SPONTANEOUS HYPOGLYCEMIA: ITS ETIOLOGY, DIAGNOSIS AND DIETARY TREATMENT

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TABLE OF CONTENTS

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INTRODUCTION

Improvements in diagnostic methods for hypoglycemia have resulted in greater clinical awareness of its existence as a cause of illness in man (1). Hypoglycemia is a disturbance of carbohydrate metabolism caused by malfunctions of the liver or the endocrine and nervous systems. It is generally defined as a fasting blood glucose level below 50 mg per 100 ml, accompanied by a characteristic group of symptoms (2,3).

Hypoglycemia occurs less frequently than its opposite condition, hyperglycemia (4,5). Hypoglycemia is not common to any particular age group, but can be a threat to normal carbohydrate metabolism throughout life. Its diagnosis and treatment are important because hypoglycemia can cause irreversible changes in the central nervous system and eventually death. Because diet affects glucose homeostasis, diet therapy is an important treatment for hypoglycemics. The purposes of this paper are a) to review the clinical state of hypoglycemia and b) to assess its dietary treatment. Emphasis is on the stimulative type of spontaneous hypoglycemia.

HISTORY OF HYPOGLYCEMIA

Insulin hypoglycemia was first noted in 1921 by Banting and Best who drastically reduced the blood sugar level of a dog to 0.076 mg per 100 ml by injecting pancreatic extract (6). Identifiable clinical signs of hypoglycemia were elucidated later.

The syndrome of spontaneous hypoglycemia was described by Harris (7) in 1924. He found that symptoms similar to those of a diabetic who had taken too much insulin sometimes occurred in nondiabetics; he postulated they might have been caused by endogenous hyperinsulinism.

Before 1930, causes of hypoglycemia other than hyperinsulinism were recognized, but either considered of minor importance or ignored. Thus, hypoglycemia and hyperinsulinism were used interchangeably. Whipple was the first to distinguish between hyperinsulinism and hypoglycemia in response to ingestion of carbohydrates. He pointed out that only fasting patients benefited from pancreatectomy; such patients invariably had an islet cell tumor(8). Marks and Rose (9) as well as Gorsuch and Rynearson (10) recommended the term hyperinsulinism be reserved for overproduction of insulin by an islet cell tumor.

Early investigators were hindered by inaccurate methods for measuring blood glucose levels. Although practical clinical procecures for estimating blood sugar were first introduced in 1913, it was much later that methods specific for glucose became available (9). The normal limits of blood glucose concentration and dependence upon the temporal relationship to food had not generally been appreciated and this, coupled with the use of inaccurate analytical methods, led many patients to be improperly diagnosed as hypoglycemics.

REGULATION OF BLOOD GLUCOSE

The amount of free glucose in man is small and unevenly distributed. It is mostly confined to extracellular fluids, including blood, and intracellular water of liver cells. Together, these comprise a pool of glucose to which molecules may be added or removed. The glucose pool in the average human being at rest is about 10 to 20 g (9).

Glucose homeostasis

Fasting blood glucose concentrations in normal children and adults range from 60 to 100 mg per 100 ml, with an average value close to 80 mg (11). Slightly higher or lower values are occasionally encountered without

clinical evidence of disease (1). Glucose homeostasis is maintained under a variety of metabolic conditions with coordinated control of metabolic processes in many tissues (12).

For glucose to be utilized, it must first gain access to the cell interior where it can be metabolized. Muscle and adipose tissue require the hormone insulin to facilitate transport of glucose across the cell membrane (5). The rate glucose enters cells of these tissues determines its rate of assimilation (13). Insulin is comparatively inactive in kidney, erythrocytes, intestinal mucosa, liver, brain and islets of Langerhans cells (5,13,14,15).

Glucose is ingested intermittently with meals and snacks. In order to maintain glucose homeostasis, glucose consuming and glucose producing processes are necessary. Glucose consuming processes include a) glycolysis, the oxidation of glucose or glycogen to pyruvate and lactate by the Embden-Meyerhof pathway; b) citric acid cycle, the oxidation of carbohydrate, fat and protein to carbon dioxide and water; c) hexose monophosphate shunt, an alternate pathway for the oxidation of glucose to carbon dioxide and water; d) glycogenesis, the synthesis of glycogen from glucose; and e) lipogenesis, conversion of carbohydrate to fat (14,16).

