

# Hypoglycemia in Children

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The questions below should help focus the reading of this article.

1. How do the manifestations of hypoglycemia in the neonatal period differ from those in older children?
2. How do the manifestations of postprandial hypoglycemia differ from those of hypoglycemia brought on by prolonged fasting?
3. How can the blood levels of insulin, glucose, ketones, and lactate help differentiate among the causes of hypoglycemia?
4. What physical findings and laboratory data in a newborn infant with hypoglycemia will suggest that the hypoglycemia is due to hypopituitarism?

Hypoglycemia, although rare in childhood beyond the newborn period, remains a vexing problem for the pediatrician. First, the symptoms may be vague and nonspecific, thus making diagnosis particularly dependent on a high index of suspicion. Second, the pathogenic mechanisms that result in hypoglycemia are as numerous and complicated as the physiologic mechanisms that maintain euglycemia. Finally, although most patients have no permanent sequelae, a catastrophic episode of hypoglycemia can cause neurologic deficit and mental retardation. In this brief review, the most common cause for hypoglycemia, namely, insulin-dependent type I diabetes mellitus, will not be considered. Instead, we will focus on those metabolic disorders that result directly in a loss of the ability to maintain normal serum glucose concentrations.

## SYMPTOMS

In the older infant (older than 2 months), child, and adult, a rapid de-

crease in blood glucose to levels less than 40 mg/dL (2.2 mmol/L) may produce hunger and trigger an excessive release of epinephrine, causing weakness, anxiety, cold sweat, inward trembling and tachycardia. These adrenergic symptoms tend to occur in persons with postprandial hypoglycemia. In contrast, fasting hypoglycemia generally is progressive and gradual and produces neuroglycopenic symptoms which include headache, mental dullness, fatigue, confusion, abnormal behavior or psychosis, amnesia or other neurologic deficit, seizures, or frank coma.

Symptoms associated with hypoglycemia are nonspecific but generally relate to adrenergic responsiveness initially and later to the central nervous system.

The definition of hypoglycemia in the neonate remains controversial. Earlier criteria were based on extensive surveys of preterm and term neonates, not all of whom were on optimal caloric regimens. It was determined that normal term infants had blood glucose levels greater than 30 mg/dL (1.67 mmol/L), and "normal" preterm infants had levels greater than 20 mg/dL (1.11 mmol/L) during the first 72 hours of life. An alternate view holds that the neonate should not tolerate a glucose level less than the fetus. Thus, the lowest maternal level (less 15% for maternal-fetal gradient) is recommended as the cutoff level. With this criteria, hypoglycemia is defined as a blood glucose concentration less than 40 mg/dL (2.2 mmol/L) at any age. It should be noted that there have been inadequate long-term neurodevelopmental studies to help choose among these criteria.

Symptoms in the neonate are nonspecific and include tremors, jitteriness, apnea and cyanosis, hypotonia, irritability, feeding difficulties, convulsions, coma, high pitched cry, tach-

## EDUCATIONAL OBJECTIVE

24. The pediatrician should have knowledge to make an appropriate evaluation of an afebrile 9-month-old girl with seizures and hypoglycemia, growth hormone deficiency (panhypopituitarism, perinatal asphyxia), adrenal insufficiency, ketotic hypoglycemia, organic aciduria, defect in gluconeogenesis, glycogen storage disease, factitious hypoglycemia, and Reye syndrome, and develop an appropriate plan for management (Topics, 89/90).

ypnea, and pallor. These clinical manifestations may be seen in the absence of hypoglycemia in infants with a variety of primary central nervous system abnormalities including congenital defects, birth injury, microcephaly, hemorrhage, and kernicterus. In addition, hypoglycemia may be associated with sepsis, heart disease, severe respiratory distress or asphyxia, multiple congenital anomalies, or endocrine deficiencies.

A person of virtually any age may have hypoglycemia but be asymptomatic. Infants with type I glycogen storage disease have tolerated blood glucose levels too low to measure without obvious symptoms. Normal children may tolerate fasts of 24 hours without symptoms of hypoglycemia despite blood glucose levels less than 40 mg/dL (1.67 mmol/L)

Neonates and children of all ages may have asymptomatic hypoglycemia (blood glucose concentration <40 mg/dL), especially with fasting.

