Dietary Management of Glycogen Storage Diseases

Noel W. Solomons, M.D.
Division of Nutrition and Health
Institute of Nutrition of Central America and Panama
Guatemala City, Guatemala, Central America

Glycogen storage diseases (GSDs) are rare inborn errors of metabolism involving complete or partial deficiencies in the enzymes related to the metabolism of glycogen. Understanding of the defect in intermediary metabolism led to the development of a specific dietary therapy involving frequent daytime feedings and continuous nasogastric nocturnal perfusions with glucose-rich foods for type I GSD (von Gierke disease). This therapy prevents debilitating hypoglycemia and makes free glucose available for glucose-dependent tissues. It suppresses the hormonal signals for glycogenolysis and corrects hyperlipidemias, lactic acidosis, ketosis, and hyperuricemia. Most important, health, well-being, and growth are improved by nutritional therapy. Other GSD states also benefit from specific dietary therapy. This situation illustrates how clinical genetics and modern techniques in enteral nutrient delivery can be combined to the benefit of a specific subclass of pediatric patients with genetic disorders. (CLIN NUTR 1985;4: 95-102)

"Sound nutrition is not a panacea. Good food that provides appropriate proportions of nutrients should not be regarded as a poison, a medicine, or a talisman. It should be eaten and enjoyed."[1]

DIET THERAPY IN METABOLIC DISEASES

This quotation from the Food and Nutrition Board's 1980 report *Toward Healthful Diets*[1] expresses a strong opinion as to how diet is to be viewed by the public and the health profession in terms of its influence on health and nutrition. The statement was intended to reduce excessive popular expectations about the potential of diet per se to prevent or cure disease states. For those involved in human and clinical nutrition, it is indeed a sound principle not to impute to foods or specific nutrients more attributes than they actually possess. On the other hand, in specific health conditions the diets consumed can be crucial components in prevention and therapy, and the management of innumerable infirmities is based largely or exclusively on scientifically sound manipulation of dietary intakes.

The issue of *diet therapy* comes under the purview of all professionals involved with nutrition. However, it is important to identify some distinctions between and among different forms of diet therapy. The most basic form involves nutrient *deficiency* states and dietary maneuvers aimed at restoring and maintaining adequate body stores of a given nutrient(s). The treatment of protein-energy malnutrition[2] is an example. Diet strategies for patients with short-bowel syndrome is another.[3] A second approach in dietary therapy is the *elimination* of potentially offending constituents of the diet. Reduction of energy intake is fundamental to obesity therapy. In uremia the amount of dietary aminonitrogen must be controlled. In hypersensitivity states specific dietary allergens should be withdrawn. Finally, when the pathogenesis of a given *metabolic* disorder is known, clues as to how the balancing and tempering of metabolic substrate availability from the diet can benefit metabolism are often present. In diabetes, for instance, control of total energy intake, reduction of intake of simple sugars and disaccharides in favor of complex carbohydrates, addition of dietary fiber sources,[4] and substitution of fructose as a sweetener[5] are among the principles of dietary management advocated to improve control. In a similar manner glycogen storage disease (GSD) is a metabolic disorder in which diet plays an important role in therapy.

GSD is cited here not because it is a prevalent condition or a major public health problem; in fact, most practitioners of pediatric medicine or dietetics are unlikely to encounter a patient with GSD. However, it represents a classic example of a state in which fundamental understanding of biochemical and genetic defects, combined with modern techniques of nutrient delivery, has been developed into effective therapy. A discussion of GSD is illustrative of the steps in scientific reasoning and clinical experimentation that can lead to improved patient management. Understanding these principles can possibly provide for successful *new* approaches to diet-based therapies for other, as yet unresolved, problems in the treatment of hereditary or acquired metabolic disorders.

THE ROLE OF GLYCOGEN IN GLUCOSE METABOLISM

Except for the time immediately following meals, when dietary monosaccharide is taken up, blood glucose levels depend on *hepatic* sources. This is summarized by Leonard et al.[6]:

"Plasma glucose levels are maintained by the release of glucose from the liver. The glucose is formed either by the breakdown of glycogen or it is synthesized from substrates such as fructose, galactose, glycerol or amino acids. The final common step in all these pathways is the hydrolysis of glucose-6-phosphate by glucose-6-phosphatase to form glucose."

The pathways by which glucose is formed from various metabolic intermediates in the liver is illustrated in Fig. 1. In the fed-state liver, glycogen comprises 5 to

Reprint requests: Noel W. Solomons, M.D., Division of Nutrition and Health, Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala, Central America.