Glucose producing processes include a) glycogenolysis, the breakdown of glycogen to glucose in the liver and breakdown of glycogen to pyruvate and lactate in muscle; b) gluconeogenesis, the formation of glucose from noncarbohydrate sources such as glucogenic amino acids, lactate and glycerol; and c) glucose formation from the conversion of galactose and fructose (14,16).

In a fasting state, the blood glucose concentration depends on the rate of hepatic glucose output and the rate of peripheral glucose uptake

(1,17). Hepatic glucose released is derived from 2 sources a) glucose absorbed in excess of requirements during the phase of temporary hyperglycemia after eating and b) glucose precursors transported to the liver from extrahepatic tissues (11). Hepatic glucose output and peripheral tissue uptake occur continuously and simultaneously. Their relative rates determine whether there is overall net glucose influx, efflux or equilibrium.

The brain is totally dependent on blood glucose for its supply of energy (18,19). Brain cells are readily permeable to glucose, independent of insulin action (5). The effects of hypoglycemia on the brain are caused by decreased availability of glucose. Hypoglycemia causes neuroglycopenia, a variety of symptoms that develop when the supply of metabolizable carbohydrate is inadequate for normal neuronal function (9). The type of symptom that occurs depends on many factors, including the nature of the neuroglycopenic stimulus, its rate of development, the age of the patient, and the structural and functional condition of the nervous system.

Hormones

Endocrine glands are important in ensuring homeostatic control of blood glucose under a wide range of conditions. Hormones of the pancreas, adrenal, thyroid and anterior pituitary glands are involved in glucose homeostasis.

Insulin. Insulin facilitates intracellular uptake of glucose (1,13,15). Studies indicate the rate-limiting step for the movement of glucose into muscles is at the cell membrane in the absence of insulin; in its presence, glucokinase-activated phosphorylation becomes rate-limiting (15).

Insulin is produced in the pancreas by beta cells of the islets of Langerhans (15,20). Although the primary stimulus for insulin secretion is hyperglycemia, substances other than glucose can induce it (table 1).

Agents that act on the beta cells modify their secretory responsivity to glucose, probably by altering the sensitivity of the microtubules and microfilaments to cytosolic calcium (21).

TABLE 1

Factors stimulating insulin secretion

Carbohydrates
Glucose
Mannose
Hormones
Secretin
Gastrin
Pancreozymin
Glucagon
Nucleotide
Cyclic adenylic acid
Oral hypoglycemic agents
Tolbutamide
Chlorpropamide
Tolazamide
Amino acids
Arginine
Lysine
Leucine
Phenylalanine

Randle et al. (22) stated that glucose-induced insulin secretion may be closely related to glucose utilization. Mannose, which can be utilized by the beta cell, will simulate glucose, but nonmetabolizable sugars fail to stimulate secretion.

The gastrointestinal hormones, secretin, gastrin and pancreozymin, stimulate insulin secretion following ingestion of food (2,23). Another hormone, glucagon, increases cyclic adenylic acid (3', 5'-AMP) and stimulates insulin synthesis and release (24). Goldfine et al. (25) reported that glucagon normally stimulates insulin release in man, but during hypoglycemia or starvation, glucagon inhibits insulin release.

Oral hypoglycemic drugs are used to control diabetes and more recently, hypoglycemia. The most common orally effective sulfonamide drugs that stimulate insulin are tolbutamide, chlorpropamide, and tolazamide (14).

Amino acids also evoke insulin release. The most potent are arginine and lysine, although leucine and phenylalanine also are effective (11,26). Floyd and co-workers (26) administered a mixture of essential amino acids to healthy human subjects and found that the mixture induced release of insulin. This is important, as diet therapy for hypoglycemia consists of a high protein, low carbohydrate diet.

Certain hormones and carbohydrates can inhibit the secretion of insulin (table 2). Although both epinephrine and norepinephrine inhibit insulin secretion, epinephrine is the more effective (15). Glucose-induced insulin secretion is blocked by inhibitors of glucose metabolism such as mannoheptulose, glucosamine and 2-deoxyglucose (14,20).

TABLE 2

Factors inhibiting insulin secretion

Hormones
Epinephrine
Norepinephrine
Carbohydrates
Mannoheptulose
Glucosamine
2-Deoxyglucose

Insulin secretion is regulated in part by hormones and by blood sugar level. Together, these regulatory mechanisms constitute an extremely sensitive control system, resulting in glucose homeostasis.

Insulin enhances all glucose consuming processes as well as amino acid accumulation by muscle cells and lipogenesis (14,15). Insulin diminishes the action of hepatic glucose-6-phosphatase, either directly or through

effects of other reactions, so that less glucose is formed from hepatic glycogen (11).

