disrupted, and patients with abetalipoproteinemia suffer from multisystem defects, including severe neurologic dysfunction and retinopathy that are presumably caused by deficiency of vitamins E and A. Drugs that interfere with MTP function lower lipids but, not surprisingly, cause the accumulation of triglyceride in the liver. The apo B gene is normal in patients with abetalipoproteinemia. Mutations in the apo B gene cause another condition known as hypobetalipoproteinemia, caused by shortened forms of the apo B protein. Subjects with hypobetalipoproteinemia have very low, but not absent, levels of circulating lipids and appear to be healthy.

Nascent VLDL containing one apo B100 molecule per particle is secreted into the plasma, where it acquires apo E, apo CII, and apo CIII. In a process analogous to that occurring with chylomicrons, apo CII on VLDL activates LPL, and fatty acids hydrolyzed from triglycerides by LPL are released in capillary beds and transported into tissues. With continued hydrolysis and the loss of both phospholipids and apolipoproteins to HDL, VLDL is converted to IDL, a cholesteryl ester–rich particle with an apolipoprotein

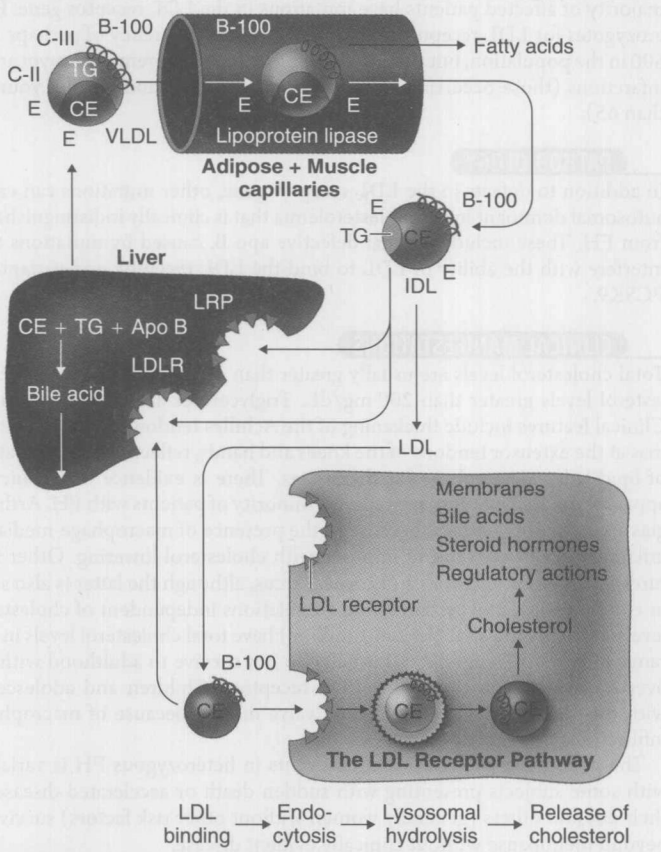

FIGURE 213-1. Endogenous lipid metabolism. In the liver, triglycerides (TG), cholesteryl esters (CE), and apolipoprotein B100 are packaged as very low density lipoprotein (VLDL) particles. TG is hydrolyzed by lipoprotein lipase to generate intermediate-density lipoprotein (IDL), which is further metabolized to generate low-density lipoprotein (LDL). This particle can be removed by the liver or by peripheral cells. Cholesterol derived from LDL regulates several processes and can be used for the synthesis of bile acids, steroid hormones, and cell membranes. LDLR = low-density lipoprotein receptor.

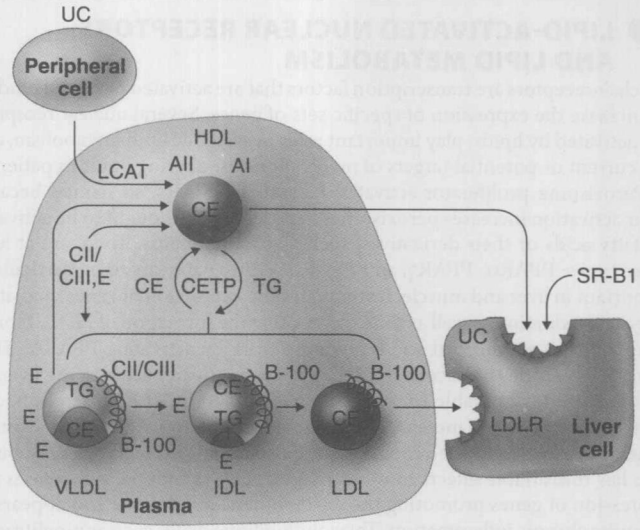

FIGURE 213-2. Reverse cholesterol transport and high-density lipoprotein (HDL) metabolism. Unesterified cholesterol (UC) in peripheral cells can be transferred to HDL and esterified by lecithin-cholesterol acyltransferase (LCAT). This cholesterol ester (CE) in HDL can be transferred to the liver directly through scavenger receptor B1 (SR-B1). Alternatively, it can be transferred to apolipoprotein B100–containing lipoproteins in exchange for triglycerides (TG) through the action of cholesteryl ester transfer protein (CETP). IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; VLDL = very low density lipoprotein.