(Fig 1).<sup>1</sup> Children with symptomatic hypoglycemia may be subject to variable long-term effects. Acute hypoglycemia which responds rapidly

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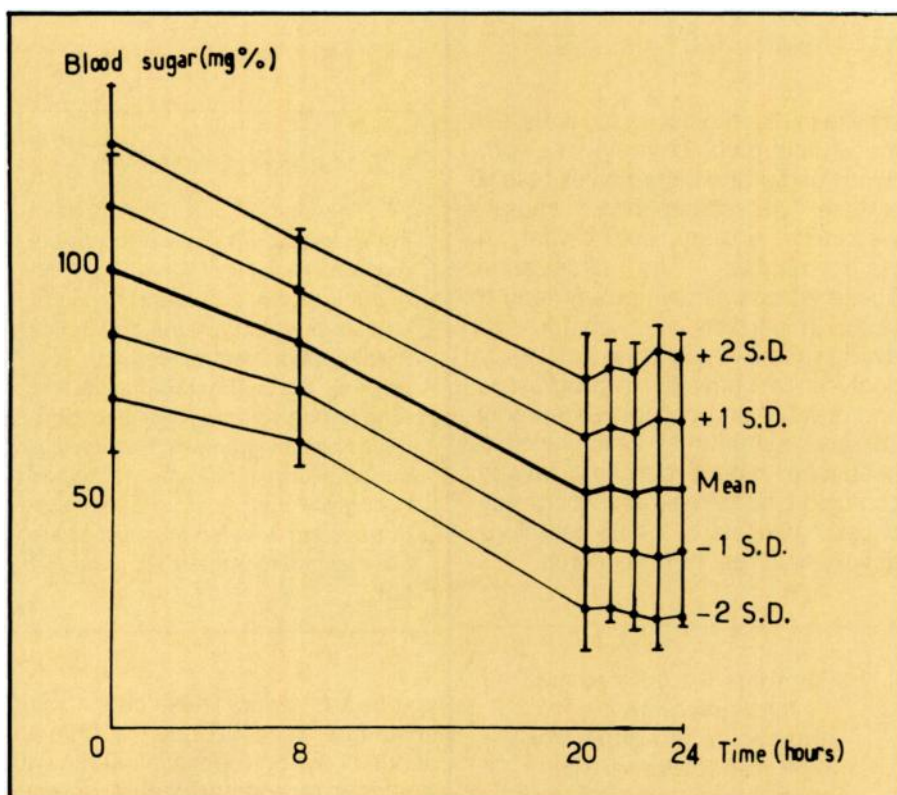


Fig 1. Mean blood sugar value with standard deviation and extreme values for each time during 24-hour fast in group of 56 "normal" children. Abscissa is time in hours after onset of fast. (Used with permission; from Chaussain JL. Glycemic response to 24-hour fast in normal children and children with ketotic hypoglycemia. *J Pediatr.* 1973;82:438-443.)

(within minutes) to correction is usually benign. In contrast, repetitive episodes of intractable hypoglycemia, if not treated promptly (within hours), may result in mental retardation.

## ANALYTIC METHODS

Formerly, glucose measurement depended on metal reduction, in which iron or copper react with simple sugars and some glycolytic intermediates as well as amino acids. Specificity was added by using protein precipitation techniques which removed reactant other than simple sugars. Today, highly specific methods include enzymatic techniques with glucose oxidase, hexokinase, or glucokinase. Additionally, gas-liquid chromatography can identify specific sugars. Currently, clinical chemistry laboratories use an automatic analysis technique with glucose oxidase or a commercial glucose oxidase immobilized electrode. Sensitivity and specificity are high.

Because of the increased glycolysis found in newborn blood, artifactually low blood glucose values may be found if the sample sits at room temperature in the absence of glycolytic inhibitors (eg, fluoride). Iced samples and prompt analysis produce optimal results.

In the past decade several reagent strips have been developed for home blood glucose monitoring of diabetic control. These reagent tapes vary in their ability to measure accurately low blood glucose levels (<40 mg/dL). They are now used with automatic reading devices which respond variably to low blood glucose levels. These determinations are *not diagnostic* because both false-positive and false-negative values may occur. A symptomatic infant must have a chemical determination of blood glucose concentration. An abnormal screening test result with a glucose reagent strip requires chemical verification. In no infant should the diagnosis of hypoglycemia be based on a screening reagent strip test. A chem-

ical determination is recommended before therapy.

## EVALUATION FOR HYPOGLYCEMIA

Those laboratory studies most helpful when diagnosing hypoglycemia are given in Table 1. Initial blood levels to be measured at the time of actual or suspected hypoglycemia should include, in addition to glucose by a specific enzymatic method,  $\beta$ -hydroxybutyrate, lactic acid, free fatty acids, amino acids (quantitative), and electrolytes (to assess the anion gap). Plasma hormone measurements should include insulin, growth hormone, and cortisol. Urine analysis should include examination for ketones and quantitative measurement of amino acids. If the initial evaluation is not diagnostic, but the patient has become asymptomatic, further assessment may be deferred for an evaluation coincident with a symptomatic episode.

If history indicates a possible relationship to fasting, then a monitored fast of 24 or more hours' duration may be indicated. This should be performed as an inpatient procedure and requires an intravenous heparin lock both for sampling and for treatment with 25% dextrose should symptomatic hypoglycemia occur. Sequential blood specimens should be obtained for plasma glucose, hydroxybutyrate, and insulin at 8, 16, and 20 hours and then hourly until termination with an intramuscular injection of (30 to 100  $\mu$ g/kg). The initial and final samples should also be analyzed for plasma growth hormone and cortisol levels.