Glucagon and epinephrine. The action of glucagon on metabolism is limited mainly to the liver where it promotes glycogenolysis, gluconeogenesis and lipolysis (27). Epinephrine stimulates the breakdown of glycogen in liver and muscle by catalyzing the conversion of the inactive form of phosphorylase into the active form (14). Both epinephrine and glucagon stimulate the biosynthesis of cyclic 3', 5'-AMP that is necessary for glucose formation (28). Both hormones are secreted in response to a fall in blood glucose.

Glucocorticoids. Adrenal steroids are potent catabolic agents that promote lipolysis and gluconeogenesis (12). In general, glucocorticoids antagonize the effects of insulin (14). In adrenal cortical insufficiency, the ability of the liver to mobilize glucose during fasting is limited, a situation that can lead to fatal hypoglycemia.

Growth hormone. Insulin and growth hormone are present in inverse concentrations in plasma, and each can indirectly induce secretion of the other (15). Hoffman (11) stated that growth hormone may stimulate hypersecretion of beta cells directly. Hypoglycemia elevates the level of plasma growth hormone independent of insulin (29,30). Glucose administration decreases the plasma growth hormone level (29).

Growth hormone antagonizes the effects of insulin on muscle (31). Impairment of glycolysis may occur as well as inhibition of glucose transport. In the liver there is an increase in glycogen, probably arising from gluconeogenesis.

Thyroid hormones. Like growth hormone, insulin and adrenal glucocorticoids, the thyroid hormones have a general stimulatory metabolic

effect on numerous tissues (15). Thyroid hormones regulate the rate of oxidation within cells and therefore affect the metabolism of all nutrients (14). Intestinal absorption of glucose is increased by thyroid hormones. This rapid absorption may be a factor in abnormal glucose tolerance often observed in hyperthyroidism (14).

ETIOLOGY OF SPONTANEOUS HYPOGLYCEMIA

Spontaneous hypoglycemia denotes an abnormally low level of blood glucose, usually in association with a characteristic group of symptoms that occur without exogenous insulin (8). Clinically, it is classified as fasting and stimulative (table 3) (1,9).

TABLE 3

Clinical classification of spontaneous hypoglycemia (Adapted from 8,9,15)

Fasting	Stimulative
Insulinoma	Reactive
Extrapancreatic tumor	Diabetic
Hepatic disease	Alimentary
Endocrine disease	Postgastrectomy
Hypopituitarism	Essential
Hypoadrenalism	Alcohol-induced
Neonatal hypoglycemia	Hereditary fructose intolerance (HFI)
Idiopathic hypoglycemia of childhood (IHC)	Galactosemia
	Familial fructose and galactose intolerance

Fasting hypoglycemia

Fasting hypoglycemia is applied to those conditions where the blood glucose falls below 50 mg per 100 ml in a fasting state, i.e. four hours or more after the last meal (2). Whipple said 3 criteria must be met for fasting hypoglycemia a) symptoms occur while the patient is fasting, b) the blood glucose level is 50 mg percent or less during an attack and c) the attack terminates upon administration of glucose (2,8). Known as Whipple's

triad, these criteria are the fundamental differences between fasting and stimulative hypoglycemia (9). Fasting hypoglycemia is often revealed by the way it attacks a person, either before breakfast or when a meal is missed. Symptoms are progressive, gradually becoming more serious and longer lasting. If fasting hypoglycemia is diagnosed, an extensive investigation is required to determine the etiology. Treatment depends on the cause.

Insulinoma. Insulinoma is a tumor of the pancreatic beta cells resulting in hyperinsulinism. This type of hypoglycemia seldom occurs in children (11).

Extrapancreatic tumor. Slow-growing tumors in the thoracic or retroperitoneal area sometimes cause hypoglycemia. They evoke hypoglycemia by a) overuse of glucose by the tumor, b) deficient liver gluconeogenesis, c) insulin-like material secreted by the tumor and d) suppression of physiologic insulin antagonists (31).

Hepatic disease. Most forms of liver disease that impair enzymes associated with glycogen degradation cause hypoglycemia. The impairment results in accumulation of glycogen in the liver and reduces the glucose available to body cells (2,31).

