ANESTHESIA and UNCOMMON DISEASES:

Pathophysiologic and Clinical Correlations

KATZ and KADIS

ANESTHESIA and UNCOMMON DISEASES: Pathophysiologic and Clinical Correlations

EDITED BY

JORDAN KATZ, M.D.
Professor and Associate Chairman
Department of Anesthesiology
University of Wisconsin Medical School
Madison, Wisconsin

AND

LESLIE B. KADIS, M.D.
Assistant Professor of Anesthesiology
Stanford University School of Medicine
Palo Alto, California

W. B. SAUNDERS COMPANY Philadelphia · London · Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, Pa. 19105

12 Dyott Street
London, WC1A 1DB

833 Oxford Street
Toronto, Ontario M8Z 5T9, Canada

Anesthesia and Uncommon Diseases: Pathophysiologic and Clinical Correlations

SBN 0-7216-5299-9

Print No.: 9 8 7 6 5 4 3

To our wives
Ruby and Jo

parva saepe gravissima

Contributors

J. ANTONIO ALDRETE, M.D., M.S.
Professor and Chairman, Department of Anesthesiology, University of Louisville School of Medicine. Chief of Anesthesiology, Louisville General Hospital, Children's Hospital, Norton Memorial Infirmary, Veterans Administration Hospital, and Kosair Crippled Children Hospital, Louisville, Kentucky.

LAWRENCE V. BASSO, M.D.
Clinical Instructor, Internal Medicine, Stanford University. Staff Endocrinologist, Stanford University Hospital, Stanford; Endocrinologist, Palo Alto Medical Clinic, Palo Alto, California.

THOMAS B. CALDWELL, III, M.D.
Assistant Professor of Anesthesiology, Vanderbilt University, School of Medicine. Attending Anesthesiologist, Vanderbilt University Hospital, Nashville, Tennessee.

MICHAEL J. COUSINS, M.B., B.S., F.F.A.R.A.C.S., F.F.A.R.C.S.
Assistant Professor of Anesthesia, Stanford University School of Medicine. Staff Anesthesiologist, Stanford University School of Medicine, Stanford, and Veterans Administration Hospital, Palo Alto, California.

LAWRENCE G. CROWLEY, M.D.
Professor of Surgery, Stanford University Medical School, Stanford, California.

PEDRO M. DIAZ, M.D.
Assistant Professor, Department of Anesthesia, University of Miami School of Medicine. Attending in Anesthesiology, Jackson Memorial Hospital and Veterans Administration Hospital, Miami, Florida.

JOHN H. EISELE, M.D.
Associate Professor of Anesthesiology and Physiology, University of California School of Medicine. Affiliated with Sacramento Medical Center, Sacramento, California.

MAURICE FOX, M.D.
Clinical Assistant Professor of Medicine, Stanford University. Staff Endocrinologist, Stanford University Hospital, Stanford; Head, Department of Endocrinology, Palo Alto Medical Clinic, Palo Alto, California.

RALPH E. GIANELLY, M.D.
Chief of Cardiology, Springfield Hospital Medical Center, Springfield, Massachusetts.

STEPHEN H. JACKSON, M.D.
Assistant Professor of Anesthesia, Stanford University School of Medicine, Stanford, California.

LESLIE B. KADIS, M.D.
Assistant Professor, Department of Anesthesia, Stanford University, Stanford, California.

JORDAN KATZ, M.D.
Professor and Associate Chairman, Department of Anesthesiology, University of Wisconsin Medical School, Madison, Wisconsin.

RONALD L. KATZ, M.D.
Professor of Anesthesiology, Columbia University. Attending Anesthesiologist, The Presbyterian Hospital in the City of New York.

SHOICHI KOHATSU, M.D.
Associate Professor of Surgery, Stanford University Medical School. Chief of Surgery, Veterans Administration Hospital, Palo Alto, California.

J. ALASTAIR LACK, M.B., B.S., F.F.A.R.C.S., D.I.C.
Clinical Assistant Professor of Anesthesia, Stanford University Medical Center, Stanford, California.

GEORGE B. LEWIS, JR., M.D.
Associate Clinical Professor of Anesthesiology, University of Southern California School of Medicine. Attending Anesthesiologist, Childrens Hospital of Los Angeles, Los Angeles, California.

