

Congenital Metabolic Diseases of Pediatric Patients:

Anesthetic Implications

Burnell R. Brown, Jr., M.D., Ph.D.,* Philip D. Watson, M.D.,† Lynn M. Taussig, M.D.‡

THE LARGE NUMBER of congenital metabolic disorders makes a complete discussion of the biochemical problems, hazards, pharmacologic implications and anesthetic recommendations for each impossible. This review is confined to discussion of certain aspects of several genetically acquired diseases of metabolism which the anesthesiologist may be called upon to manage in pediatric patients. Most of these conditions are rare, but it is incumbent on the anesthesiologist to be able to manage such cases on sound, scientific grounds. The rationale for therapeutic agents used in these patients is stressed because the mechanism involved may be unknown to the anesthesiologist. Pediatric patients with these diseases have particular anesthetic problems and/or illustrate how a thorough understanding of pathophysiology and natural history leads to a more rational approach to management. As more information is gained about a genetic disorder, therapy and responses to therapy will become more understandable and adverse reactions more preventable.

Every genetic metabolic disease is the result of a specific enzyme defect (or defects) in function or in amount. In this review, diseases in which defects are known (*e.g.*, homocystinuria), suspected (*e.g.*, myotonia congenita), and unknown (*e.g.*, cystic fibrosis) are discussed. Therapeutic approaches to genetic metabolic disease include: a) supplying the missing product; b) preventing sub-

strate accumulation; c) preventing alternate product synthesis; d) enzyme induction; e) enzyme replacement; f) increasing deficient function with cofactor administration; g) compensatory therapy. Obviously, the ideal way to treat the consequences of a genetic disease is to normalize the patient biochemically. For diseases where the pathophysiology is clear, this goal is approachable; for conditions where the pathophysiology is unknown, only compensatory therapy is possible.

Homocystinuria

Homocystinuria illustrates many of the problems of diagnosis and treatment of rare congenital metabolic diseases and demonstrates that understanding the biochemical defects is important. This condition is associated with particular anesthetic hazards that may well be avoided by careful consideration of its pathophysiology. It is characterized by excretion of large amounts of the amino acids homocystine and methionine in the urine. Clinically, the disease manifests as osteoporosis, mental retardation, hypoglycemia, and repeated venous and arterial thrombotic episodes, associated with a high surgical mortality rate.¹⁻³ Sudden occlusion of cerebral, pulmonary, renal, and myocardial vessels in the perioperative period presents the anesthesiologist with a high risk of mortality and a great challenge in management. The disease is transmitted as an autosomal recessive. It is one of the more common aminoacidopathies.¹

The biochemical defect initially elucidated was a deficiency of cystathionine synthetase. Mudd *et al.*⁴ reported the deficiency of this enzyme in livers of homocystinuric patients. Since this enzyme has a pyridoxine (vitamin B₆) cofactor, attempts have been made to increase the activity of any residual cystathionine synthetase activity using large

*Professor and Head, Department of Anesthesiology.

†Assistant Professor, Department of Pediatrics and Pharmacology.

‡Assistant Professor, Department of Pediatrics. Received from the University of Arizona, College of Medicine, Tucson, Arizona 85724. Supported in part by USPHS Grant #1 T22-CM00071-01.

Address reprint requests to Dr. Brown.

doses of B₆.^{1,2,4-7} Such therapy has met with variable success, and is not completely benign.^{1,2,5,7-9} For example, Schimke *et al.*¹ reported homocystinuric patients who not only did not respond to B₆ therapy but also developed seizures when treated with this vitamin. In addition, there are theoretical disadvantages to pyridoxine therapy because the enzyme responsible for cystathionine metabolism (cystathionase) is also B₆-dependent, and any B₆ administration may reduce residual cystathionine, with consequent adverse effects. In patients with complete absence of cystathionine synthetase or a defect different from cystathionine synthetase deficiency, B₆ would not be expected to correct the biochemical abnormality. Supplying the missing product (cystathionine) has been unsuccessful because of rapid renal clearance.¹ Increased synthesis of cystathionine by the administration of homoserine and cysteine to patients with homocystinuria leads to cystathionine excretion.^{10,11} Whether cystathionine is formed in the human brain is unknown, although the reaction occurs in mice.^{12,13}

Responses to treatments vary widely, probably because the condition is caused by a variety of defects. The most common variant of the disease is cystathionine synthetase deficiency. However, it is apparent that there are many causes of the disease. The association between the clinical manifestation and the biochemical defect is unclear, which makes evaluation of therapy difficult. The incidence of thromboembolism in non-cystathionine synthetase deficiency is unknown. Reported regimens employed for homocystinuria have included all of the possible therapeutic approaches listed except enzyme induction or replacement.