Endocrine disease. Endocrine diseases that cause hypoglycemia include hypopituitarism and hypomedullaryadrenalism. Patients with hypopituitarism are extremely sensitive to insulin because of a decrease in growth hormone and adrenalcorticotropic hormone, which is necessary for the secretion of adrenal steroids. Both growth hormone and adrenal steroid hormones antagonize the effect of insulin (9). Hypomedullaryadrenalism reduces epinephrine secretion that promotes glycolysis (12).

Neonatal hypoglycemia. Most hypoglycemias of the newborn are of the temporary idiopathic types (31). These may occur in infants of diabetic mothers, particularly when prenatal hypoglycemic agents have been administered

to the mother (32). Idiopathic neonatal hypoglycemia occurs mainly in low birth weight babies with reduced glycogen stores (31). Greenburg (17) stated that abnormalities of pyruvic carboxylase may be the cause of hypoglycemia in infants. Pyruvic carboxylase is an enzyme necessary for gluconeogenesis.

Idiopathic hypoglycemia of childhood (IHC). Persistent hypoglycemia of childhood, absent or unrecognized in early infancy, may be caused by ketosis or leucine sensitivity (33). Leucine sensitivity may be genetically determined and is referred to as familial leucine sensitivity (11). Leucine stimulates insulin secretion and decreases hepatic gluconeogenesis (31).

Stimulative hypoglycemia

Stimulative hypoglycemia develops after carbohydrate ingestion, never during fasting (34). The various forms of stimulative hypoglycemia are listed in table 3. The reactive hypoglycemias are self-limited in nature and pose no threat to life. However, alcohol-induced hypoglycemia and hypoglycemias caused by inborn errors of metabolism can cause mental retardation, coma and death.

Reactive hypoglycemia. Reactive hypoglycemia is extremely common and is the most frequent type of spontaneous hypoglycemia (35). There are 3 conditions in which a glucose load results in postprandial (fed state) hypoglycemia a) latent diabetes, b) postgastrectomy and c) emotional and autonomic instability as found in essential reactive hypoglycemia.

Diabetic reactive hypoglycemia may occur in patients before they have diabetes mellitus. Seltzer and co-workers (36) suggested that delayed secretion of insulin in response to hyperglycemia acts as a stimulus to excessive insulin secretion. However, Luyckx and Lefebvre (37) found that patients with diabetic-type hypoglycemia had normal plasma insulin levels.

This indicates that factors other than delayed insulin secretion are responsible for diabetic hypoglycemia.

The mechanism of alimentary hypoglycemia is reported to be an excessive response to the normal stimulus for insulin secretion by hypersensitive, histologically normal islet cells (31). Rapid glucose absorption from the small intestine evokes a moderate hyperglycemia that causes an excessive stimulation of insulin resulting in hypoglycemia (11). This may occur after gastrectomy, at times in hyperthyroidism and in other instances for no recognizable reason as in essential or idiopathic reactive hypoglycemia (31,38).

Rehfeld et al. (39) suggested that an increased release of intestinal glucagon may cause alimentary hypoglycemia. Intestinal glucagon, which is unable to promote glycogenolysis may compete with pancreatic glucagon for receptor sites in the liver. In the study by Rehfeld et al. (39), infusion of pancreatic glucagon after ingestion of glucose prevented hypoglycemia in subjects with reactive hypoglycemia.

The hyperinsulinemia of alimentary reactive hypoglycemia may occur from vagal nerve stimulation or from release of glucagon and gastrointestinal hormones. In man, vagal nerve stimulation may influence hypoglycemia indirectly by increasing intestinal activity causing hyperglycemia with a resulting reactive hypoglycemia (40). McIntyre et al. (41) hypothesized that vagal nerve stimulation caused increased gastric acidity that released stomach and intestinal hormones that, in turn, induced insulin secretion. Marks and Rose (9) stated that patients with psychiatric instability may be inclined to develop hypoglycemia and thus initiate a cycle with nervous factors, intestinal factors and hypoglycemia augmenting each other.

There is universal recognition of the biochemical existence of reactive hypoglycemia but not everyone regards this syndrome as hypoglycemia because it is associated with mild symptoms resembling acute neuroglycopenia, but never with more serious and prolonged neuroglycopenic symptoms (9,42). Marks and Rose (9) and the American Medical Association (43) reported that only a few of the patients with reactive hypoglycemia actually have a true defect in glucose homeostasis. The practical importance of the recognition of reactive hypoglycemia is that it may prevent the clinician from too readily dismissing his patient's symptoms as neurotic. Further investigation may lead to an underlying and curable cause such as insulinoma or some other disease simulating neuroglycopenia (44).