RICHARD I. MAZZE, M.D.
Associate Professor of Anesthesia, Stanford University School of Medicine. Staff Anesthesiologist, Stanford University School of Medicine, Stanford; Chief, Anesthesiology Service, Veterans Administration Hospital, Palo Alto, California.

JORDAN MILLER, M.D.
Assistant Professor of Clinical Anesthesiology, Columbia University. Assistant Attending Anesthesiologist, The Presbyterian Hospital in the City of New York.

JOHN WILLIAM PENDER, M.D.
Clinical Professor of Anesthesiology, Stanford University. Staff Anesthesiologist, Stanford University Hospital, Stanford; Chairman, Department of Anesthesiology, Palo Alto Medical Clinic, Palo Alto, California.

DENNIS J. RUDZINSKI, M.D.
Anesthesiologist, Jackson Memorial Hospital, Miami, Florida.

MICHAEL A. SKIVINGTON, M.B., B.S.
Consultant Anesthetist Bournemouth and East Dorset Group of Hospitals, England.

RICHARD G. SPADEMAN, M.D.
Clinic Assistant Professor of Orthopedic Surgery, Stanford University. Affiliated with Stanford University Hospital, Stanford, Veterans Administration Hospital, Palo Alto, and Santa Clara Valley Medical Center, San Jose, California.

PHILIP SUNSHINE, M.D.
Associate Professor of Pediatrics, Stanford Medical Center Director of Nurseries, Stanford Medical Center, Stanford, California.

CLAUDE A. TAYLOR, M.D.
Professor of Anesthesiology, University of Wisconsin Medical School, Madison, Wisconsin.

BERNARD L. WALTUCK, M.D.
Clinical Instructor, Department of Anesthesiology, University of Miami Medical School. Anesthesiologist, Homestead Air Force Base, Homestead, Florida.

HERSCHEL S. ZACKHEIM, M.D.
Clinic Professor of Dermatology, Stanford University Hospital; Clinic Assistant Professor of Dermatology, University of California at San Francisco. Active staff member, Sequoia Hospital, Redwood City, California.

Preface

This book is an undisguised attempt to cover the exception rather than the rule. Its purpose is to present selected disease entities whose underlying pathophysiologic processes might profoundly affect normal anesthetic management. By the very nature of this design, the diseases covered tend to be uncommon. The "normal" for frequently managed diseases may be so sufficiently all-embracing as to eliminate the unexpected, at least within the context of this work.

To avoid putting together an excessively cumbrous text, a second sifting was done. Those disorders thought to be adequately discussed in other readily available texts were eliminated from consideration. Then began an exhaustive search for anesthesia-related information, and it was at this point that we first became aware of a major problem. In general, the information we wanted to present has never been published. We knew, for example, that surgical procedures for patients with various aortic arch syndromes are being performed with greater and greater frequency and that obviously these patients receive anesthesia; we might even intuitively anticipate some special problems related to the anesthesia, but there are few significant reports. In other words there seemed to be huge gaps in the anesthesia literature. At this point in our deliberations we made a decision to present the material as best we could, based on currently available knowledge, emphasizing the underlying pathophysiology and suggesting guidelines for anesthetic management.

Eventually the book assumed its present form. We asked for help from those of our medical, surgical and pediatric colleagues who have a special interest in anesthesia-related problems and are able to look at patients and their problems from the head of the table. We encouraged them to collaborate with anesthesiologists who have similar interests. The result, we think, is a compendium of that which is and is not known about unusual diseases, as they may or may not relate to anesthesia.

There is a recognized unevenness in the presentation. We think that this unevenness reflects the state of our knowledge as well as the diversity of authors. Occasionally the suggestions made may appear contradictory to current practice in some areas. As mentioned previously, the suggestions for management may be based solely on information from the literature rather than extensive personal experience, and we can only hope that the volume will provide the impetus for those of our colleagues with greater knowledge in any area to publish their experience and share the knowledge with us.

The principal thesis of this book is that sound anesthetic management must revolve around an understanding of disease processes. As such, we hope it is a useful addition to the medical literature.

Any endeavor of this type requires the support of many. We would like to thank particularly the secretarial staffs of the Anesthesia Departments at Wisconsin, Stanford and Miami Medical Schools. Advice from faculties and residents at these schools was given generously. A special debt of thanks goes to Jack Hanley of the W. B. Saunders Company, whose gentle prodding many times provided the necessary stimulus.