Attempts have been made to prevent substrate accumulation through the limitation of dietary methionine and through stimulation of the remethylation of homocysteine. This is done by administration of vitamin B₁₂, folic acid, and other biochemical stimulants of methylation reactions (*e.g.*, betaine, glycine, serine, and choline). The responses to these therapeutic modalities depend on the exact biochemical abnormality. In homocystinuria secondary to tetramethylfolate methyltransferase deficiency, for example, such

therapy would be expected to be more efficacious than vitamin B₆.^{16,17} However, since patients with homocystinuria due to pure cystathionine synthetase deficiency also appear to require larger amounts of B₁₂ and folate than do normal individuals,^{5,6,14,15,17} such remethylation stimulation is logical. Another approach to preventing substrate accumulation has been the limiting of dietary methionine.^{1,2} This has had some success, but does not in itself provide the missing product (cystathionine). Although the function of cystathionine is unknown, there are large amounts in normal brain. Homocystinuric patients have low brain levels of this substance.^{12,18} Limiting methionine intake also limits alternate product synthesis—an area still inadequately explored in this disease. When homocysteine cannot be converted to cystathionine, cysteine (or cystine) becomes an essential amino acid, and use of high-cystine diets is another method of supplying the missing product, cystathionine.^{1,2,7,9,19}

These approaches to therapy, coupled with varying responses of patients, are partially explained by the many biochemical causes of the disease. Subtypes of the abnormality include:

- A. Cystathionine synthetase deficiency—most common
 - B₆-responsive
 - B₆-unresponsive
- B. Methylene tetrahydrofolate reductase deficiency^{16,17,20}
 - Methylmalonic acidemia¹⁷
 - Defective B₁₂ metabolism^{20,21}

Obviously, elucidation of the basic biochemical defect in any patient with homocystinuria makes a rational approach more possible. Until this is achieved, the usual approach includes a low-methionine–high-cystine (cysteine) diet, B₆, B₁₂, and folic acid. The use of cysteine and homoserine administration to enhance cystathionine content has not been adequately evaluated, but the addition of homoserine to the regimen might be warranted. This approach will frequently lead to correction of the most obvious biochemical abnormality, high homocystine levels.

The particular anesthetic problems of the

homocystinuric patient are 1) thrombotic episodes, especially pulmonary, intracranial, renal, and intestinal,^{2,22} and 2) hypoglycemia secondary to hyperinsulinemia.²³ The cause of the thromboembolic episodes is unclear. Investigators have reported increased platelet adhesiveness in some homocystinuric patients^{2,6} while others have been unable to demonstrate such a platelet abnormality.^{1,15} There is evidence that homocystine activates Hageman factor.²⁴ Successful attempts to prevent thromboembolic phenomena through anticoagulation and the use of platelet aggregation inhibitors have been reported.^{2,22,24} (Although the relationship between elevated homocystine levels and thromboembolic phenomena is unclear, recent work has indicated that there is a direct relationship between homocystine levels and shortened platelet survival.^{2,26}

Attempts have been made to lower homocystine levels empirically by a variety of approaches, mentioned above. In addition, heparin and dextran have been used to prevent thrombosis. Recently it was shown that heparin was unable to lengthen platelet survival in two pyridoxine-resistant homocystinuric patients, but that in these two patients dipyridamole (100 mg, q.i.d.) did correct platelet survival.^{2,26} On the basis of this recent evidence, heparin is not drug of choice in the perioperative management of these patients. The same work demonstrated in a baboon homocystinuric model that: 1) shortening of platelet survival is in direct proportion to homocystine level, and, 2) elevated homocystine levels are associated with appearance of circulating endothelial cells (a manifestation of vascular injury).^{2,26}

It is possible that elevated homocystine itself causes vascular injury, which secondarily causes platelet thromboemboli. If true, the rational approach to prevention of this phenomenon would include biochemical normalization of homocystine, methionine and cystine levels and the use of antiplatelet utilization drugs (dipyridamole and aspirin).^{2,26} In patients unresponsive to attempts to lower homocystine levels, or where an emergency situation exists, it appears rational to inhibit platelet utilization with aspirin and dipyridamole.

The second complication of concern to the

anesthesiologist in homocystinuric patients is the combination of hyperinsulinemia and hypoglycemia.²³ It is postulated that the pancreatic islet cell is sensitive to the balance of sulfur amino acids and that the hypermethionemia associated with this disease induces hypoglycemia secondary to hyperinsulinemia. Holmgren *et al.*²³ postulate that seizures in homocystinuric patients may be secondary to hypoglycemia as well as to thromboembolic phenomena. Again, therapy aimed at correcting the biochemical defect, especially the hypermethionemia, seems warranted. In lieu of adequate biochemical response or an emergent procedure, it would appear prudent to be prepared to treat hypoglycemia and to monitor glucose levels at 30-minute intervals during operation and anesthesia.