Alcohol-induced hypoglycemia. Alcohol-induced hypoglycemia occurs independently of alcohol intoxication; fasting and depletion of liver glycogen are prerequisites (11). It appears that oxidation of excessive ethyl alcohol interferes with gluconeogenesis in the liver when the liver is the chief source of blood glucose (45,46). Gluconeogenesis may be inhibited by lack of NAD and the increase of NADH that depresses glucose formation from three-carbon compounds (47).

Hereditary fructose intolerance (HFI). In many, but not all cases, HFI is inherited as a recessive trait (48). The metabolic defect is a deficiency of fructose-1-phosphate-aldolase (49,50). The cause of hypoglycemia in HFI is unknown, but possibly is the result of accumulation of intermediate metabolites in liver cells and interference with the action of enzymes concerned with glucose homeostasis (9).

Galactosemia. Galactosemia is a rare hereditary disease characterized by an inability to metabolize exogenous galactose because of a defect in galactose-1-phosphate-uridyl-transferase activity (51). Upon ingestion of galactose or substances that yield galactose in digestion, hypoglycemia

develops. This hypoglycemia is often severe and may cause mental retardation and death.

Familial fructose and galactose intolerance (Dormandy's syndrome). In spite of similarities with galactosemia and HFI, Dormandy's syndrome is distinct from both. The hypoglycemic symptoms are caused by either hexose and appear to be attributable entirely to low blood sugar and not, as in the case of HFI and galactose intolerance, partly to toxic effects of accumulated intermediate metabolites (52). This is a rare disease with only a few cases documented.

SYMPTOMATOLOGY OF STIMULATIVE HYPOGLYCEMIA

The clinical pattern of hypoglycemia is extremely varied, but in a given person the same symptoms tend to recur even though they vary in severity (8). Depending on the cause of the hypoglycemia, 2 groups of symptoms arise a) neuroglycopenia manifested by poor concentration, speech disturbances, diplopia, drowsiness, confusion, lethargy, memory loss, stupor and coma and b) epinephrine discharge characterized by nervousness, apprehension, hunger, anxiety, palpitations, sweating, faintness and nausea.

The onset and magnitude of all symptoms depend on the severity and duration of the hypoglycemia. Generally, neuroglycopenia predominates in fasting hypoglycemia and symptoms of epinephrine excess occur mainly in postprandial hypoglycemias (53).

Reactive hypoglycemia

Clinically, patients with reactive hypoglycemia conform to a well-defined pattern (54). Women are affected more often than men with the most common age at diagnosis between 25 and 45 years. However, reactive hypoglycemia has been described in children and in elderly people (55).

Acute symptoms usually occur 2 to 5 hours after a meal and subside spontaneously in 10 to 30 minutes. Marks and Rose (9) reported that symptoms

are more common after breakfast and lunch than after dinner. Exercise may provoke symptoms (8).

Patients may be emotionally labile individuals whose symptoms are mainly weakness, faintness, nervousness, palpitations, anxiety, irritability or inward trembling (35,40,54). Hunger, nausea and headaches are also common. Moorehouse (56) stated that loss of consciousness seldom occurs. Between attacks the patient may feel normal but more often is lethargic. Missing a meal aggravates the symptoms but abstinence from food for longer periods, such as during a 3 day fast, is often associated with clinical improvement (9). The disorder does not become progressively worse as in insulinoma (31,57).

Alcohol-induced hypoglycemia

Hypoglycemia develops typically 6 to 36 hours after ingestion of a moderate to large amount of alcohol (9). Schneeberg (31) reported that hypoglycemia commonly appeared within 12 hours. The skin is often covered with sweat, the pulse rapid and body temperature subnormal (9). The breath does not typically smell of alcohol and the blood alcohol level is low (58).

Hereditary fructose intolerance

Symptoms of hereditary fructose intolerance include anorexia, nausea, vomiting, alterations in consciousness and even coma. Because gastrointestinal symptoms often dominate the clinical picture, the neuroglycopenic nature of the symptoms may be unsuspected (59).

Galactosemia

Cataracts, vomiting and listlessness are symptoms of galactosemia (9). The liver enlarges, jaundice and edema develop, the child becomes marasmic and in more severe cases, death occurs (50). Children who survive are dwarfed and may be mentally retarded (60).

Familial fructose and galactose intolerance

Neuroglycopenic symptoms occur in familial fructose and galactose intolerance with moderate cerebral impairment. Dormandy and Porter (52) reported one case associated with severe epilepsy commencing at puberty after a normal childhood. Moderate aminoaciduria and slight glucosuria may occur (9).