JORDAN KATZ
LESLIE B. KADIS

Contents

CHAPTER 1

Genetic and Metabolic Disease

Inborn Errors of Metabolism

By STEPHEN H. JACKSON, M.D.

The purpose of this article is to define and discuss errors of human metabolism and their relation to anesthesia. These metabolic disorders are genetically determined and involve either enzymatic deficiencies—quantitative and/or qualitative—or defective regulatory mechanisms.

Genes that control biochemical reactions do so through the mediation of the enzymes that catalyze these reactions. *Structural genes* determine the specific structure of their respective enzymes. A mutation at a structural gene site might result either in a complete absence of the gene and its enzyme or in an abnormal gene which equates with the synthesis of an abnormally structured and therefore abnormally functioning enzyme. In either event, such a genetic mutation results in a complete or partial inhibition of the metabolic pathway in which the enzyme participated. *Regulatory genes* regulate and modulate the activity of the structural genes and therefore, indirectly, the enzymes they control. Consequently, a mutation at a regulatory gene site might result in a disorder of regulation of its respective metabolic pathway.

For each of the inborn errors of metabolism, the following will be discussed: (1) normal biochemistry, (2) specific biochemical lesion(s), and (3) pathobiochemical and pathophysiological sequelae.

The anesthetic management will usually be a logical consequence of this information. The objective scientific literature concerning such anesthetic management is, essentially, nonexistent, and therefore it is hoped that the following pages will stimulate and guide anesthesiologists to properly investigate and report on any such interesting patients they may encounter.

INBORN ERRORS OF LIPID METABOLISM

The lipids present in the human represent a mixture of a variety of classes of substances and include the fatty acids, triglycerides (fatty acid esters of glycerol), phospholipids (derivatives of

sphingosine phosphate and glycerolphosphate) and nonphosphorylated lipids (the steroids, the most abundant of which is cholesterol). Free fatty acids may be metabolized to provide energy, or they may be stored as a readily reconvertible energy reserve in the form of triglycerides. The phospholipids serve as essential structural components of cellular (plasma) and subcellular (mitochondrial, microsomal) membranes. These water-insoluble lipids concentrate at polar-apolar interfaces and stabilize lipoprotein structures in the basically aqueous milieu of the body. In addition to being a precursor of steroid hormones and bile acids, unesterified cholesterol is also an important component of cell membranes. The cholesteryl esters are found mainly in the plasma, adrenals and liver, but their function remains unclear.

A close interrelationship exists between fatty acid and carbohydrate metabolism. Energy is stored in the form of fatty acids when glucose is readily available to the cell (postprandial), and is derived from fatty acids when glucose availability diminishes. In fact, it has been estimated that in the basal state, free fatty acids provide as much as one half of the caloric demands of the body.

Fatty acid metabolism is strongly influenced by hormones. Norepinephrine, released at the postganglionic adrenergic nerve endings, is more potent than epinephrine (blood-borne from the adrenal medulla) in affecting lipid metabolism in the human. These catecholamines mobilize adipose tissue triglycerides and cause release of the hydrolytic products into the circulation, thereby effecting an elevation of the levels of free fatty acid and glycerol in the blood.

The biochemical mechanism involved is as follows:

1. Norepinephrine increases the activity of the enzyme adenyl cyclase.
2. Adenyl cyclase catalyzes the conversion of adenosine triphosphate (ATP) to adenosine 3′,5′-phosphate (cyclic AMP, cyclic adenylic acid).
3. Adenosine 3′,5′-phosphate increases the activity of the enzyme lipase.
4. Lipase catalyzes the hydrolytic degradation of triglycerides to free fatty acids plus glycerol.

There is a concomitant increase in fatty acid uptake and utilization (for energy) by the vital organs and skeletal muscle. The liver may reesterify the fatty acids and glycerol and release the triglyceride product into the blood, thereby causing a hypertriglyceridemia. Overnight fasting and/or preoperative apprehension will invariably effect such a lipid profile in an otherwise metabolically normal patient. Both alpha and beta adrenergic blocking drugs will partially inhibit fat mobilization from adipose tissue. Insulin, whose secretion by the pancreatic beta cells is stimulated by increased blood levels of free fatty acids, is a potent inhibitor of adipose tissue lipase and thereby an antagonist of the fat-mobilizing properties of the catecholamines. That the catecholamines inhibit the pancreatic secretion of insulin is, however, not the primary mechanism involved in catecholamine lipogenicity.