It is probably best to avoid any drug which may predispose to a hypercoagulable state, although this situation has been inadequately studied. Thus, it has been recommended that older homocystinuric patients avoid oral contraceptives.^{1,22} Likewise, agents such as epsilon-aminocaproic acid, an anti-fibrinolytic, are contraindicated.

Obviously, anesthesia and surgery present significant risks to the homocystinuric patient. The elective procedure most commonly performed in homocystinuric children is excision of the ectopic lens of the eye. Several additional precautions should be observed: a) anesthetic agents and levels associated with the least possible decreases in cardiac output should be employed to minimize peripheral circulatory stagnation; b) the extremities should be wrapped with elastic bandages and manipulated intraoperatively to prevent pooling of blood. If the biochemical defects are managed preoperatively as carefully as possible, if platelet "stickiness" and/or shortened survival are prevented, and if general measures to maintain circulation and minimize trauma are instituted, it is possible to reduce surgical mortality and morbidity.²³ In these cases surgery should be kept to a minimum. For example, for ectopia lentis complete luxation into the vitreous or at least out of the visual axis is *not* an indication for lens removal unless phacolytic glaucoma is present; while acute dislocation into the anterior chamber is an absolute indication

for surgery.²⁷ Also, patients with conditions common to homocystinuria (such as ectopia lentis or unexplained thromboembolic phenomena) should be screened for the disease before operation.^{27,28}

An understanding of the varied pathophysiology and therapies of homocystinuria should allow more rational and safer anesthetic management of these rare but difficult cases.

Congenital Myotonic Diseases

There are three congenital myotonic diseases: 1) paramyotonia congenita (Eulenburg), 2) myotonia congenita (Thomsen's disease), and 3) myotonia atrophica. Although there is reason to suspect an association between the myotonias and adynamia episodica hereditaria (Gamstorp) and paralysis periodica paramyotonia, the relationship between these conditions is unclear. There is ample evidence that the three myotonias result from different genetic defects.²⁹ These are extremely rare disorders, and little is known about their pathogenesis, treatment or particular problems. Myotonia congenita, paramyotonia and myotonia atrophica are discussed as separate disease entities. There appears to be sufficient dissimilarity to justify classifying them as separate entities, but there are also clinical as well as biochemical similarities. More than one of these disorders have occurred in a single family. This indicates that the diseases may be due to the same or related defect with variable presentation.³⁰

Paramyotonia congenita is defined as: a) myotonia that is manifested in childhood, is generalized, is frequently paradoxical, with symptoms greatly increased by cold; b) episodes of flaccid paralysis with or without exposure to cold; c) absence of dystrophic features; d) no tendency to improve; e) autosomal dominant inheritance.³¹

The clinical picture, together with a positive family history, should make diagnosis possible. The pathophysiology of this disease is unknown; however, hyperkalemic periodic paralysis and paramyotonia have features in common, including the induction of myotonia by potassium administration. Also,

symptoms are exaggerated by exercise and cold, both of which increase muscle water and sodium while concomitantly lowering muscle potassium concentration.³¹

There is no specific treatment except avoidance of initiating factors such as cold and exercise. It is significant that neostigmine and acetylcholine have been reported to induce myotonia and thus should be avoided.³¹

The paramyotonic child scheduled for surgery does not present a serious problem unless profound muscular relaxation is required. Since both neostigmine and potassium may enhance paralysis in these individuals, depolarizing and nondepolarizing neuromuscular blocking agents appear to be relatively contraindicated, particularly if reversal is needed with the latter. The use of potent inhalation agents such as halothane, diethyl ether, or enflurane for intubation and relaxation appears to be a rational approach. During operation, hypothermia should be minimized by use of warming blankets and constant temperature monitoring. Potassium administration should be avoided. Fresh blood is indicated if transfusion is required. Drugs that alter potassium balance (thiazide diuretics and digitalis, for example) should be excluded or used only with extreme caution. The Block-Aid type of neuromuscular monitoring device may be of considerable value in managing these patients.

Myotonia congenita, or Thomsen's disease, is another disorder characterized by myotonia (inability to relax contracted skeletal muscle). The condition appears to be inherited, either as an autosomal dominant or in an autosomal recessive manner.³² The pathogenesis is unknown, and there is no specific therapy despite some claims for the efficacy of quinine, procainamide, and prednisone. Usually, patients learn to live with their disease without therapy.³³

There appears to be no specific anesthetic risk related to this condition, with the exception of cold and depolarizing neuromuscular blocking agents. Succinylcholine should be avoided, since there are scattered reports in the literature of severe tetanus resulting from its use. Like paramyotonia, the condition appears to be made worse by the administra-

tion of neostigmine.³³ Since some patients with Thomsen's disease later develop signs of myotonia atrophica,³⁴ the complications of this myotonia in the following discussion should be looked for and avoided if possible.