If specific enzymatic defects are suspected, then specialized organic acid analyses of plasma and/or urine may be necessary.

Symptomatic hypoglycemia may be treated with oral carbohydrate provided the patient has no neurologic impairment that would alter swallowing. If hereditary fructose intolerance is not a diagnostic consideration, then orange juice with added sucrose (2 tsp per glass) will usually be effective. Simple dextrose or starch polymers are not usually readily available. Intravenous therapy with 15% to 25% dextrose may be given



**TABLE 1.** Laboratory Studies for the Diagnosis of Hypoglycemia\*

	Substrates	Hormones
At time of symptoms	Blood (plasma) glucose Blood lactic acid Blood $\beta$ -hydroxybutyrate Plasma quantitative amino acids, Plasma-free fatty acids Plasma electrolytes (anion gap) Blood gases Urinary quantitative amino acids Urinary quantitative organic acids	Plasma insulin Plasma growth hormone Plasma cortisol Plasma glucagon Plasma catecholamines
Serial blood specimens, every 2–4 h before and after feedings	Blood (plasma) glucose	Plasma insulin
Prolonged fast 24–30 h, hourly blood specimens after 20 h	Blood (plasma) glucose Blood $\beta$ -hydroxybutyrate Plasma quantitative amino acids†	Plasma insulin Plasma growth hormone† Plasma cortisol†
For suspected defects in glycogen metabolism or gluconeogenesis	Blood (plasma) glucose† Blood lactic acid†	Plasma insulin‡
Glucagon tolerance (100–300 $\mu$ g/kg)		

\* Glucose and insulin determinations are performed on all samples, others according to clinical findings.

† Initial and final samples.

‡ Every 15 minutes.

rapidly in a dose of 0.25 to 0.50 g/kg. Because of rebound hypoglycemia, a continuous infusion of dextrose should be maintained at 4 to 6 mg/kg per minute until the patient is stabilized with normoglycemia.

Hypoglycemia was evaluated prospectively by Gutberlet and Cornblath<sup>2</sup> from 1971 to 1973. The frequency in the neonate was 4.4 per 1000 total live births and 15.6 per 1000 low birth weight infants. The frequency figures would be modified with more current criteria. The changing character of patients in special care nurseries (ie, more very low birth weight infants) will also change current incidence data. There are no reliable incidence data for older children; however, estimates indicate two to three per 1000 older children admitted to hospitals have hypoglycemia.

## **PATHOGENESIS AND MANAGEMENT**

Successful management of hypoglycemia requires an understanding of its pathogenesis. Hypoglycemia can result from disorders of glycogen metabolism, gluconeogenesis, lipid oxidation, or amino acid metabolism. A simplified schema of these metabolic pathways is presented in Fig 2.

After hypoglycemia has been confirmed, the cause can be best pursued by distinguishing ketosis-associated hypoglycemia from nonketotic hypoglycemia. A prominent metabolic effect of insulin is suppression of lipolysis and ketogenesis. Because hypoglycemia suppresses insulin secretion, ketosis should result. Inappropriate secretion of insulin results in a relative absence of ketonemia (Fig 3). Measurement of plasma  $\beta$ -

hydroxybutyrate concentration is useful in the diagnosis of hyperinsulinemic hypoglycemia,<sup>3</sup> especially in patients who do not demonstrate obvious elevations in circulating insulin concentration. It should be noted, however, that disorders resulting in impaired oxidation of fatty acids, including carnitine deficiency, will also result in nonketotic hypoglycemia.

The ketosis usually associated with hypoglycemia in the patient with appropriately suppressed insulin secretion and intact fatty acid oxidation may not occur in those with glucose 6-phosphatase deficiency and hereditary fructose intolerance. In these disorders, lactic acidosis in the absence of ketosis occurs despite profound hypoglycemia. However, patients with accelerated starvation (see Ketotic Hypoglycemia), hypopituitarism, and most inborn errors of metabolism associated with hypoglycemia will have associated ketosis.

The most critical diagnostic maneuver in the infant with hypoglycemia is obtaining a blood sample at the time of symptoms. The oral glucose tolerance test has no role in defining the cause of hypoglycemia in children, because reactive hypoglycemia may well be normal following glucose loading in children.

**Oral glucose tolerance test contributes little and should not be used in evaluating hypoglycemia in an infant or child.**

The diagnostic workup for hypoglycemia may be presented in the form of an algorithm, as developed by Philip et al.<sup>4</sup> Such an approach is likely to differentiate among specific diagnoses (listed in Table 2), some of which will be discussed here.

## **Hyperinsulinism**

Hyperinsulinemic hypoglycemia can result from a number of distinct pathologic lesions including diffuse or focal adenomatosis of the pancreas.<sup>5</sup> Hyperinsulinemia in infants and children is often attributed to adenomas or insulinomas, but these lesions probably represent adenomatosis.