DIAGNOSIS OF STIMULATIVE HYPOGLYCEMIA

The fasting blood glucose concentration in normal children and adults ranges from 60 to 100 mg per 100 ml, with an average value close to 80 mg (11). Slightly lower or higher values are occasionally encountered without clinical evidence of disease (1).

Some laboratory techniques for measuring blood sugar depend on the reducing properties of glucose. There are, however, reducing substances besides glucose in blood, collectively referred to as saccharoids. Estimates of their quantity vary from person to person, from time to time in the same person and according to the method used. The value obtained with a nonspecific method, such as the Folin Wu filtrate, may be 10 to 30 mg per 100 ml higher than that for the true glucose present (11). The glucose-oxidase method, on the other hand, is specific for glucose. In the investigation of hyperglycemic states, the choice of method is of little significance, but in conditions with hypoglycemia, it may be critical (9). In this paper, blood glucose will refer only to that fraction measured by glucose-oxidase while blood sugar will refer to total substances measured by nonspecific reducing methods.

Provocative tests

Usually the patient is not seen by a clinician during a spontaneous hypoglycemic attack. Instead of waiting for symptoms to recur, provocative tests are used to diagnose hypoglycemia (table 4).

TABLE 4

Results of diagnostic tests for varieties of spontaneous hypoglycemia
(Adapted from 1,4)

	Stimulative			Fasting			
Provocative test	Reactive	Alcohol-induced	HFI[1] and Galactosemia	Hepatic disease	Hyperinsulinism	IHC[2]	Leucine sensitive
6 hour OGTT[3]	+++		0	+++	±	±	±
IVGT[4]		+			++		
Prolonged fast	0			++	+++	+++	+++
Glucagon	0	±		0	+++	+	+
Tolbutamide	0	±		±	+++	0?	
Fasting insulin assay	0				±	0	0
Leucine		±			±	0	+++

0 = normal
± = variable
\+ = often positive
++ = usually positive
+++ = characteristic
? = insufficient data
blank = no data

[1] hereditary fructose intolerance, [2] idiopathic hypoglycemia of childhood, [3] oral glucose tolerance test, [4] intravenous glucose tolerance test

Oral glucose tolerance test (OGTT). The oral glucose tolerance test (OGTT) is one of the oldest and most widely used of all laboratory procedures. However, there is some lack of standardization in its administration. Therefore the results of an OGTT need to be interpreted with care.

The patient, having been on a high carbohydrate diet for at least 3 days, is fasted overnight (9). A venous blood sample is withdrawn before a solution containing 50 g glucose dissolved in 300 to 500 ml flavored water is given to the patient to drink (11). Thereafter, at 30 minute intervals for 6 hours, venous blood samples are taken. Blood glucose levels are then plotted against time.

According to Middleton (61), it is essential that a specific glucose-oxidase method be used. Spontaneous variation in the saccharoid content of blood during the test limit the usefulness of results obtained by other methods. Exercise and emotional disturbance should be avoided before and during the test. The examination should not be made when the patient is acutely ill (11). The high carbohydrate intake during the period prior to the test tends to prevent the abnormal hyperglycemic response near the beginning of the test and also helps to standardize the situation under which the test is made. Because there are so many types of hypoglycemia and because of lack of standardization in giving the OGTT, the curves may vary.

Normally, the level of blood glucose rises during the first hour after glucose ingestion, falls to a low level $2\frac{1}{2}$ to 4 hours later, then rises to its postabsorptive level (figure 1). In hypoglycemia, the blood glucose level falls below 50 mg per 100 ml. This occurs approximately $4\frac{1}{2}$ to 5 hours after glucose ingestion. Therefore it is important to continue the test for the full 6 hours.