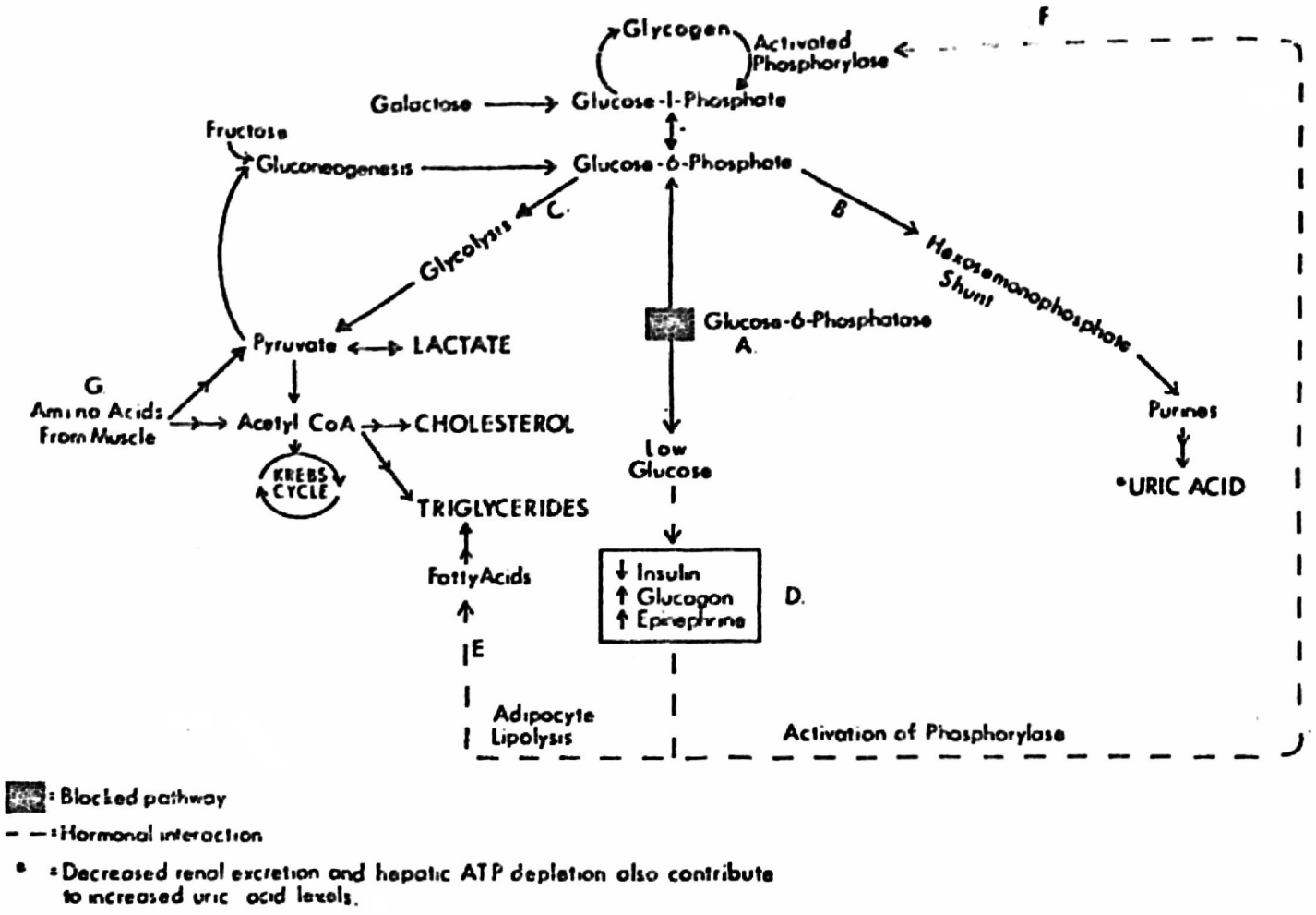

Fig. 1. Metabolic consequences of GSD type I: A, Lack of the enzyme glucose-6-phosphatase prevents dephosphorylation of G-6-P, leading to hypoglycemia. B-C, G-6-P is metabolized via alternative pathways, resulting in elevations of blood lactate, cholesterol, triglycerides, and uric acid. D, Compensatory hormonal activity results in (E) adipocyte lipolysis and (F) stimulation for glycogenolysis. G, Hypoglycemia stimulates gluconeogenesis from noncarbohydrate sources, such as amino acids from muscle and glycerol from adipocyte triglyceride.