Myotonia atrophica is associated with myotonia, muscle wasting, weakness, frontal baldness, cataracts, Raynaud's phenomenon, occasional diabetes mellitus, testicular atrophy, ptosis, and mental retardation.³⁵ The pathophysiology is unknown, and there is no known treatment. The disease is inherited as an autosomal dominant, and the linkage of an identifiable gene product (although not the gene itself) makes prenatal diagnosis possible in 40 per cent of couples at risk. Of the myotonias, this is the most severe, and it is associated with many surgical problems. Many surgical and anesthetic complications, including cardiac, pulmonary, gastrointestinal and endocrinologic abnormalities, are attributed to the disease.³⁵⁻³⁹ Although the skeletal muscle defects are well recognized, there is also widespread involvement of involuntary (cardiac and smooth) muscles.^{35,40} In fact, a few patients with solely involuntary muscle involvement have been reported.⁴⁰ Such widespread muscle disease makes the patient with myotonia atrophica a poor anesthetic risk.³⁴

Dysphagia, hoarse voice, nasal regurgitation, frequent tracheal aspiration, decreased esophageal contraction with prolonged relaxation, swallowing abnormalities, biliary tract abnormalities, malabsorption, cardiac abnormalities with arrhythmias, uterine dysfunction, alveolar hypoventilation, and bladder dysfunction all occur, and are associated with difficult anesthetic management.³⁵

Of particular anesthetic importance are the swallowing and aspiration abnormalities and the cardiac involvement. There are also unusual pharmacologic responses that must be considered. Abnormalities of swallowing and aspiration are particularly troublesome, especially since there may be extensive involvement of the deglutition mechanism before the patient is aware of any motor dysfunction. Thus, aspiration pneumonia is a common cause of death in these patients.³⁵ These problems, coupled with alveolar hypoventilation and weak cough due to diaphragmatic

involvement, require all procedures be done with particular care to preserve and protect the airway. An endotracheal tube is mandatory in these patients. Postoperative aspiration is an ever-present hazard, and should be assiduously avoided.

Cardiac muscle involvement is common in this disorder.^{37,39,40} Electrocardiographic and vectorcardiographic changes consistent with myocardial infarction but without tissue necrosis are not uncommon.^{37,39} Cardiac arrhythmias (especially tachyarrhythmias) occur,^{30,37-39} and sudden death is not uncommon. Since unusual responses to digitalis have been reported, and because heart block is common, digitalis (and probably diphenylhydantoin) should be given only cautiously. The low muscle potassium concentration in this disease and the susceptibility to antiarrhythmic drugs are perhaps related. Other medications reported to cause abnormal responses have included thiopental anesthesia.^{34,39,41,42} Patients who have this disease may develop prolonged apnea with an abnormal degree of muscle relaxation following this hypnotic. Sudden death after intravenous injection of thiobarbiturates has been reported, and is probably related to an abnormal negative inotropic response.

Succinylcholine has also been reported to be hazardous in patients with myotonia atrophica,⁴³ and although the problem appears related to the muscle membrane rather than to the endplate, unusual responses to neuromuscular blocking agents are to be expected. Antibiotic drugs with neuromuscular effects such as kanamycin, gentamicin and neomycin should be used only with extreme caution.

The relationship between the three myotonias is unclear. The clinical picture and severity vary greatly among patients. There is a large amount of clinical overlap between diseases, and patients may appear to progress from a relatively mild disease (Thomsen's disease or myotonia congenita) to a severe disabling form (myotonia atrophica). Anesthetic management of any patient with myotonia must involve extreme care or avoidance of any factor known or suspected to have adverse effects on this condition.

Thus, cold, exercise, changes in potassium

balance, cholinergic or anticholinergic drugs, antiarrhythmic agents, barbiturates, and neuromuscular blocking agents should be avoided if possible or used with extreme care in these cases. In addition, any patient who manifests an unusual response to any of these should bring to mind the possibility of a myotonic condition. Probably all patients with obscure clinical problems involving nonvoluntary muscle such as the myocardium, the gastrointestinal tract, and the neuromuscular apparatus of respiration should be considered to represent possible cases of myotonia dystrophica. When the diagnosis is known, avoidance of any unnecessary surgical procedure, use of regional anesthesia if possible, and careful consideration of the peculiar problems of the myotonic patient should lessen mortality and morbidity and reduce anesthetic risks.