The actual blood levels of fatty acids may vary as much as thirty-fold when the extremes of the normal postprandial state and diabetic ketoacidosis are considered, but they constitute an insignificant percentage of the total serum lipids. Free fatty acids are normally transported by albumin, but even in the analbuminemic patient, the free fatty acid serum level is only minimally diminished, their transport being handled by the lipoproteins. There is no proved disease entity that specifically involves a defect in fatty acid metabolism, although adverse effects of very high blood levels of unbound fatty acids have been suggested by several studies.

Without an interaction with specific plasma proteins only a small fraction of the water-insoluble lipids would be in true molecular solution and thereby available for blood transport. Although most plasma proteins bind little or no lipid, except for free fatty acids, apolipoproteins possess the unique property of binding from one to twelve times their

weight of lipid. The soluble and transportable apolipoprotein-lipid complex is called lipoprotein, and its structure is such that the protein and phospholipid surround other lipids in the core of the complex. Plasma lipoproteins and lipid particles, in turn, have been classified on the basis of their densities (ultracentrifugation) and electrophoretic mobilities:

1. Chylomicrons are lipid particles consisting almost entirely of exogenous triglycerides absorbed from the intestine; about 2 per cent is protein.
2. Very low density (pre-beta) lipoproteins consist mainly of endogenous triglycerides, but also contain smaller amounts of cholesteryl ester and phospholipid; 5 per cent is protein.
3. Low density (beta) lipoproteins are composed largely of cholesteryl ester and phospholipid; 25 per cent is protein.
4. High density (alpha) lipoproteins are similar in composition to the beta lipoproteins except that about 50 per cent is protein.

Perhaps the key function of the lipoproteins is the transport of triglycerides. Many of the interrelationships existing among the four classes of lipoproteins reflect this function. The lipoproteins may also play an important role in the regulation of the cholesterol and cholesteryl ester contents of cells and tissues.

Significant differences have been detected between the sexes in the distribution of plasma lipoproteins, the levels of which are generally related to age, but the mechanisms involved as well as their functional importance remain obscure. Because specific types of hyperlipoproteinemia accelerate the development of atherosclerosis, which is the major cause of premature death in the United States, the genetic and environmental factors influencing the regulation of plasma lipoprotein concentrations are subjects of great importance. The following are three biochemical factors involved in such regulation: (1) Adequacy of apoprotein—typified by the inherited disease abetalipoproteinemia, in which the normal apo-low density lipoprotein is absent. (2) Adequacy of lipid and/or lipoprotein catabolism—exemplified by hyperchilomicronemia and hyperbetalipoproteinemia (see below). (3) Demand for fatty acid transport—thought to be the key determinant of changes in lipoprotein concentration. Although availability of carbohydrate and other dietary factors are important, the activity of insulin is perhaps paramount. In fact, Fredrickson believes that the genetic changes responsible for diabetes mellitus are not clearly separable from some of those causing certain forms of hyperlipoproteinemia.

The effects of anesthetic drugs on lipid metabolism have been incompletely examined. Cyclopropane, fluroxene, nitrous oxide and diethyl ether raise human norepinephrine blood concentrations, and therefore should produce elevated free fatty acid and triglyceride blood levels. Halothane, methoxyflurane and barbiturates would not be expected to produce such effects. However, Cooperman was unable to confirm the expected free fatty acid elevation during diethyl ether anesthesia. A significant sympathetic blockade produced by intrathecal or epidural anesthesia will lower free fatty acid concentrations in the blood. The beta adrenergic blocking drug, propranolol, will prevent and/or reverse the elevation of blood free fatty acid levels induced by cyclopropane anesthesia. Via their catecholamine stimulation, preoperative stresses—physical, psychological or both—are so potent in effecting fat mobilization that they may outweigh any initial effects produced by anesthetic drugs. By preventing the tendency to hypoglycemia, intravenous glucose would minimize the necessity for homeostatic catecholamine-mediated maintenance of euglycemia and the resultant fat mobilization. Hypercarbia, hypoxia and hypotension would have significant fat-mobilizing effects indirectly, through their stimulation of the sympathoadrenal system. On the basis of current information, it would be difficult to predict what effects anesthetics might have on cholesterol, cholesteryl ester and phospholipid metabolism.