7 gm/100 gm wet weight.[7] There is a synthetic limb for glycogen involving enzymes such as glycogen synthetase (UDGP-glycogen glycosyltransferase) and branching enzyme (amylo-1-4, 1-6-transglucosylase). Galactose entering the liver can be metabolized to glucose-1-phosphate (G-1-P). Dietary fructose becomes fructose-1-phosphate, which is split to triose sugars (glyceraldehyde-3-phosphate; dihydroxyacetone-3-phosphate) only to be metabolized to pyruvate as part of the glycolytic process or to become glucose-6-phosphate (G-6-P) by way of two phosphorylated fructose intermediates (fructose-1,6-phosphate and fructose-6-phosphate).

In specific health conditions the diets consumed can be crucial components in prevention and therapy.

The degradation of glycogen is affected by debranching enzyme (minor route), with the release of free glucose, and by phosphorylase, which yields G-1-P, which is converted to G-6-P. Ordinarily this G-6-P is destined for glycolytic energy production within the liver or for the final liberation into the bloodstream of free glucose. All hepatic pathways that would release free glucose (except the action of debranching enzyme) lead to G-6-P. Although the metabolite levels driving the system are mediated by hormonal release and sympathetic nervous discharge, the proximal regulators of glycogen synthesis (glycogenesis) or glycogen degradation (glycogenolysis) are cyclic adenosine monophosphate, glucose, and glycogen itself, as these substrates control the activation or deactivation of phosphorylase.[8]

The pivotal role of G-6-P is obvious from the relationships of glycogen metabolism illustrated in Fig. 1. If glucose-6-phosphatase activity is absent (as in type I GSD), glucose levels in the peripheral circulation would remain depressed except immediately after a meal. Thus the local (intrahepatic) mediators and the systemic hormonal mediators (the hepatotropic hormones such as glucagon and catecholamines) would be trying, in vain, to call upon the release of glucose by signaling glycogenolysis. This leads to an enormous production rate of G-I-P. However, this substrate is rapidly cycled in the liver to G-6-P and down the glycolytic pathway to pyruvate and lactate, then back up the chain to G-6-P and G-1-P and on into the synthesis of new glycogen only to be released from glycogen and return to the G-1-P and G-6-P, and so on up and down the line at high rates of turnover.

This is apparently futile cycling, but it does have a physiologic rationale, for each time that debranching of the glycogen takes place under the influence of *debranching enzyme*, a single molecule of *free* glucose is released. Although this cannot supply the needs of the body for glucose by any means, the hormonal messages continually mediate glycogenolysis in the absence of effective glucose-6-phosphatase activity in the liver. This results in a tiny supply of free glucose and an enormous flux of glycolytic intermediates.

THE GLYCOGENOSES

The GSDs or glycogenoses are a series of varied, inborn errors of carbohydrate metabolism, having their bases in the partial or complete deficiency of enzyme activity in a pathway related to glycogen formation or degradation. This results in the abnormal accumulation of intracellular glycogen in one or another tissue of the body. GSDs primarily affect liver and skeletal muscle enzymes, but the heart and kidneys are also affected in certain types. The clinical entities were described before the specific enzyme defects were identified, and thus the first six types of glycogenoses carry eponymic names associated with the individuals who provided the initial clinical descriptions. Today, however, there are eight types of GSD, each with a specific enzymatic defect. The disorders of glycogen deposition and mobilization with their eponyms, their generic names, identity of the enzymatic defect, nature of the glycogen formed, and tissue/organ specificity, compiled from several reviews on the subject,[7,9-11] are summarized in Table I.

Type I (von Gierke disease) or hepatic or hepatorenal GSD is the most important of the glycogenoses; it is also the GSD that will occupy the major attention of this article. It is described in greater detail herein. Of historic note is the fact that this was the first genetic disorder for which a defect in a *hepatic* enzyme was proved. This occurred in 1952[12] when the Nobel prize laureates, the Coris,

Table I. Synopsis of clinical and biochemical/genetic features of the human glycogenoses