Cystic Fibrosis

Cystic fibrosis (fibrocystic disease of the pancreas; mucoviscidosis) is a common, fatal, autosomal recessive disease of the Caucasian race. (It occurs less often among people of the Negro race). It is a generalized disorder of the exocrine glands but may involve other organs as well. The sweat glands have increased electrolyte (sodium, chloride, potassium) concentrations, and measurement of chloride concentrations in sweat is used to confirm the diagnosis of this disease. The major clinical manifestations are chronic pulmonary disease and malabsorption.⁴⁴

The etiology is unknown. The basic pathogenetic mechanism for the production of most of the signs and symptoms involves obstruction of the ducts of the various exocrine glands by viscid secretions. In the lungs this initially causes obstruction of the small airways, but as the disease progresses larger airways become occluded. This predisposes to chronic obstructive pulmonary disease which is progressive and eventually fatal. Outside of the immediate newborn period, the main causes of death of patients who have cystic fibrosis are these pulmonary manifestations and secondary cor pulmonale. Initially these patients manifest decreases in maximum flow rates, especially at low lung

volumes; mild air trapping (as demonstrated by an increased residual volume to total lung capacity ratio); and slight hypoxemia due to ventilation-perfusion imbalance.⁴⁴ Deficiencies in pancreatic exocrine function lead to malabsorption, steatorrhea, and various forms of intestinal obstruction.

As the disease progresses, the pulmonary symptoms become worse, with increased coughing and sputum production. The sputum is very thick and tenacious, and may have a green color typical of *Pseudomonas* colonization, although *Staphylococcus aureus* is also commonly found in the sputum. Flow rates and vital capacity progressively decrease, and pulmonary reserve becomes minimal. The findings, then, are consistent with both obstructive and restrictive patterns of pulmonary involvement. With advanced disease, airway resistance increases, and hypercapnia develops as a near-terminal event. The therapy for the pulmonary component of cystic fibrosis includes postural drainage, appropriate antibiotics, and good nutrition. Antibiotics are often used continually in the more severe cases, but otherwise they are used for acute exacerbations. The use of aerosols, mist tent therapy, and n-acetylcysteine is presently controversial.⁴⁴

A distinctive type of biliary cirrhosis often develops in patients who have cystic fibrosis. Initially it is focal, asymptomatic, and may be associated only with an abnormal SGOT. In approximately 2 to 3 per cent of the patients it progresses on to a multifocal pattern, with subsequent portal hypertension, esophageal varices, and hypersplenism.⁴⁵ Numerous other organs may be involved either primarily or secondarily. The variety of organs involved in cystic fibrosis predisposes the patient to a number of surgical procedures that either are peculiar to this disease or are used more often in management of patients who have it.⁴⁶⁻⁴⁹ These are indicated in table 1. Of course, the cystic fibrosis patient may also undergo surgical procedures unrelated to the basic disease. The first manifestation of cystic fibrosis may be meconium ileus of the newborn secondary to deficient pancreatic function.

Because of extensive pulmonary involvement in cystic fibrosis, the anesthetic management and the pre- and postoperative care

of these patients may be difficult. Prior to any surgical procedure, a roentgenogram of the chest, complete blood count, arterial blood gases, liver function tests,⁵⁰ urinalysis, and blood urea nitrogen should be obtained. In the case of the older patient who is able to cooperate, detailed pulmonary function testing should be undertaken to determine function and reserve. Elective surgical procedures should be avoided when a patient has a vital capacity less than 50 per cent of that predicted for sex and height, a P_{aCO_2} above 50 mm Hg, and a FEV₁/FVC ratio less than 65 per cent, and when no pulmonary reserve can be demonstrated on a maximum expiratory flow-volume curve.

If the patient is currently having an acute pulmonary exacerbation or a slow, progressive deterioration of pulmonary function has been demonstrated over the previous months, then appropriate antibiotics together with extensive postural drainage should be given for at least 10 days prior to the surgical procedure. It may be beneficial to perform fiberoptic bronchoscopy with topical anesthesia to aspirate as much of the secretions as possible. If the patient's condition has been stable and he has no acute pulmonary infection (the patient with cystic fibrosis almost always has bacterial organisms in his sputum; these are not necessarily indicative of an acute exacerbation), then antibiotics should be given for two days prior to operation and continued until the patient is able to cough well and participate actively in the postural drainage. Often the antibiotics must be continued for most of the postoperative period. Postural drainage should be instituted upon admission to the hospital, and usually involves as many as four treatments per day, with all segments of the lungs treated. It has been recommended by several authorities that tracheostomy be performed several days prior to operation in severe cases in order to facilitate good pulmonary toilet during surgery and the postoperative period.⁴⁸ Other physicians caring for cystic fibrosis patients question the need for an elective tracheostomy and use an endotracheal tube, with removal of the tube when the patient is able to cough effectively. Certainly, the approach to pulmonary toilet should be individualized

TABLE 1. Surgical Procedures Used More Frequently in Cystic Fibrosis

Newborn period
Laparotomy
Meconium ileus
Small-bowel atresia
Volvulus
Infants, children, young adults
Nasal polypectomy
Thoractomy
Lobectomy
Bronchiectasis
Hemoptysis
Pneumothorax
Bronchial lavage
Laparotomy
Meconium ileus equivalent (bowel obstruction)
Intussusception
Volvulus
Appendicitis
Splenorenal or portocaval shunts for portal hypertension
Herniorrhaphy

depending on the patient, the severity of the pulmonary manifestations, and the nature of the operative procedure.