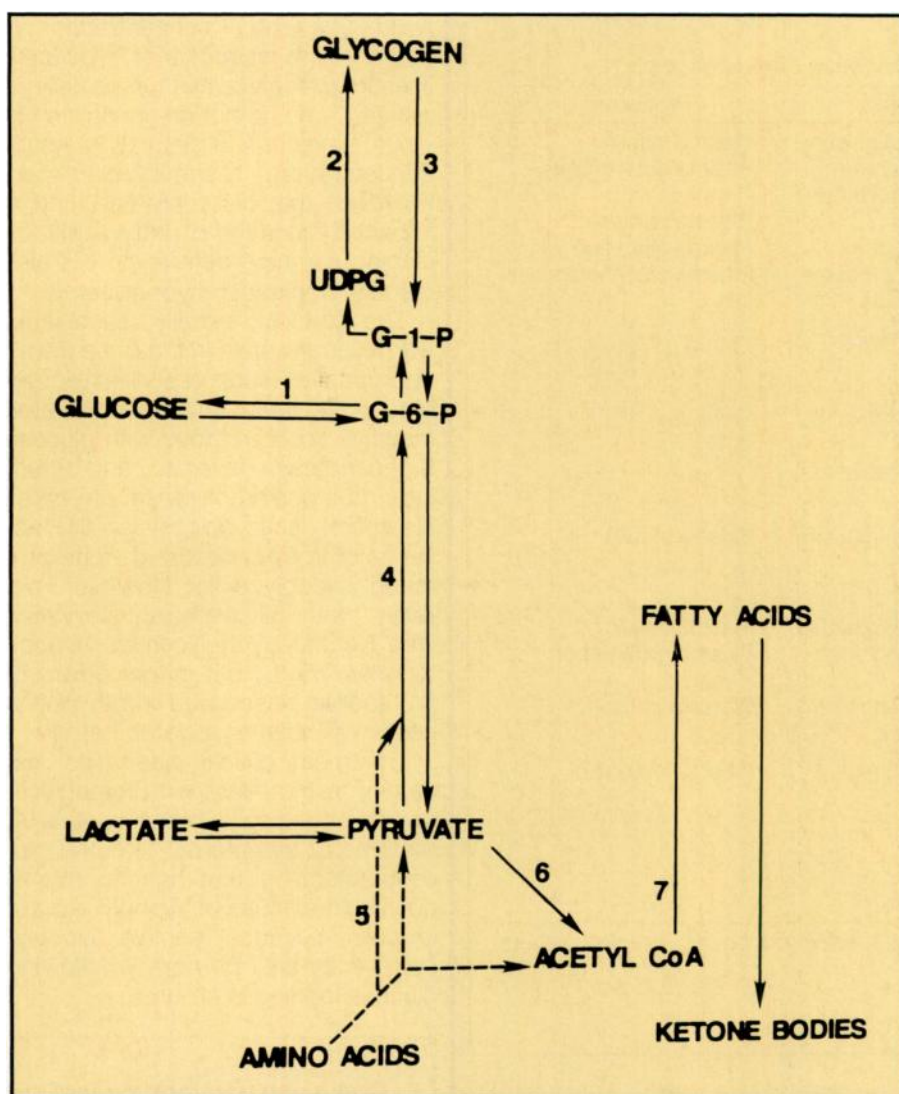


Fig 2. Interrelationships between glycogen metabolism, gluconeogenesis, glycolysis, and fatty acid metabolism. Numbers depict key enzymes: 1, glucose-6-phosphatase; 2, glycogen synthase; 3, phosphorylase; 4, fructose-1,6-diphosphatase; 5, phosphoenolpyruvate carboxykinase; 6, pyruvate dehydrogenase; 7, acetyl CoA carboxylase. Note that arrows represent pathways and not specific enzymatic reactions. Abbreviations: G-1-P, glucose-1-phosphate; G-6-P, glucose-6-phosphate; UDPG, Uridyl-diphospho-glucose.

Hyperinsulinemia has also long been attributed to "nesidioblastosis," an appearance caused by budding of developing islet tissue from ducts. This is not a pathologic finding in the infant pancreas, however, and is therefore not an anatomic correlate of hyperinsulinism. Hyperinsulinemia may also be associated with the pancreatic endocrine hyperplasia found in infants or diabetic mothers with Beckwith-Wiedemann syndrome and with hemolytic disease of the newborn (erythroblastosis fetalis).

The oversecretion of insulin results in augmented glucose utilization,

mostly by skeletal muscle. In addition to the suppression of ketosis, an increased rate of glucose utilization is one of the hallmarks of hyperinsulinemic hypoglycemia. Whereas a hypoglycemic infant with a normal rate of glucose uptake (as would be the case with hypopituitarism or a defect in hepatic glucose production) will require 6 to 8 mg/kg per minute of glucose (the normal endogenous production rate during fasting), a hyperinsulinemic infant will often require >12 mg/kg per minute to prevent hypoglycemia.