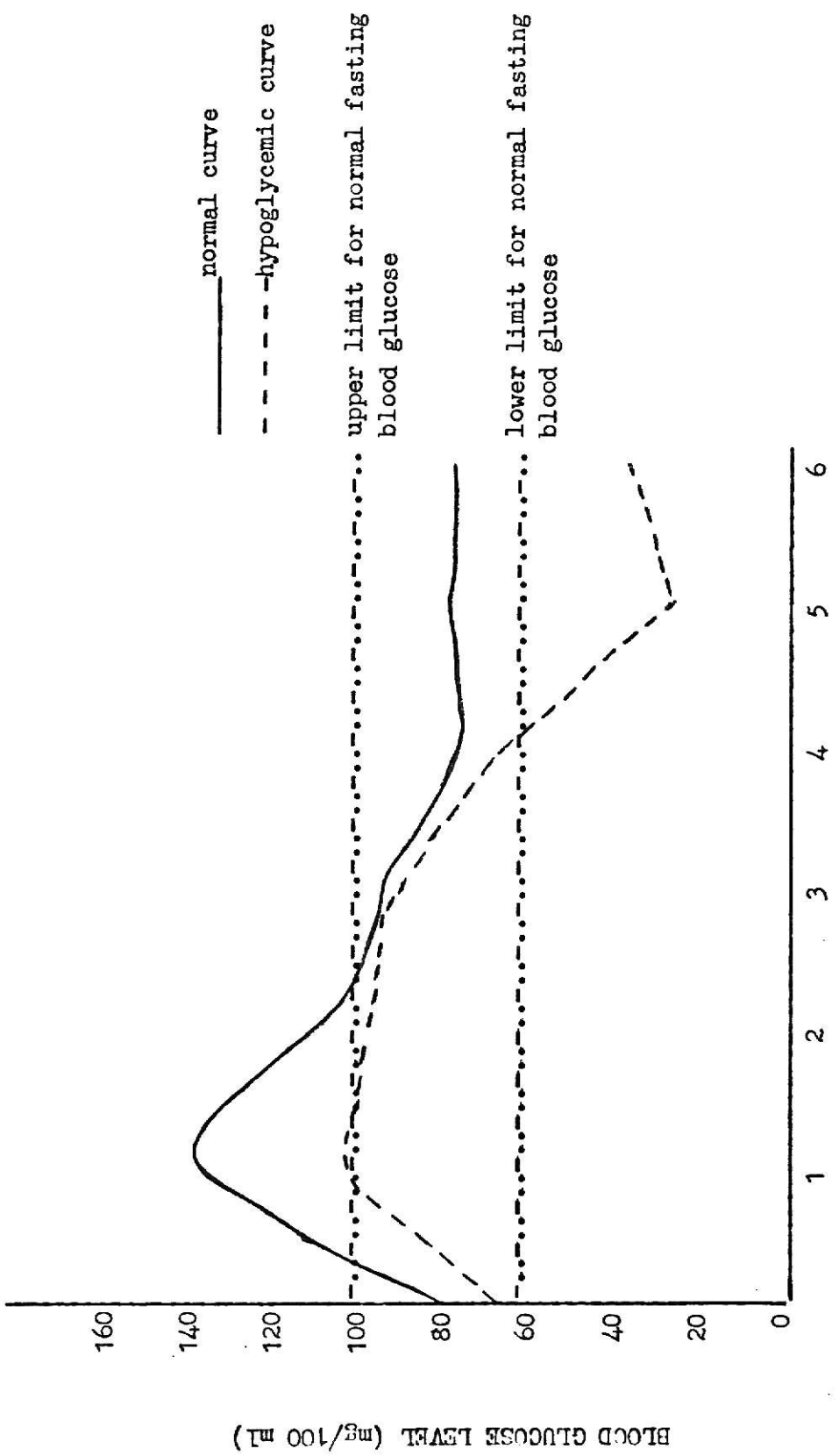

Fig. 1 Normal and hypoglycemic glucose tolerance curves following ingestion of 50 g glucose (5,11, 63).

Intravenous glucose tolerance test (IVGT). The chief disadvantage of the oral glucose tolerance test is that the curve depends as much on the speed of absorption of glucose as on the mechanism for glucose disposal (11). Thus an intravenous glucose tolerance test (IVGT) has been devised where the patient is fasted overnight and then given an injection of 50 ml of a 50 percent solution of glucose over the course of 2 to 4 minutes (62). Venous blood is withdrawn before the injection and at 10 minute intervals thereafter for 1 hour. The blood is then analyzed for glucose content. Marks and Rose (9) stated that the IVGT yielded inconsistent results in varieties of spontaneous hypoglycemia except for malignant insulinoma and therefore is of little diagnostic value.

Prolonged fast test. Most patients with hyperinsulinism, a fasting hypoglycemia, will show a low overnight fasting blood glucose level on occasion, depending on the severity of the illness (1). According to Breidahl et al. (64), the prolonged fast test (48+ hours) is still the most reliable single test for hyperinsulinism. Patients with stimulative hypoglycemia remain normoglycemic during the prolonged fast test.