When the patient is hypoxic, transfusion of packed cells to increase the hemoglobin to a minimum of 12 g/100 ml may be beneficial in the perioperative period to provide an increased oxygen-carrying capacity. Infants with cystic fibrosis, especially those less than a year old, have an increased risk for hemorrhagic phenomena due to vitamin K deficiency because of decreased gastrointestinal synthesis of vitamin K and malabsorption of fat-soluble vitamins. Therefore, infants (and possibly all patients) with cystic fibrosis undergoing surgical procedures should be given vitamin K parenterally.

The increased ventilation-perfusion abnormalities that occur in cystic fibrosis predispose to slow induction of anesthesia with inhalation anesthetics. Therefore, induction of anesthesia may be aided by an intravenous agent such as thiopental or ketamine. This can then be followed by an inhalation anesthetic such as halothane. It must be kept in mind that these patients may have pre-existing hepatic impairment.⁵⁰ However, there is no documentation of evidence to indicate whether these patients are more

prone than others to exacerbation of pre-existing hepatic problems when halogenated anesthetics such as halothane are used. Muscle relaxants such as succinylcholine or *d*-tubocurarine may also be used. There is no absolute contraindication to any common preanesthetic drug. It must be kept in mind that the cardinal rules of management of these patients are prevention of respiratory depression and avoidance of inspissation of tracheobronchial secretions. Therefore, agents such as narcotics and anticholinergics should be employed only with good clinical judgment.⁴⁸

During the course of the surgical procedure, extensive aspiration of secretions in the tracheobronchial tree should be performed frequently. High-humidity anesthetic systems are desirable. A heated nebulizer in the inspiratory circuit of an Ayre's T-piece system is ideal for the neonate or young child. Before the endotracheal tube is removed, extensive aspiration should again be done. Assisted or controlled ventilation during the operation may prevent hypercapnia. Hyperventilation during surgery should be avoided, as the hypocarbia may result in relative hypoventilation postoperatively.

When a lobectomy is performed for localized bronchiectasis, the opposite lung should have its major bronchus occluded by a ventilating tube in order to prevent contamination of the relatively good lung by secretions from the area being excised. High FL_{50} 's are necessary when such an endobronchial blocking technique is employed. When abdominal operations are performed, an effective cough mechanism may not be available for several days postoperatively, since the patient will be unable to generate adequate abdominal pressure. Tracheobronchial secretions may become somewhat more viscous during and immediately after the surgical procedure because of the medications used. Therefore, increased hydration of the patient by the intravenous route may be indicated, provided cor pulmonale with congestive cardiac failure is not a problem.

In the postoperative period arterial blood gases should be monitored to evaluate respiration. Postural drainage should be instituted as soon after the operation as possible.

Atelectasis and pneumonia are frequent postoperative complications. In some patients who apparently have had stable pulmonary function preoperatively rapid pulmonary deterioration has occurred postoperatively, and this possibility should be kept in mind.

Glycogen Storage Diseases

Ten types of glycogen storage diseases have been described, classified on the basis of enzyme deficiencies.⁵¹ The basic abnormality shared in common by these entities is a defective pathway of glycogen metabolism. These various biochemical defects may produce either excessive amounts of normal glycogen or abnormal glycogen. Clinically, two groups of glycogen storage diseases are identified: a group that includes abnormalities mainly involving the liver, and a group of primarily skeletal and cardiac muscle abnormalities. The Coris⁵² described the decreased content of the enzyme glucose-6-phosphatase in patients with von Gierke's disease (Type I), and inaugurated studies linking enzyme deficiencies with hereditary metabolic disorders.

TYPE I (VON GIERKE'S DISEASE)

Type I glycogen storage disease is the most common of this constellation of syndromes. It is inherited as an autosomal recessive.⁵³ The patients have hepatomegaly and renomegaly, stunted growth, and tend towards severe hypoglycemia and acidosis. The basic defect is a deficiency of the enzyme, glucose-6-phosphatase. In fact, the confirmatory diagnosis of the disease rests on demonstration of this quantitative enzyme abnormality in hepatic biopsy specimens.