Numerical designation	Eponym	Clinical name	Enzyme defect	Nature of glycogen	Organs and tissues affected
Type I	von Gierke disease	G-6-P deficiency hepatorenal glycogenosis	G-6-P	Normal	Liver, kidney
Type II	Pompe disease	α-1,4-Glucosidase deficiency glycogenosis; lysosomal acid maltase deficiency	α-1,4-Glucosidase (lysosomal acid maltase)	Normal	Generalized (liver, muscle, wbc, connective tissue, heart)
Type III	Forbes disease	Debrancher enzyme deficiency; limit dextrinosis	Amylo-1,6-glucosidase (debranching enzyme)	Abnormal	Generalized (liver, muscle, heart, wbc, rbc, connective tissue)
Type IV	Andersen disease	Branching enzyme deficiency; amylopectinosis	Amylo-1,4-1,6-transglucosidase (branching enzyme)	Abnormal	Liver, wbc
Type V	McArdle disease	Myophosphorylase deficiency glycogenosis	Muscle phosphorylase	Normal	Skeletal muscle
Type VI	Hers disease	Liver phosphorylase deficiency glycogenosis	Liver phosphorylase	Normal	Liver, wbc
Type VII	—	Muscle phosphofructokinase deficiency glycogenosis	Muscle phosphofructokinase	Normal	Muscle, rbc
Type VIII	—	Muscle phosphohexoisomerase deficiency glycogenosis	Presence of an inhibitor of phosphohexoisomerase in muscle	Normal	Muscle

wbc = white blood cells; rbc = red blood cells.

demonstrated a specific defect of hepatic glucose-6-phosphatase in a patient with von Gierke disease. The Coris' laboratory remained active in the pursuit of the enzymatic bases of other types of GSD as well. This represents a major story in the history of clinical-pathophysiologic correlations in the field of genetics.

Type II GSD (Pompe disease) is a severe and generalized glycogenosis resulting from α-1,4-glucosidase (acid maltase) deficiency. Skeletal and cardiac muscle are major target tissues of this disorder. Affected children are flaccid, hypotonic, and growth retarded. Death due to cardiac failure usually occurs before the first birthday.

Type III GSD (Forbes disease) is clinically similar to type I glycogenosis, with growth retardation, hepatomegaly, and hypoglycemia as predominant manifestations. The defect, however, is due to a failure of the degradation of glycogen due to a deficiency of the debranching enzyme. This leads to the accumulation of an abnormal form of glycogen in liver and muscle, but not in kidney. Muscle weakness and fatigue are often profound. Serum lipids are variably elevated.

The pivotal role of G-6-P is obvious from the relationships of glycogen metabolism.

Type IV GSD (Andersen disease) results from a defect in the brancher enzyme, with abnormal, unbranched glycogen strands accumulating in liver, spleen, and other organs such as heart and nerves. Children show poor development, muscular atrophy, poor weight gain, and hepatic decompensation. Only one child with type IV glycogenosis has survived to 4 years of age.

Type V GSD (McArdle disease) is due to a defect in muscle phosphorylase. Liver phosphorylase activity is normal. This points out an important genetic feature, namely, that the phosphorylase proteins of skeletal muscle and of liver are under distinct genetic control. McArdle disease is a form of muscular dystrophy, with progressive myopathy due to infiltration of the skeletal muscle with glycogen. This leads to muscle weakness and atrophy. Survival into middle age, however, is the rule. Lactate levels are low in this disease.

Type VI GSD (Hers disease) involves the reduction of *hepatic* phosphorylase activity, with muscle phosphorylase remaining normal. Clinically it has features in common with types I and III glycogenoses, such as hepatic enlargement and growth failure, but the course of the disease is generally more benign as subjects are able to maintain normal glucose levels, primarily through continuous gluconeogenesis, and the catastrophic cascade of derangements of metabolic intermediates seen in the other two disorders does not evolve in Hers disease.

Type VII GSD is muscle phosphofructokinase deficiency. Symptoms are of a myopathy similar to McArdle disease. Curiously, *red cell* phosphofructokinase is deficient and erythrocytes have only a 13- to 16-day life-span.[7] There is a compensatory reticulocytosis and bone marrow hyperplasia. The disease is exceedingly rare in its occurrence.

Type VIII glycogenosis is poorly defined both clinically and biochemically because of the scant number of reported cases and the presentation of manifes-

tations late in life. It has tentatively been ascribed to an in vivo inhibition of phosphohexoisomerase activity in the metabolism of glycogen in muscle. It presents clinically as a myopathy commencing in adulthood. The course is relatively benign.

Obviously, for the ordinary practitioner, the nutrition specialist, and the dietitian, the details of the clinical syndromes and differential biochemical bases are difficult to retain. The glycogenoses are rare. However, as I will illustrate here clues to the management of some—if not all—of the disorders are to be found in the specific metabolic disruptions. In several, dietary manipulations influence the clinical outcome and quality of life.