Hyperglyceridemia

Hyperglyceridemia is a genetically determined disease in which the serum triglyceride concentration is elevated. There are two major types, depending on whether exogenous or endogenous hypertriglyceridemia exists.

Fat-Induced Hyperglyceridemia (Hyperchylomicronemia, Type I Hyperlipoproteinemia). In this disorder, the blood glyceride (chylomicron fraction) concentration is markedly elevated and the serum appears lactescent after ingestion of fatty foods. The low- and high-density lipoproteins are concomitantly decreased. This defect involves a rate-limitation in removal of the exogenous glycerides (chylomicrons) from the blood and may be related to a deficiency in activity of the lipolytic plasma enzyme, lipoprotein lipase, which is present in adipose tissue and vascular walls. Heparin is an essential cofactor for this enzyme. This disorder, which is most frequently diagnosed in childhood, is characterized by hepatosplenomegaly, abnormal (lipid-containing) cells in the bone marrow and the reticuloendothelial system, localized fatty deposits and frequent episodes of abdominal pain with or without fever. Hepatic function is essentially normal, and coronary artery disease is no more prevalent than it is among the general population. Treatment necessitates dietary restriction of fats.

Carbohydrate-Induced Hyperglyceridemia (Hyperprebetalipoproteinemia). This is characterized by an exaggerated elevation of endogenous triglycerides (very low density lipoprotein fraction) following ingestion of food that is predominantly carbohydrate in content. The biochemical mechanism inducing this hypertriglyceridemia has not been elucidated but certainly must involve the normal Embden-Meyerhof glycolytic conversion of glucose to glyceraldehyde-3-phosphate, the three carbon moiety essential for triglyceride synthesis. Some form of impaired carbohydrate tolerance can usually be demonstrated in these patients, whose diagnosis is usually made in adulthood. As would be expected, these patients have a significant incidence of vascular disease, including that of the coronary arteries. Treatment primarily requires diets with high-fat and low-carbohydrate content. Recent studies have indicated that drugs such as chlorophenoxybutyrate and nicotinic acid may significantly lower these abnormal lipid values.

The anesthetic management of hyperglyceridic patients is relatively straightforward. Although the hyperchilomicronemics have moderate hepatomegaly, their liver function is undisturbed and consequently of no significance to the anesthetist. The carbohydrate-induced hyperglyceridemics should receive the same anesthetic approach as any patient who is prone to coronary arterial disease. These hyperprebetalipoproteinemic patients would benefit chemically by restraint in the total amount of glucose administered intravenously. Lactated solutions would provide a satisfactory alternative source of energy without the simultaneous tendency to form the triglyceride precursor, glyceraldehyde-3-phosphate. As discussed above, cyclopropane, fluroxene and diethyl ether would tend to intensify a pre-existing hypertriglyceridemia. Nevertheless, it is unknown what undesirable effect, if any, would be produced in any anesthetized patient by the acute onset of catecholamine- or carbohydrate-induced hyperglyceridemia.

Hyperbetalipoproteinemia (Hypercholesterolemia, Type II Hyperlipoproteinemia)

This is a genetically determined disease in which the blood low density (beta) lipoprotein level, particularly cholesterol, is increased. It is inherited in an autosomal dominant fashion, and its prevalence is estimated at 3 to 8 per cent of the general population. The biochemical aberrations effecting the hypercholesterolemia are poorly understood. Clinically, this disease is characterized by an increased probability of the premature development of significant vascular athero-

sclerosis. Although the coronary arteries are the most clinically important of the affected vessels, peripheral vascular involvement is quite common. Rarely, the valvular endocardium may be affected as the primary manifestation. Localized fatty deposits may be found throughout the body. These unfortunate individuals comprise a large proportion of the increasingly frequent occurrence of myocardial infarction during the first decades of life. Indeed, it is interesting to speculate that the sporadic instances of acute myocardial infarction with cardiovascular collapse in allegedly normal young people undergoing elective surgery might represent patients with undiagnosed hypercholesterolemia. The only diagnostic clue for this disease in otherwise apparently healthy patients is the demonstration of a hyperbetalipoproteinemia, which certainly is not a routine laboratory determination. Therapy is largely dietary in nature, although recently there have been varying degrees of success with drug and hormonal regimens as well.