The diagnosis of hyperinsulinemia

based on circulating plasma insulin concentrations alone is a problem. Serum or plasma insulin concentrations must be interpreted in relation to serum glucose, because insulin concentrations at times of hypoglycemia may be in the "normal" range. In general, insulin is appropriately suppressed if the ratio of insulin to glucose (in microunits per milliliter to milligrams per deciliter) is less than 0.3. Hyperinsulinism should be associated with the expected secondary effects: suppressed levels of plasma  $\beta$ -hydroxybutyrate relative to glucose, a similar suppression of total branch chain amino acids (leucine + isoleucine + valine),<sup>6</sup> increased glucose requirements, and an excessive glycemic response to glucagon due to increased glycogen stores.<sup>7</sup>

**Hyperinsulinemia is best diagnosed by the finding of an elevated insulin to glucose ratio in the presence of low plasma  $\beta$ -hydroxybutyrate concentrations.**

The demonstration of hyperinsulinemia or the biochemical consequences of hyperinsulinism is an indication for therapy aimed at suppressing insulin secretion. This is best accomplished with diazoxide, given in three divided doses for a total of 5 to 10 mg/kg per day, and no more than 20 to 25 mg/kg per day. This may be augmented by the use of corticosteroids (for example, with prednisone, starting at 2 mg/kg per day [60 mg/m<sup>2</sup> per day]) which impair responsiveness to insulin. In addition, after intravenous dextrose infusions are no longer necessary, frequent feedings (every 3 to 4 hours) should be given until resolution of the hyperinsulinism. Most recently, feedings of raw cornstarch, which is slowly absorbed, have been used to maintain a safe level of glycemia.

If medical therapy is not adequate (ie, there is persistent hypoglycemia and/or excessive weight gain), surgical removal of the pancreas is indicated. The initial procedure most often advocated is subtotal pancreate-



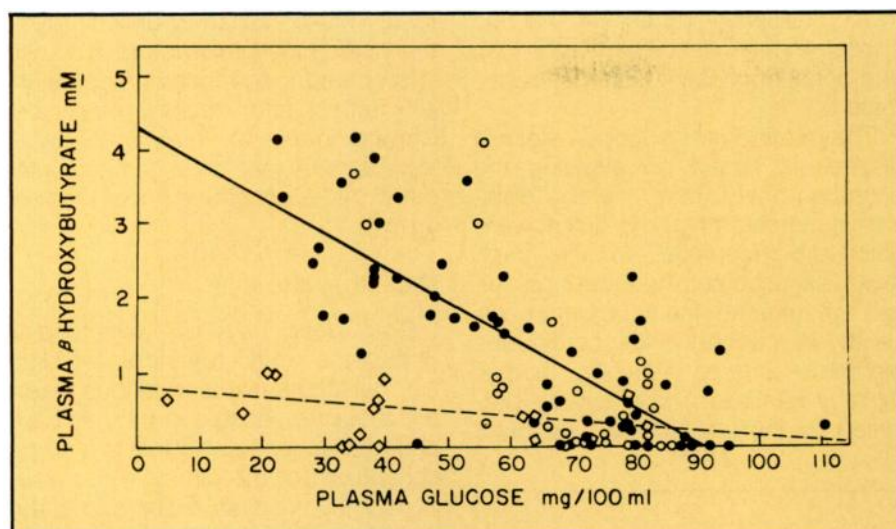


Fig 3. Relationship of plasma glucose and  $\beta$ -hydroxybutyrate levels during fasting in infants with hyperinsulinism ( $\diamond$ ), control infants ( $\bullet$ ), and children with ketotic hypoglycemia ( $\circ$ ). Two regression lines refer to former group (---) compared to latter two combined (—). (Used with permission; from Stanley CA, Baker L. Hyperinsulinism in infancy: diagnosis by demonstration of abnormal response to fasting hypoglycemia. *Pediatrics*. 1976;57:702-711.)

**TABLE 2. Causes of Hypoglycemia**

Hyperinsulinism
Hypopituitarism
Glycogen storage disease
Hereditary fructose intolerance
Galactosemia
Disorders of gluconeogenesis
Fructose-1,6-diphosphatase deficiency
Phosphoenolpyruvate carboxy-kinase deficiency
Amino acids disorders
Methylmalonic acidemia
3-hydroxy,3-methyl glutaric acidemia
Ethylmalonic-adipic aciduria
Glutaric acidemia type II
Maple syrup urine disease
Disorders of fatty acid metabolism
Defects in carnitine metabolism
Acyl CoA dehydrogenase defects
Ketotic hypoglycemia

tectomy. In this procedure 80% to 90% of the pancreas is removed. It should be noted that focal lesions are rarely apparent on radiologic examination (angiography, computed tomography) and often are not palpable to the surgeon. In addition, focal lesions are often in the head of the pancreas, thereby evading resection during subtotal pancreatectomy. This has led some to recommend "near