TYPE I GLYCOGEN STORAGE DISEASE

Type I glycogen storage disease or von Gierke disease (also known as hepatorenal glycogen storage disease) primarily affects the liver and kidneys in its pattern of glycogen accumulation. The biochemical defect is in hepatic (and renal) glucose-6-phosphatase. The disorder is rare. Both sexes are affected. Its transmission is autosomal recessive.

Type I GSD presents most often in infancy, but delayed recognition is not uncommon. The predominant features are growth retardation, with children often falling below the third percentile in height for age, and the protuberant abdomen, reflecting massive hepatomegaly from a glycogen-engorged liver. The victims have excessive body adiposity and poor muscular development. There is osteoporosis due to acidosis-induced hypercalciuria.[7] A bleeding tendency, leading to spontaneous epistaxis and prolonged hemorrhage necessitating surgery or dental extractions, is due to a defect in platelet adhesiveness.

By far, the major clinical problem is profound hypoglycemia, with blood glucose levels falling below 15 mg/dl and precipitating convulsions. Patients are relatively resistant to hypoglycemia in the range of 20 to 70 mg/dl. If death occurs in early life it is usually the result of profound hypoglycemia and acidemia resulting from a lactate buildup with a variable component of ketoacidosis as well.

In Type I GSD there is a tendency to recurrent acute infections in early childhood. Hyperuricemia in adults leads occasionally to gout and gouty arthritis. Diagnosis is established on the basis of a liver biopsy that shows absent or extremely low glucose-6-phosphatase activity in in vitro assay and at least a 4% or greater glycogen content of the liver.

As with the clinical syndrome the biochemical and metabolic pathogenesis centers on the hypoglycemia or, more specifically, on the inability of virtually all of the potentially glucogenic substrates of metabolism to pass the barrier of G-6-P dephosphorylation to become free glucose (see Fig. 1). As a consequence, while glucose levels remain low, concentrations of pyruvate and lactate are enormously elevated. Lactate production rates can be increased from 10- to 300-fold.[13,14] This produces the acidemia that promotes vomiting and loss of urinary calcium.

The pyruvate excess leads to excessive formation of acetyl-CoA, which drives cholesterol synthesis, and to glycerol production[15] for the esterification of the fatty acids, released in response to hypoglycemia and low insulin level, into triglycerides.[16] Triglyceride levels in untreated type III GSD often exceed 1500 mg/dl[16] and xanthomas are clinically apparent.[7]

Controversy persists as to the origin(s) of the elevated uric acid levels, a problem that becomes troublesome in adulthood. One component of the hyperuricemia is thought to be a competition for renal tubular secretion along with elevated lactate levels. However, uric acid *production* per se is elevated in type III GSD.[7] Recent revelations concerning the mechanism of the increased urate formation come from studies of Benke and Gold.[17] They infused 1-^{14}C-glycine into an 8-year-old patient with von Gierke disease and confirmed an increased de novo synthesis of purines, the parent compounds from which uric acid is formed. Purine metabolism, however, was normalized when this patient was placed on a nocturnal feeding regimen. In summary, the blockade of free glucose release from G-6-P can explain the existence and persistence of virtually all of the metabolic abnormalities in hepatorenal glycogenosis.

Rationale for Continuous Glucose Feeding

In the past it was obvious to the clinicians who treated patients with von Gierke disease that the hypoglycemia and associated convulsions were the major day-to-day clinical problem. They treated patients as best they could with oral glucose-rich substances. The nocturnal "fits," however, became a prime manifestation. However, the advent of total parenteral nutrition supplied through cannulas inserted into major veins, pioneered at the University of Pennsylvania, ultimately led to both the conceptual and practical breakthroughs that would set the stage for unraveling the therapeutic address to several GSDs.

The initial observation was quite serendipitous, in fact. In the early 1970s attempts at palliating type I GSD by surgical interventions involving portal diversion (portacaval shunts) came into vogue.[18,19] In Boston Folkman et al.[18] found that provision of intravenous nutrition, ostensibly for nutritional reconstitution prior to major surgery, had unexpected by-products in patients with von Gierke disease: (1) the reduction of liver size and glycogen accumulation, (2) the correction of the bleeding tendency, and (3) the metabolic abnormalities. Greene et al.[20,21] at Vanderbilt University seized upon this observation, not so much as an adjuvant to successful surgical preparation, but as the basis of a comprehensive therapy *in itself*. In 1974 they published a prospective study in which a 16-year-old patient was studied sequentially with parenteral nutrition, then continuous intragastric feeding, and finally portacaval shunt surgery as therapies.[22] In terms of metabolic correction all treatments had measurable success, but the two infusion options provided better control of hypoglycemia, uric acid levels, and platelet dysfunction and bleeding.