The anesthetic management of such a patient, whether or not there is evidence for coronary atherosclerosis, should be similar to that of any patient with coronary artery disease. This includes successful sedation and relief from apprehension with premedicant drugs, intubation (when necessary) only when the patient is well anesthetized, avoidance of extreme deviation from normal in blood pressure and pulse, concern for adequate oxygenation both during anesthesia and in the postanesthetic recovery period, and adequate postanesthetic analgesia and sedation.

In addition to the aforementioned inborn errors of lipid metabolism, there are instances in which blood lipid concentrations are elevated secondary to other diseases, such as hypothyroidism, nephrotic syndrome and diabetes mellitus, for which the reader is referred to the appropriate chapters of this book.

The extent or degree of elevation of blood lipids in the lipid disorders already discussed varies from slight to massive, the latter being most spectacularly exemplified by a postprandial hyperchilomicronemic patient. It is interesting to speculate as to the effect that hyperlipemia would have on the blood-gas solubility coefficient of the volatile anesthetic drugs. Hyperlipemia would be expected to increase the partition coefficient and consequently alter the expected pattern of uptake and distribution of the anesthetic gas. For example, would a halothane anesthetic more closely simulate that of methoxyflurane? Or would a methoxyflurane or diethyl ether anesthesia be practically achieved? The extremely rare hypolipoproteinemias, only briefly mentioned above, might produce the opposite effects.

Another question of interest is whether the accumulation of lipid in the liver—as might be encountered in the fasting or nutritionally deprived state—might lead to the accruement of supranormal hepatic concentrations of lipid-soluble anesthetics. The role that this might play in the development of hepatocellular injury is even more speculative.

The tissue lipoidoses and adipose tissue disorders are discussed elsewhere.

REFERENCES

Allison, S., Tomlin, P., and Chamberlain, M.: Some effects of anesthesia and surgery on carbohydrate and fat metabolism. Brit. Journal Anaesth. *41*:588, 1969.

Bosomworth, P., and Morrow, D.: Metabolic significance of catecholamines released during anesthesia. Internat. Anesth. Clin. 5:481, 1967.

Bruce, D.: Anesthetic implications of fasting. Anesth. Analg. *50*:612, 1971.

Cooperman, L.: Plasma free fatty acid levels during general anesthesia and operation in man. Brit. J. Anesth. *42*:131, 1970.

Fredrickson, D., Levy, R., and Lees, R.: Fat transport in lipoproteins—an integrated approach to mechanisms and disorders. New Eng. J. Med. *276*:34, 94, 148, 215, 273, 1967.

Fredrickson, D.: The regulation of plasma lipoprotein concentrations as affected in human mutants. Proc. Nat. Acad. Sci. *64*:1138, 1969.

Gotto, A., Jr.: Recent studies on the structure of human low- and high-density lipoproteins. Proc. Nat. Acad. Sci. *64*:119, 1969.

Hallberg, D., and Oro, L.: Free fatty acids of plasma during spinal anesthesia in man. Acta Med. Scand. *178*:281, 1965.

Havel, R.: The autonomic nervous system and intermediary carbohydrate and fat metabolism. Anesthesiology 29:702, 1968.

Mays, E., Ransdell, H., and DeWeese, B.: Metabolic changes in surgical delirium tremens. Surgery 67:780, 1970.
Merin, R., Samuelson, P., and Schalch, D.: Major inhalation anesthetics and carbohydrate metabolism. Anesth. Analg. 50:625, 1971.
Nichols, A.: Functions and inter-relationships of different classes of plasma lipoproteins. Proc. Nat. Acad. Sci. 64:1128, 1969.
Oncley, J., and Harvie, N.: Lipoproteins: A current perspective of methods and concepts. Proc. Nat. Acad. Sci. 64:1107, 1969.
Oyama, T., and Takazawa, T.: Effect of methoxyflurane anaesthesia and surgery on human growth hormone and insulin levels in plasma. Canad. Anaesth. Soc. J. 17:347, 1970.
Peltier, L.: A few remarks on fat embolism. J. Trauma 8:812, 1968.