total" (99%) pancreatectomy as the initial procedure of choice.<sup>8</sup>

### Hypopituitarism

Hypoglycemia is a potent stimulus for the release of growth hormone and cortisol. If serum growth hormone concentrations were less than 10 ng/mL and cortisol levels less than 20  $\mu$ g/dL at the time of symptomatic hypoglycemia, such findings would indicate the possibility of an abnormality in hypothalamic-pituitary function. Indeed, although hypopituitarism is rarely diagnosed in the newborn period, it is more likely to occur with hypoglycemia and hyperbilirubinemia (secondary to hypothyroidism) than growth failure, the latter taking at least 6 months to occur. An important physical sign often present in the male newborn with hypoglycemia due to hypopituitarism is micropallus. Normal values for penile length have been published<sup>9</sup> and should be used to assess the male infant in whom hypopituitarism is suspected. Abnormalities of the palate, of antidiuretic hormone secretion, or of vision should also alert the pediatrician to the possibility of hypopituitarism because of their association with optic chiasm, septum pellucidum, and hypothalamic dysmorphism (septo-optic dysplasia).

The diagnosis of hypopituitarism

as a cause of hypoglycemia is best made by documenting subnormal concentrations of growth hormone and cortisol at the time of symptomatic hypoglycemia. In addition, provocative stimuli, the discussion of which is beyond the scope of this paper, may be used to test for growth hormone, ACTH, and thyroid-stimulating hormone release. In older children, the production of insulin-induced hypoglycemia is a useful test because it allows simultaneous evaluation of growth hormone and cortisol secretion.

The prevention of hypoglycemia due to hypopituitarism may require daily therapy with growth hormone, in contrast to the thrice-weekly regimen used in the treatment of short stature. Cortisol replacement should be undertaken with caution because administration of cortisol in physiologic doses will suppress the hypothalamic-pituitary-adrenal axis. In a patient with marginal cortisol secretion, such therapy may further impair the response to unpredicted stress (eg, trauma). If glucocorticoids are used, maintenance doses (15 to 20 mg of hydrocortisone per square meter per day) should be increased three- to fivefold during febrile illnesses.

Hypopituitarism as a cause of hypoglycemia usually is self-limited in duration. The child older than 3 to 4 years, like the adult, does not require normal growth hormone secretion to maintain euglycemia. On the other hand, of course, adrenal crisis in an older child with hypopituitarism may be associated with hypoglycemia.

### Glycogen Storage Disease

During fasting, euglycemia is maintained initially by mobilization of glycogen stores following which gluconeogenesis is required for adequate hepatic glucose production. Type I glycogen storage disease, a paradigm for metabolic defects that cause hypoglycemia, results from a deficiency of glucose-6-phosphatase. Because the dephosphorylation of glucose via glycogenolysis or gluconeogenesis, this defect prevents

maintenance of glycemia postabsorption. Furthermore, the mobilization of glycogen and induction of gluconeogenesis result in lactate rather than glucose production. This metabolic error also leads to accumulation of hepatic glycogen and fatty infiltration of the liver, the latter being responsible for marked hepatomegaly.

The diagnosis of glucose-6-phosphatase deficiency should be suspected in patients with fasting hypoglycemia, metabolic acidosis with an increased anion gap (due to lactate accumulation), and hepatomegaly. Despite appropriate suppression of insulin secretion, such patients have a relative absence of ketosis, probably due to the shunting of glycolytic intermediates toward fatty acid synthesis. A hallmark of this disorder is the absence of a glycemic response to glucagon, a potent glycogenolytic hormone. The administration of 30  $\mu\text{g/kg}$  of glucagon intramuscularly (or as much as 100  $\mu\text{g/kg}$  in a newborn) should result in a greater than 50% increase in serum glucose concentration within 30 minutes. In patients with glucose-6-phosphatase deficiency, this increase in glucose does not occur, whereas blood lactate increases markedly.

**Response to glucagon, following a prolonged fast, may provide clues as to the cause of hypoglycemia.**

When suspected, the diagnosis of glucose-6-phosphatase deficiency may be confirmed by direct determination of enzyme activity in a liver biopsy specimen. It should be noted, however, that type Ia glycogen storage disease is associated with deficient in vitro activity of this enzyme, and type Ib has normal in vitro activity. In the latter condition, the in vivo activity of glucose-6-phosphatase is impaired because of a defect in glucose-6-phosphate transport. In addition, three other types of glycogen storage disease may occur in infancy with findings similar to those in infants with glucose-6-phosphatase deficiency. They are amylo-1,6-glucosi-

dase deficiency (type III), hepatic phosphorylase deficiency (type VI), and phosphorylase kinase deficiency (type IX).

The treatment of glycogen storage disease is based on avoiding the postabsorptive state, thereby eliminating hepatic metabolic flux toward glucose-6-phosphate. In the past, this was accomplished through the use of frequent feedings, more recently in concert with continuous nighttime enteral infusions. Today, therapy has been considerably simplified by the use of raw, uncooked

**Raw, uncooked cornstarch given orally provides a slow-release glucose mechanism from the intestine which prevents hypoglycemia during brief fasting as in type I glycogen storage disease (glucose-6-phosphatase deficiency).**

cornstarch, given by mouth.<sup>10</sup> Cornstarch is slowly hydrolyzed in the intestine, allowing prolonged, steady absorption of carbohydrate. It is taken every 4 to 5 hours as a slurry to provide sufficient carbohydrate (6 to 10 mg/kg per minute) to suppress hepatic lactate production.