complement of only apo B and apo E. These particles, like chylomicron remnants, are thought to have high atherogenic potential. Unlike chylomicron remnants, IDLs are included in current management schemes because reporting of LDL cholesterol levels by most clinical laboratories includes IDL. IDL can be taken up by either the LRP or the LDL receptor in the liver. In the presence of a normal apo E molecule, IDLs are converted to LDL, consisting of one molecule of apo B100 per particle and a cholesteryl ester with essentially no triglycerides. About 75% of LDL is removed from the plasma by the LDL receptor pathway, and most of this takes place in the liver. The uptake of LDL results in the migration of LDL particles to lysosomes, where cholesterol is released for (depending on the cell type) plasma membrane localization, bile acid synthesis, steroid hormone synthesis, and interaction with Scap for the control of SREBP activation. A minority of LDL enters the subendothelial space of the vascular wall, where its modification by oxidation or other processes promotes its uptake by macrophages in atherosclerotic lesions.

Most VLDL particles are large and are not thought to promote vascular disease. However, some small VLDL particles as well as IDL and LDL are atherogenic. Because the majority of VLDL is triglyceride, most patients with elevated levels of fasting triglyceride have either increased numbers of VLDL particles or an increased triglyceride content in each VLDL. LDL has a plasma half-life of 2 to 5 days. The detection of elevated levels of fasting cholesterol usually reflects the presence of either increased numbers of LDL particles or increased cholesteryl ester in each LDL. LDL also exists in a range of sizes. Small, dense LDL tends to occur in the setting of concomitant hypertriglyceridemia. This type of lipoprotein is thought to have greater atherogenic potential than larger LDL species, perhaps because of easy access to the vascular wall and greater susceptibility to oxidative modification. Lipoprotein particle size and number can be quantified by nuclear magnetic resonance techniques, but it is not clear that these data provide diagnostic advantages beyond the determination of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol.

REVERSE CHOLESTEROL TRANSPORT AND HIGH-DENSITY LIPOPROTEIN METABOLISM

Lipid metabolism is dynamic. At the same time lipoproteins are being processed to modify their nonpolar lipids, particles are interacting with one another, exchanging surface materials, apolipoproteins, and nonpolar lipids. HDL is an important reservoir for components cast off during the metabolism of other lipoproteins as well as lipids discarded by cells. Nascent HDL is generated by the liver and intestine as a phospholipid disc containing apo AI and apo AII. It accepts unesterified (free) cholesterol (UC in Fig. 213-2) and phospholipids shed from cells. This unesterified cholesterol is converted to cholesteryl ester by the action of LCAT and stored in the center of the disc, allowing it to become a spherical particle. The particle is further modified as a consequence of the action of LPL on triglycerides in apo B–containing lipoproteins. As the core triglycerides of VLDL are metabolized, the particle collapses, leaving redundant surface lipids (phospholipid in the form of lecithin and unesterified cholesterol) and excess apolipoproteins such as apo CII, apo CIII, and apo E, which are transferred to HDL. LCAT again esterifies the cholesterol to increase the content of cholesteryl ester in the HDL.

Reverse cholesterol transport is the beneficial process by which cholesterol present in peripheral cells, such as foam cells in a growing atherosclerotic lesion, is transported back to the liver for excretion. There are at least two well-defined pathways mediating this transfer. First, after accepting cholesterol from peripheral cells and esterifying it through the action of LCAT, HDL can interact directly with the liver by binding to SR-B1 and transferring cholesteryl ester to the hepatocyte. Second, HDL can transfer cholesteryl ester to apo B100–containing lipoproteins such as VLDL (see bottom of Fig. 213-2) through the action of CETP. This cholesteryl ester can ultimately be transported to the liver after conversion of VLDL to IDL to LDL and uptake by the LDL receptor (LDLR in Fig. 213-2). This pathway is not direct because the transfer of cholesteryl ester to apo B–containing lipoproteins results in cholesterol-enriched particles that may be taken up by foam cells in atherosclerotic plaques before being cleared by the liver. Humans with genetic defects in CETP have high HDL levels and appear to be healthy. An inhibitor of CETP, torcetrapib, increases HDL cholesterol but also increases adverse events, perhaps in part related to its adverse effects on blood pressure. The benefits of raising HDL with medications are uncertain; a meta-analysis of more than 100 randomized trials showed no reduction in coronary heart disease events by simply increasing HDL.[1]