After assessing the panorama of the interrelated cascade of events set off by the glucose deprivation in the peripheral tissues and the surfeit of metabolites cycled in the liver, Greene et al.[20,21] postulated that the source of the metabolic defects—the paradoxic situation in which the peripheral tissues were in a *fasted* state hormonally and the liver in a *fed* state at the same time—could be addressed by ensuring that the peripheral tissues come harmoniously into the fed state by a continuous protection of the circulating glucose level by providing infusions of exogenous glucose. The exact sequence of reasoning that derived from the observation of Folkman et al.[18] and from their own observations[22] is outlined in Table II. Reversal of the growth

retardation was not even mentioned in the original postulation, but time has shown that the defect in linear growth is also amenable to correction with continuous glucose infusion therapy. During the past decade at various centers there has been an accumulation of experience with various regimens that has allowed us to assess the correctness of the Greene postulates, the degree of reversibility of the manifestations of von Gierke syndrome, and the pitfalls and limitations of the approach.

Results of Continuous Glucose Infusion Therapy for Type I Glycogen Storage Disease

Since the first observation by Folkman et al.[18] concerning parenteral nutrition, and its exploitation in an enteral context by Burr et al.,[22] there have been at least 22 reports, including abstracts, brief reports, and full scientific papers, of continuous or nocturnal intragastric infusion therapy with glucose or glucose polymers for type I GSD.[6,17,20,21,23-40] The results are generally favorable, demonstrating efficacy at low risk, but findings are not consistent among all groups. I cannot review here all of the observations, but the important lessons and principles highlighted here serve to illustrate the central theme of tailored dietary manipulation in diet therapy based on understanding of biochemical lesions.

A group of pediatricians at Vanderbilt led the way. Greene et al.[21] reported in 1976 the results of the growth responses and other metabolic changes wrought in three juvenile patients with type I GSD who were treated with diurnal feedings every 3 to 4 hours and continuous nocturnal intragastric feedings to stabilize their blood glucose levels at above 70 mg/dl. Nocturnal infusions consisted of Vivonex (Eaton Laboratories), a mixture of glucose and glucose oligosaccharides along with amino acids. The perfusions were pump driven. In each patient dramatic decreases in levels of triglycerides were accomplished in the hospital and maintained later at home. Cholesterol was more resistant to change in these patients. Uric acid levels fell from 9 to 10 mg/dl, but did not fall below 6 mg/dl into the normal range. Lactate levels normalized with the combined oral/infusion therapy. The most outstanding changes, however, were in linear growth. Monthly rates of height increase changed from 0.0 to 0.2 mm to 8 to 10 mm with the nocturnal infusion regimen. Similarly impressive results emphasizing catch-up growth were reported by others[27,33,35,41] and lactate production rates were suppressed to normal levels in many reports.[35] Even in infants aged 4 days[31] to 3 months[27] with early diagnoses of type I GSD, the continuous infusion therapy resolved acidosis and hypoglycemia and established normal growth patterns.

Daeschel et al.[40] have recently presented a comprehensive review of five patients with GSD type I, including details of the mechanics of in-hospital institution and home maintenance of nocturnal infusion therapy. Because fructose and galactose are metabolized to G-6-P eventually, thus contributing to the buildup of substrates (see Fig. 1). table sugar (sucrose) and milk sugar (lactose) should be excluded from the diet. Daeschel et al. present dietary exchanges including vegetables and meats to go along with the glucose, glucose polymers, and starches that form the basis of the glucose-rich diet.

Before infusion therapy was advanced it was realized that the course of von Gierke disease improved with time. One patient treated by the Vanderbilt group[36] was provided with nocturnal feedings of Vivonex from ages 16 to 23 years. However, the authors showed that they could successfully *wean* her to a regimen of frequent diurnal feedings and an 11 PM snack with maintenance of average glucose levels in the range of 63 mg/dl. Lactate levels remained at 3.2 mEq/L (normal) and triglycerides and uric acid were stable at 147 and 4.3 mg/dl (from 2000 and 19.5 mg/dl, respectively, up to age 16 years). The optimistic note for children with type I GSD consigned to nocturnal infusion is that it may be only a temporary treatment until the normal cessation of growth.