### Hereditary Fructose Intolerance

This disorder (deficiency of hepatic 1-phosphofructose aldolase) is characterized by vomiting, diaphoresis, tremor, convulsions, and/or coma following the oral ingestion of fructose. It may occur in infancy with failure to thrive accompanied by recurrent vomiting, hypoglycemia, and hepatomegaly. In childhood, the aforementioned symptoms occur in concert with hypoglycemia and metabolic acidosis. Patients with this disorder have an extraordinary aversion to sweets which may lead one to suspect the diagnosis. Confirmation may be obtained through the controlled administration of parenteral or oral fructose with monitoring of serum glucose, lactate, and phosphate concentrations and acid-base status. Treatment is the avoidance of fruc-

tose. This is extremely difficult given the ubiquitous presence of fructose in prepared foods, some vegetables, all fruits, and many medicines. Chronic intake of small amounts of fructose will lead to a renal tubulopathy and a continued impairment of growth.

### Galactosemia

The deficiency of galactose-1-phosphate uridyl transferase ("classic" galactosemia) is a serious disorder that often occurs in the newborn period. Because galactose is a major constituent of the diet of most newborns, hepatic dysfunction due to the inability to use galactose may occur early in life. In fact, galactose of maternal origin may result in hepatic damage in the affected fetus.

Hypoglycemia in this disorder is rare but is presumably due to accumulation of galactose-1-phosphate; however, the precise mechanism by which glucose production by the liver is impaired is unknown. The diagnosis should be suspected in the infant with hepatomegaly, jaundice, vomiting, irritability, and failure to thrive. Preliminary diagnosis is often based on the presence of nonglucose-reducing substances in urine specimens collected while the patient is receiving galactose. Glucose oxidase urine dipsticks will not detect galactose. The enzymatic defect can be confirmed by the analysis of erythrocyte galactose-1-phosphate uridyl transferase activity. Neither liver biopsy nor galactose challenge are required to confirm the diagnosis. Treatment consists of the elimination of galactose from the diet. If the diagnosis is made before the development of hepatic cirrhosis and mental retardation, the prognosis is favorable.

### Disorders of Gluconeogenesis

Disorders of gluconeogenesis in which specific enzymes are affected include fructose-1,6-diphosphatase deficiency and phosphoenolpyruvate carboxykinase (PEPCK) deficiency.

Patients with fructose-1,6-diphosphatase deficiency have hepatomegaly, lactic acidosis, ketonuria, and hypoglycemia. Conversion of galactose to glucose is normal but conversion

of fructose to glucose is blocked. The elimination of fructose from the diet and avoidance of prolonged fasts are effective therapy. In contrast to persons with hereditary fructose intolerance (in which fasting hypoglycemia does not occur), these patients do not have an aversion to sweet foods.

Deficiency of PEPCK is associated with feeding problems, failure to thrive, metabolic acidosis, and hypoglycemia. Hepatomegaly may occur secondary to fatty infiltration of the liver. This is a rare disorder and little is known about therapy; frequent feeding is indicated to prevent stimulation of hepatic gluconeogenesis.

### Disorders of Amino Acid Metabolism

A number of metabolic defects resulting in hypoglycemia and the excretion of abnormal organic acids in the urine have been characterized. In general, children with these disorders have failure to thrive, poor feeding, vomiting, and hepatomegaly. Laboratory data often demonstrate hyperammonemia and hypochloremic (increased anion gap) metabolic acidosis in conjunction with hypoglycemia. Specific diagnoses are often based on identification of specific organic acids in the urine by gas chromatography/mass spectroscopy. In many cases, definitive diagnosis is based either on *in vitro* analyses of liver biopsy specimens or on investigation of specific metabolic pathways in cultured fibroblasts.

Specific metabolic defects associated with organic aciduria and causing hypoglycemia include methylmalonic acidemia, 3-hydroxy-3-methylglutaric acidemia, ethylmalonic aciduria, and glutaric acidemia type II. The enzymatic defects in the latter two disorders also affect fatty acid oxidation.

Maple syrup urine disease is a disorder of branched chain amino acid metabolism which may occur in the newborn period and manifest as poor feeding, severe metabolic acidosis, and hypoglycemia. Progressive neurologic deterioration leading to death in infancy occurs in untreated patients. Blood and urine contain excessive levels of the three branched chain amino acids, leucine, isoleu-

cine, and valine, and their respective ketoacids. The enzymatic defect, which involves decarboxylation of these ketoacids, can be demonstrated in leukocytes.

Treatment of the aforementioned disorders involves limiting the intake of the offending amino acids. This requires a limited protein intake with supplementation of essential amino acids where applicable.