The pathophysiology is fairly well understood. Glucose-6-phosphate may enter into one of four reactions: 1) conversion to glucose; 2) dephosphorylation to free glucose; 3) oxidation via the hexose monophosphate (HMP) shunt; 4) anaerobic glycolysis to pyruvate and lactate. Glucose-6-phosphatase is a microsomal enzyme catalyzing reaction 2, that is, conversion of glucose-6-phosphate to glucose. The glucose this normally produces leaves the liver to enter the blood stream.

Since this reaction is inhibited, hypoglycemia occurs. The hypoglycemia is persistent, and is not overcome by injection of catecholamines. The glucose tolerance curve is typically diabetic. Galactose and fructose are rapidly converted to lactate.⁵⁴ Fructose infusions are not tolerated because of rapid conversion to lactic acid with concomitant metabolic acidosis. Glycogen synthesis is not inhibited, however, and this carbohydrate accumulates in excessive amounts in the liver and kidney. The levels of glucose-6-phosphate are not low in the disease because of enhanced gluconeogenesis. Gluconeogenesis from protein catabolism is one of the primary causes of stunted growth. Since hypoglycemia inhibits insulin and growth hormone secretion, body growth is additionally decreased. Hypoglycemia also encourages utilization of fat by peripheral tissues, so that ketones accumulate and a further cause of acidosis occurs. The acidosis is further augmented by increased lactic acid, as the glycolytic pathway is quite active. Hepatomegaly, hypoglycemia, and acidosis usually appear within one month of age.

Several other characteristic pathologic features of Type I glycogen storage disease are of interest to the anesthesiologist. Osteoporosis occurs secondary to alterations in calcium balance produced by the lactic-acid acidosis. Undefined bleeding abnormalities occur in some of these patients, making surgical and certain regional anesthetic procedures hazardous.⁵⁵ Hyperuricemia is common. Patients in the first decade of life may have gout.⁵⁶ The mechanism of hyperuricemia is probably manifold, due to lactate-uric acid tubular competition, exaggeration of uric acid retention in the face of ketonemia, and uric acid retention secondary to hypoglycemia.

Anesthetic management of these infants and children should focus on prevention of hypoglycemia and lactic-acid acidosis.⁵⁷ It has been postulated that those inhalation anesthetics that customarily induce hyperglycemia by sympathetic stimulation (cyclopropane, ether, fluroxene) are probably of little value in this regard in von Gierke's disease because epinephrine injection itself does not stimulate glycogenolysis.⁵⁸ An indwelling arterial catheter should be

employed intraoperatively for frequent determinations of pH and standard bicarbonate. Sodium bicarbonate solution should be infused as needed to neutralize the metabolic acidosis. Blood glucose should be determined frequently, either with standard laboratory methods or by use of Dextrostix (Ames). Ten per cent dextrose solution should be administered throughout the procedure. Maintenance of a high level of plasma glucose may decrease the metabolic acidosis.⁵⁹ It would appear that these metabolic abnormalities worsen with length of time of the operative procedure, so that the hallmark of surgery in these cases should be cautious speed.

TYPE V (MCARDLE'S DISEASE)

McArdle⁶⁰ described a patient with limited performance of strenuous muscle activity in whom ischemic exercise produced no increase in venous blood lactic acid. Several other patients with this disability have been reported since. Subsequently, it was found that the basic biochemical defect is an absence of muscle phosphorylase.⁶¹ More than half the patients have myoglobinuria.⁶²

Muscle phosphorylase in resting skeletal muscle exists ordinarily in the inactive ("b") form. Upon exercise, phosphorylase "b" is converted to active phosphorylase "a." Phosphorylase "a" catalyzes the conversion of muscle glycogen to utilizable glucose. Since the preferred substrate for resting muscle is fatty acid, no abnormality is seen in patients with Type V glycogen storage disease when they are quiescent. With exercise, however, the abnormal muscle of this disease is unable to convert glycogen to glucose for energy utilization. Consequently, muscle cramps, weakness, and failure occur during stress due to substrate lack. No other organ is affected in these individuals. Healthy muscle builds up lactic acid during exercise as the glycolytic pathway is enhanced. Muscle with phosphorylase deficiency cannot produce lactic acid due to unavailability of the substrate, glucose. In contrast to normal muscle, muscle with Type V disease is able to utilize fructose efficiently. Symptoms of this disease can be quickly ameliorated by intravenous infusion of either glucose or fructose.

TABLE 2. Clinical Features of Familial
Dysautonomia

Absence of lacrimation
Smooth tongue with hypotrophic or absent papillae
Failure to respond to painful stimuli
Motor weakness
Postural hypotension; paroxysmal hypertension
Aspiration pneumonitis, recurrent
Inhibition of growth
Drooling and difficulty in deglutition
Erratic temperature

The major anesthetic risk presented by these patients is obviously respiratory failure due to muscle fatigue. Careful attention to administration of glucose solutions during the operative period is essential. It is suggested that a bolus of 50 per cent glucose be given near the termination of the procedure to facilitate respiratory muscle function postoperatively.