Not all reports of continuous nocturnal gastric feeding, however, are as favorable as those cited above. Baker et al.[26] could not force lactate levels below 7.2 and 5.4 mEq/L with nocturnal intragastric glucose infusions in two patients with type I GSD. Likewise, perhaps as a *result* of this failure there was also a plateau of triglyceride concentrations above the 550 mg/dl level. Michels et al.[39] treated two patients with von Gierke disease whose growth, triglycerides, and cholesterol levels improved, but in whom lactate, acid-base balance, and urate levels remained poorly controlled. The most serious drawback to therapy with nocturnal infusion, however, seems to be the great *dependence* on glucose that is established. As noted, untreated patients with this disorder have a relative resistance to hypoglycemia, but sensitivity to hypoglycemia in the middle range (20 to 70 mg/dl) returns with continuous nocturnal gastric infusion therapy. Thus severe complications were seen in two Dutch patients in whom the connection between pump and tubing became inadvertently dislodged during the night. One child died and the other had severe hypoglycemic seizures from which she eventually recovered without sequelae. This report alerted clinicians to provide *alarm systems* as part of the pump apparatus for nocturnal feeding. Interestingly, aspiration and tube retraction during nighttime feeding have not been even rarely reported with this therapy.

Hepatic adenomas have been recognized as a late complication of type I glycogenosis.[41] When the patient survives through the dietary therapy outlined above, the emergence of this complication must be anticipated. Michels et al.[39] reported a patient with von Gierke disease who developed hepatocellular carcinoma after 4.4 years of treatment, presumably arising from a premalignant adenoma. Another patient with this malignancy was seen by Roe et al.[42] They

Table II. Postulates of the Vanderbilt group regarding the management of type I GSD with continuous glucose infusions*

1. Blood glucose levels below a critical value (approximately 70 mg/dl) cause compensatory release of hepatotropic hormones (glucagon, epinephrine), which stimulate the degradation of glycogen to G-6-P (see Fig. 1).
2. Absence of G-6-P impairs normal release of free glucose to correct the hypoglycemia; this results in increased glycogenolysis.
3. The continued stimulus for glycogen breakdown causes excess formation of other metabolic intermediates such as lactate, uric acid, and triglycerides.
4. Thus treatment with continuous infusions of exogenous glucose to maintain blood glucose concentrations above the critical 70 mg/dl level should *inhibit the release of the hepatotropic hormones* and thus correct the phenotypic anomalies of type I GSD.

*After Greene et al., 1979[21] and 1980.[21]

then studied 14 patients with GSD type I, including seven over 15 years of age, who were being treated with an intragastric nocturnal feeding regimen. Serial liver scans over a follow-up of 1 to 4 years showed no emergence of or changes in focal hepatic defects detected and monitored by scintigraphy. The exact magnitude of malignant degeneration of adenoma in these patients will be known only as therapy-aided long-term survivals increase.

The foregoing reports of therapeutic responses are characterized by variability from center to center and among patients. The best perspective on the reasons for this variability comes from a report from London by Dunger et al.[38] who conducted metabolic challenge tests on a series of patients with von Gierke disease who underwent forms of diet therapy from intensive to mild to untreated. They correlated the response with longitudinal growth data and found that height velocity was positively correlated with plasma somatomedin levels and inversely correlated with the glucose-to-insulin ratio. Also, the greater the growth rate, the lower were cortisol and growth hormone levels after an oral glucose load. In four previously untreated patients who were placed on a regimen of frequent glucose feedings and who improved their growth rates, basal levels of the aforementioned hormones responded in the appropriate direction. Dunger et al. concluded that growth retardation in type I GSD is in part due to the body's adaptation to its inability to maintain glucose regulation. When this regulation is established the hormonal changes reverse, allowing growth. This growth is probably also assisted by the alleviation of the burden of acidosis, vomiting, and poor appetite.

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Most reported studies used nasogastric feeding routes, but passage of the tube daily through the nostril may be tedious for children and may lead to refusal of treatment. Swallowing a weighted tube *orally* might be more comfortable, equivalent to the passage of a small pill or capsule. Thus LaVelle and Rhead[42] developed an intraoral night time feeding attachment as a protective guard both for oral tissues and for the tubing, itself, for children receiving nocturnal gastric infusions. Experience to date is limited, but this approach deserves evaluation as the oral rather than the nasal route of intubation may prove to be more tolerable over the long term.