INBORN ERRORS OF AMINO ACID METABOLISM

The term *protein* is derived from the Greek word meaning "primary," and indeed, proteins are involved with the entire spectrum of biological functions. They are the catalysts (enzymes) involved in regulation of all biological reactions, the building units of all subcellular and cellular architecture, the transport carriers of essential compounds, the regulators (hormones) of physiological relationships, the essential molecules (antibodies) of immune reactions and the crucial molecules of the contractile process and mitotic apparatus. Proteins are macromolecules, polymers of the monomeric units, amino acids. All but two of the amino acids are alpha-amino acids, which have a primary amino group and a primary carboxyl group joined to the same carbon atom; their general structure is

$$NH_2——CHR——COOH$$

The two exceptions are the alpha-imino acids, proline and hydroxyproline.

Several biochemically important amino acids and amino acid derivatives are not constituents of protein. Because the absolute configuration of all the amino acids obtained from human protein has been related to that of L-glyceraldehyde, they all are of the L-configuration. Each amino and carboxyl group of an amino acid has a characteristic pKa value. In the pH range of 4 to 9, an amino acid exists as a dipolar ion, and therefore is readily soluble in water but insoluble in the lipoproteinaceous cell membrane. Consequently, the transport of amino acids across cell membranes requires energy.

Amino acids may be obtained from food, catabolism of body protein or biosynthesis. The human body is unable to synthesize several of the amino acids, which therefore must be obtained by dietary means; these are called essential amino acids. A nonessential amino acid (such as tyrosine) may be synthesized from an essential one (phenylalanine), but if this biosynthetic pathway is blocked (as in phenylketonuria), it too becomes an essential amino acid.

Amino acids have three major metabolic fates: (1) biosynthesis of protein, (2) biosynthesis of nonprotein nitrogen-containing molecules and (3) catabolism, the end products being either excreted or metabolically utilized. Catabolism of amino acids in man commences with the removal of the amino group by either oxidative deamination or transamination, the major end product being urea. The carbon skeleton of amino acids may enter into or be derived from lipid and carbohydrate metabolic pathways.

If all amino acids are functionally available to the body, then abnormalities of protein synthesis are affected only by abnormalities of the nucleic acids determining such synthesis. Certain genetically determined diseases have been discovered in which there is a defect in the metabolism or transportation of amino acids.

Cystinuria

This is a genetically determined disease that is a likely example of a defect in the transportation of certain amino acids across cell membranes. These patients have a selective increase in the renal clearance and urinary excretion of the amino acid cystine, as well as of lysine, arginine and ornithine, in the face of low or normal plasma concentrations of

these amino acids. It has recently been demonstrated that a similar defect also exists for cysteine-homocysteine disulfide. In addition, patients with this disorder have a similar transportation defect in the small intestine, resulting in an increased fecal excretion of these amino acids following their oral administration. The renal tubules of such patients possess a functionally defective transport system only for this group of amino acids, and a similar lesion probably exists in the intestinal epithelium.

Of the amino acids that have an altered metabolism in cystinuria, only lysine is an essential amino acid, yet there appears to be no sequela of its decreased absorption and increased excretion other than a variably reported small decrease in the mean height of affected individuals. The only definite clinical sequela of these metabolic derangements is the formation of renal calculi composed of the amino acid cystine. Excessive stone formation will result in progressive renal tubular failure. Cystine, a nonessential amino acid, may be synthesized from the essential amino acid, methionine. Its solubility in aqueous solutions is the lowest of the naturally occurring amino acids and decreases even further with increasing acidity. Therapy, therefore, is directed toward maintenance of an around-the-clock urinary diuresis in order to prevent supersaturation and consequent precipitation, alkalinization of the urine in order to increase solubility, and, less important, decreased ingestion of methionine. D-penicillamine and N-acetyl-D-penicillamine are recently introduced drugs that react with cystine to form a more soluble compound, and thereby may prevent stone formation as well as dissolve preformed calculi.

In view of the fact that cystine stone formation is the only pathological consequence of cystinuria, the major anesthetic consideration for such a patient is the maintenance of diuresis. The surgical patient normally receives several potent stimuli for the release of antidiuretic hormone and a consequent antidiuresis. These include the preoperative fasting, the normal decrease in urine flow during normal sleep, and possibly the processes of anesthesia and surgery. Therefore, in order to maintain the prophylactic and already chronically established elevated urine flow, an intravenous infusion of dextrose in water (or in balanced salt solution) should be started the night before scheduled surgery. The infusion should be regulated such that a generous hourly urine output is established. A continued diuresis must be maintained during and following anesthesia and surgery by the appropriate administration of intravenous solutions. Intravenous 5 per cent ethyl alcohol is a potent anti-antidiuretic and has been used successfully to promote a brisk diuresis prior to (and during) the use of various