### Disorders of Fatty Acid Metabolism

A recently described class of disorders that can cause hypoglycemia involves defects in the  $\beta$ -oxidation of fatty acids. The various forms of carnitine deficiency as well as distinct or combined abnormalities of short-, medium-, or long-chain acyl CoA dehydrogenases result in accumulation of abnormal metabolites of fatty acids. These defects are associated with impaired ketogenesis due to impaired mitochondrial fatty acid oxidation. Diagnosis may be ascertained by the detection of the products of extramitochondrial oxidation (dicarboxylic acids) and acylcarnitine in urine. The avoidance of prolonged fasts through the use of frequent carbohydrate-rich meals is currently the only available form of therapy for primary enzymatic defects in  $\beta$ -oxidation. Dietary carnitine supplementation is successful in treating disorders of carnitine synthesis or excessive renal carnitine loss and may be indicated in other defects in fatty acid metabolism in which secondary carnitine deficiency occurs.

### Ketotic Hypoglycemia (Accelerated Starvation)

This entity should not be considered a pathologic disorder resulting in hypoglycemia. Rather, it is a non-specific designation applied to patients in whom fasting leads to physiologic hypoglycemia (Fig 1) *accompanied by hypoglycemic symptoms*. Age of onset is typically before 18 months. Episodes occur after a prolonged fast, usually in the morning. Hypoglycemia is accompanied by appropriate suppression of plasma insulin concentrations, elevated serum growth hormone and cortisol concen-

trations, acetonuria, and increased plasma  $\beta$ -hydroxybutyrate concentrations (Fig 2). Lactic acidosis does not occur. Diagnosis is based on eliciting ketosis with hypoglycemia during a monitored fast; other specific diagnoses must be excluded. The condition is self-limiting and treated effectively by the avoidance of prolonged fasts.

### Factitious Causes of Hypoglycemia

A variety of drugs and toxins can lead to hypoglycemia. Most prominent among these is insulin. The diagnosis of surreptitious insulin administration may be made by documenting hyperinsulinemia in the presence of suppressed plasma C-peptide concentrations. Because C-peptide is produced during the processing of proinsulin, its appearance in the circulation parallels insulin secretion. Conversely, suppression of endogenous insulin secretion by exogenous administration will diminish secretion of C-peptide. A second cause of factitious insulin secretion is the ingestion of oral hypoglycemic agents. These drugs can be detected in urine.

Jamaican vomiting sickness is the name given to the acute illness, accompanied by hypoglycemia, which follows the ingestion of unripe akee fruit. The offending substance, hypoglycin, probably interferes with fatty acid oxidation, thus producing a conditioning similar in its pathogenesis to the errors in fatty acid metabolism. More familiar toxins that cause hypoglycemia are aspirin and alcohol. Both result in impaired hepatic glucose production.

### CONCLUSION

Prompt recognition and treatment of hypoglycemia is important to prevention of central nervous system impairment. Diagnostic evaluation is aimed at specific physiologic and biochemical defects. Appropriate intervention can be initiated after a diagnosis is established. Hypoglycemia must be viewed as a symptom complex that requires detailed assessment.



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## Self-Evaluation Quiz

10. In the evaluation of hypoglycemia in a young child, the **least likely helpful diagnostic test among the following would be:**
  - A. Oral glucose tolerance test.
  - B. Serum ketones level.
  - C. Serum lactic acid level.
  - D. Plasma insulin level.
  - E. Plasma level of growth hormone.
11. In an infant with hypoglycemia, **simultaneous measurement of serum glucose and growth hormone levels 4 hours after a**

**feeding, at a time when the infant was symptomatic, found both levels to be abnormally low. These findings suggest that the primary defect is most likely to be:**

- A. Hyperinsulinism.
- B. Hypopituitarism.
- C. Glycogen storage disease, type I (von Gierke).
- D. Accelerated fasting.
- E. Phosphoenolpyruvate carboxykinase deficiency.

**12. In an infant or child with postprandial hypoglycemia, among the following findings the **least likely is:****

- A. Weakness.
- B. Tremor.
- C. Pallor.
- D. Bradycardia.
- E. Cold sweat.

**13. An infant with hypoglycemia has apparently suppressed serum levels of insulin and appropriately elevated levels of ketones at a time when she is symptomatic as a result of hypoglycemia. These findings suggest that among the following her primary condition is **most likely to be:****

- A. A disorder of fatty acid metabolism.
- B. Carnitine deficiency.
- C. Glycogen storage disease, type I.
- D. Hyperinsulinism.
- E. Hypopituitarism.

## Department of Corrections

In the article by Dewitt in the July 1989 issue of *Pediatrics in Review*, "Acute Diarrhea in Children," it is unfortunate that in Table 3 on page 11 the spelling of the rehydration solution "Rehydralyte" was printed as "Rydrolute." In addition, Hydra-Lyte and Infalyte are no longer marketed.