Familial Dysautonomia (Riley-Day Syndrome)

Familial dysautonomia is an unusual syndrome confined typically to Ashkenazi Jewish children. It is inherited as an autosomal recessive. The disease is characterized by deficits in all aspects of the nervous system: autonomic, motor, sensory, and psychic.⁶³ Manifestations may be detected early in infancy. Clinical hallmarks include those listed in table 2.

Because there is profound affliction of the nervous system, a variety of physiologic alterations is detectable in infants and children with this condition. Respiratory control is abnormal.⁶⁴ Dysautonomic children fail to respond in a usual manner to increased CO₂ levels, and hypoxemia fails to bring about expected respiratory increases. Both the parasympathetic and the sympathetic division of the autonomic nervous system are deranged. It has been suggested that there is a deficiency of the cholinergic transmitter, acetylcholine, in this syndrome.^{65,66} Methacholine, an agent that mimics acetylcholine, temporarily restores certain functions (knee reflex, taste, tears, etc.) that are absent in the dysautonomic child. The dose of this parasympathomimetic agent needed to produce cholinergic stimulatory effects is

less in the dysautonomic than in the normal child. The sympathetic nervous system is widely affected. The individual with the syndrome usually has an exaggerated response to the intravenous administration of norepinephrine.⁶⁷ Lack of reflex bradycardia when this catecholamine is infused has been observed, indicating altered vagal responses. Dysautonomic patients excrete in the urine more homovanillic acid (a primary metabolite of dopamine) and less vanillylmandelic acid, the normal deaminated, O-methylated metabolite of catecholamines, than normal.^{68,69} This biochemical pattern is so constant that it may be used diagnostically to identify the syndrome. Weinshilboum and Axelrod⁷⁰ have observed that dysautonomic patients have consistently low plasma levels of dopamine- β -oxidase, the enzyme that converts dopamine to norepinephrine by the process of β -hydroxylation. In fact, 25 per cent of children with the Riley-Day syndrome were found to have no dopamine- β -oxidase activity at all. Such an enzyme deficiency could rationally explain reduced sympathetic nervous system activity, and also permit understanding of the increased urinary excretion of homovanillic acid. This block of conversion of dopamine to norepinephrine is possibly a mechanism for the orthostatic hypotension common to these children.⁷¹

Anesthetic management of the patient with familial dysautonomia has been reported by several authors.⁷²⁻⁷⁴ Chronic pulmonary disease manifested as thick, viscid secretions, and acute and chronic bronchitis secondary to repeated aspiration constitutes an important element of preoperative concern. Extensive pulmonary physiotherapy and preoperative antibiotics may be indicated. The use of preanesthetic anticholinergics is questionable. Bronchial secretions may become even thicker with employment of these drugs. In spite of known alterations in autonomic activity, Meridy and Creighton⁷⁴ reported that they observed a normal tachycardic response to atropine. The emotional lability of these individuals may necessitate heavy sedation preoperatively. During anesthesia and operation, three pathologic variations of these children must be closely monitored: ten-

dency to hypotension, erratic temperature control, and abnormalities in ventilatory responses to hypercarbia and hypoxemia. Since chlorpromazine is used to control the excitability of these children, circulatory dynamics may be further compromised by the α -adrenergic blocking capacity of this drug. Obviously, temperature should be closely monitored.

The optimistic aspect of this syndrome for the anesthesiologist is the marked lack of response to pain that these children demonstrate. This problem can be turned to advantage since the concentration of inhalation anesthetics required may be kept to a minimum. In fact, nitrous oxide-oxygen alone may be sufficient for certain procedures. Concentrations of halothane and methoxyflurane greater than 0.5 per cent frequently produce cardiovascular depression.⁷⁴ In fact, the anesthesiologist should address assiduous attention to the labile cardiovascular system during the operative procedure. Positional changes should be performed slowly and carefully. Cardiovascular collapse is common during anesthesia in patients with this syndrome. Although there are leftward shifts in the dose-response curve of directly-acting sympathomimetic agents, these drugs can be cautiously used to minimize decreases in blood pressure. Apparently, neuromuscular blocking drugs such as *d*-tubocurarine are tolerated, and their effects can be reversed in a normal fashion. We can find no report of a case in which ketamine has been used at this time. Theoretically, this agent, which possesses certain sympathetic stimulating activities, might be useful for circulatory instability, but the effects on emotions are conceivably harmful. Postoperative attention should be focused on the lungs. Hypoventilation, inspissated secretions, and aspiration should be avoided by careful observation, and use of an environment with high humidity. The patient should be turned frequently to prevent decubitus ulcers.

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