Frequent feedings during the day were originally seen as a measure to avoid hypoglycemia in type I GSD. However, as early as 1969 Keusch and Oliver[43] treated a 9-year-old boy with von Gierke disease and severe metabolic acidosis and lactic acidemia, which had led to hypercalciuria and skeletal demineralization, with frequent feedings of glucose as 1 gm/kg of the sugar in lemonade every 3 hours until 9 PM. To provide calcium they violated the galactose exclusion principle by daily administration of 400 gm of milk containing 13 gm of galactose from the lactose; this had no apparent adverse effects. Indeed, over 9 months of observation and therapy the combination of reduced acidemia and increased dietary calcium intake led to radiographic improvement of bone minerals. The child on this oral regimen alone had a catch-up growth burst of 10 cm in the 9 months. Recently, again, for *selected* "milder" cases of type I GSD, Dunger and Leonard[44] have confirmed that less intensive therapy, omitting continuous intragastric infusion, can be effective. They used a short-chain glucose polymer (chosen over glucose because of the lesser sweetness), which was given hourly by day and every 2 to 3 hours by night, in three patients with type I GSD for 1 to 5 years. Growth was improved, hypercholesterolemia and hypertriglyceridemia were reduced, and liver function was normal. The two or three nocturnal awakenings might prove to be stressful for parents and/or patients, but the risks and discomforts of intubation are reduced. In selected patients the metabolic correction and growth responses obtained with frequent oral feedings given day and night are equivalent to what might be expected with more intensive perfusion regimens.

DIET THERAPY FOR OTHER GLYCOGEN STORAGE DISEASES

Type III GSD, the phenotypic twin of type I, is the other glycogenosis that benefits from specific dietary therapy. Sibury[40] makes the following comment:

> "It is interesting that the clinical manifestations of types I and III should be so similar, because, fundamentally, vis-a-vis the glycolytic intermediates, the situations are opposites. In type I glycogenosis there is a surfeit of intermediates; in type III there is a dearth. The common denominator is diminished glucose production by the liver."

The course of type III disease is generally milder, but life-threatening respiratory compromises from liver engorgement can occasionally occur, as reported by Böhles et al.[45] in a 4-year-old boy with this malady. Rescue therapy consisted of 26 days of total venous alimentation with a mixture of amino acids, fat, and glucose at dosages of 2, 2, and 12 gm/kg daily, respectively. Breathing improved with reduction of hepatomegaly, and nocturnal infusions of maltodextrins were continued at home.

Frequent feedings during the day were originally seen as a measure to avoid hypoglycemia in type I GSD.

Since in type III GSD the gluconeogenic pathways can provide free glucose, a *high-protein* diet is prescribed. Slonim et al.[31] showed that ingestion of beef by these patients increased circulating levels of glucose, insulin, and glucogen. Daeschel et al.[40] provided details of ingestion of combined frequent meals and continuous nocturnal infusions modified for patients with Forbes disease. Frequent feedings of a diet with high protein (25% to 30%), moderate carbohydrate (40% to 45%), and medium fat (25% to 30%) content are provided during the daytime. Since muscle amino acids are used for gluconeogenesis, the high protein intake limits muscle breakdown. Fructose- and lactose-containing foods are not restricted in type III GSD. The hypoglycemia, hyperlipidemia, and growth failure of the fully expressed type III syndrome are generally reversed and liver mass is reduced by dietary regimens involving continuous nocturnal feedings.[40] Michels et al.,[39] however, have reported incomplete responses with this program in patients with type III

disease. On the other hand many patients with Forbes disease can be managed with frequent diurnal feedings alone.[6,41,44]

SUMMARY AND CONCLUSIONS

Diet and its manipulation is an important but limited mode of treatment in children. A healthy appreciation for the limitations of the role of diet in medicine, however, should be accompanied by an acute sense of when and where diet might provide the crucial differential in therapeutic management. This opportunity probably exists in many situations that are yet to be exploited. The GSDs represent metabolic derangements in which the biochemical/genetic enzyme defects are precisely known. It was a combination of this understanding along with derivative scientific deduction and modern techniques in nutrient delivery that led to an exemplary breakthrough in the management of at least two of the entities: types I and III GSD. All professionals concerned with foods, nutrients, and diets can gain lessons from this illustration that might improve one's perception and acuity for recognizing those situations in pediatric metabolic disease in which a potential beneficial contribution from dietary therapy might present itself.

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