Table 1–1. *Partial Listing of Inborn Errors of Amino Acid Metabolism in Man*

Amino Acid	*Disease*
Arginine	Citrullinemia; hyperammonemia
Aspartic acid	Argininosuccinic aciduria
Cystine	Cystinuria
Glycine	Hyperglycinemia
Histidine	Histidenemia
Hydroxyproline	Hyperhydroxyprolinemia
Isoleucine	Maple syrup urine disease
Leucine	Maple syrup urine disease
Lysine	Hyperlysinemia
Methionine	Homocystinuria
Phenylalanine	Phenylketonuria
Proline	Hyperprolinemia
Tryptophan	Hartnup disease
Tyrosine	Albinism; tyrosinosis; alkaptonuria (ochronosis)
Valine	Maple syrup urine disease; hypervalinemia

anesthetic drugs. The anesthetic management of patients with renal insufficiency is discussed in another chapter.

Genetically determined abnormalities of metabolism of most of the amino acids have been detected (Table 1–1). Such abnormalities usually result in an intense degree of pathology of one or more organs. Because of their low incidence, difficulty in diagnosis and relatively recent recognition, there is only a modicum of scientific knowledge concerning these inborn errors of amino acid metabolism. Even more sparse (or nonexistent) are data concerning the anesthetic management of such disease entities. Perhaps the most frequent and practically important of these disorders is phenylketonuria.

PHENYLKETONURIA

Phenylalanine is an essential amino acid and precursor of the amino acid tyrosine. Figure 1–1 depicts the alternate pathways of phenylalanine metabolism. Its conversion to tyrosine is dependent upon the enzyme phenylalanine hydroxylase. Tyrosine, in turn, is the precursor of the catecholamines, thyroid hormone and melanin. The phenylalanine not normally hydroxylated to tyrosine is metabolized to pyruvic-, lactic-/or acetic-acid derivatives of phenylalanine and ortho-hydroxyphenylalanine and excreted in the urine. Because of a genetically determined absence of the heat labile fraction of phenylalanine hydroxylase, the phenylketonuric patient cannot convert phenylalanine to tyrosine. Rather, there is an accumulation of phenylalanine in the body and its urinary excretion is increased. Simultaneously, there is an increased utilization of the alternate metabolic pathways and a consequent elevated urinary excretion of these metabolites. The elevated levels of phenylalanine and its metabolites have other biochemical sequelae, probably by inhibiting to varying degrees a large number of enzymatic systems. Tyrosinase, an enzyme involved in melanin synthesis, is inhibited, and this probably explains the decreased pigmentation of affected individuals. Decreased blood catecholamine levels have been predicted (see Fig. 1–1) and detected. The metabolism of the amino acid tryptophan is also adversely affected, with a secondary effect occurring on the metabolism of the cerebral amine, 5-hydroxytryptamine (serotonin), a tryptophan derivative. Indeed, the major pathology (diffuse or focal demyelinization) in phenylketonuria is located in the brain, but little is known about the mechanism(s) by which brain function is disturbed. A small amount of phenylalanine may also be oxidized in the brain, and it is possible that this minor fraction may have a disproportionate effect on intellectual function.

Phenylketonuria is prevalent in about one in ten thousand persons, and, although there is a genetic heterogeneity of the disease, the classic case is inherited in an autosomal recessive pattern. Phenylketonuric infants are normal in appearance at birth, but within the first four months of life they present vomiting, irritability, musty body odor and/or eczema. With increasing age, however, the key clinical manifestation, mental retardation, usually becomes obvious. Although about 25 per cent of such children have no detectable neurologic abnormalities, the remainder may have a wide range of findings, including hyperreflexia, hypertonia, unusual body motions and behavioral abnormalities. Most have electroencephalographic abnormalities, and seizures occur in about one-third of such patients. Their hypopigmentation is accompanied by easily traumatized skin.

Successful therapy usually necessitates early detection plus early institution of a diet containing very low amounts of phenylalanine. Excessive restriction of phenylalanine, however, may result in tissue protein catabolism, which in turn may result in elevated blood phenylalanine levels. Hypoglycemic episodes have been reported, but the pathophysiology, unless related to defective catecholamine synthesis, is obscure.

The phenylketonuric child is, unless