Glucagon test. Patients with insulinomas respond in a characteristic manner to 1 mg glucagon given intramuscularly (1). There is a short, sharp rise in blood glucose within 30 minutes as in normal subjects, but whatever the fasting concentration, it is rapidly followed by a fall to hypoglycemic levels within the next $1\frac{1}{2}$ to 3 hours. Normal persons occasionally show a slight return to normal glucose level after glucagon but hypoglycemia is not observed (1).

Tolbutamide test. Fajans and Conn (65) introduced the intravenous tolbutamide test for diagnosis of insulinoma. Experience with this test is still limited, but the available evidence suggests that false diagnoses

are rare (1). Patients with stimulative hypoglycemia respond normally to the tolbutamide test.

Fasting plasma insulin assay. The immunoassay technique makes it practical to assay plasma insulin in man. Using this technique, it has been shown that plasma from approximately half the patients with proven insulinoma contains excessive insulin-like activity during fasting (66). Fasting insulin levels are normal in leucine-sensitive hypoglycemia, idiopathic hypoglycemia of infancy and stimulative hypoglycemia (1).

Leucine test. The leucine test, while of no value in distinguishing preoperatively between idiopathic leucine sensitivity and insulinoma in infants, can provide evidence of insulinoma in adults without a previous history of hypoglycemia (32). It is now apparent that about 50 percent of patients with insulinomas are sensitive to leucine (1). They lose their sensitivity when the tumor is removed.

It is obvious that the oral 6 hour glucose tolerance test is the only satisfactory test for stimulative hypoglycemias. The other tests described are useful in diagnosing fasting types of hypoglycemia.

Reactive hypoglycemia

Finestone and Wohl (3) reported that the diagnosis of reactive hypoglycemia should be made only when the hypoglycemia and its accompanying symptoms can be reproduced during a 6 hour OGTT. Williams (67) found reactive hypoglycemia on some occasions, but not on others, when an OGTT indicated low blood glucose. In a study by Luyckx and Lefebvre (37), 30 of 47 patients who had reactive hypoglycemia, had claimed signs of neuroglycopenia 2 to 4 hours after a meal. According to Marks and Rose (9), the 6 hour OGTT is essential in the diagnosis of reactive hypoglycemia, but the results must be interpreted with caution. A positive OGTT does

not give the cause of the hypoglycemia, which is necessary to know for proper treatment.

Reactive hypoglycemia of the diabetic type has a very high glucose peak of over 200 mg percent in the first hour of an OGTT. A high carbohydrate intake prior to the OGTT will not lower this peak as it will for alimentary hypoglycemia (11).

Alcohol-induced hypoglycemia

The patient with alcohol-induced hypoglycemia may be in a coma so diagnosis must be made on physical and laboratory findings. Diagnosis depends on recognition of neuroglycopenia with demonstrable hypoglycemia accompanied by alcoholemia (9). Sometimes metabolic acidosis occurs with alcohol-induced hypoglycemia (31).

Differentiation of alcohol-induced hypoglycemia from other types of hypoglycemia, especially hyperinsulinism, may be difficult or impossible without plasma insulin assay (47). During remissions, the response to intravenous tolbutamide test may be abnormal and occasionally closely resemble the response observed in patients with islet cell tumors (9). Glucose responses to leucine, glucagon, intravenous insulin and glucose tolerance tests are inconsistent and often abnormal (68). Some degree of hypoglycemic unresponsiveness during the standard intravenous insulin tolerance test is usual and slight impairment of glucose tolerance is common.

Moderate doses of alcohol after an overnight fast are almost pathognomic of alcohol-induced hypoglycemia. Neame and Joubert (69) reported that even with rigorous therapy, some patients with alcohol-induced hypoglycemia die.

Hereditary fructose intolerance

When HFI is inherited, breast-fed babies present feeding problems upon weaning and / or when foods containing sucrose or fructose are added to the diet. There is difficulty in finding an acceptable milk formula for formula-fed infants with HFI as most formulas contain sucrose, which is converted to glucose and fructose during absorption.

In mild cases of HFI, the problem foods are recognized by trial and error, but HFI may not be recognized until middle life (48). In severe cases, if the dietary problem is not recognized, death occurs.

If a nonspecific method for measuring glucose is used, the possibility of hypoglycemia may be dismissed because the low blood glucose is obscured by the high concentration of fructose. The glucose-oxidase method, however, avoids this mistake.

Galactosemia

Clinically, galactosemia is characterized by failure to thrive, liver enlargement, galactosuria and aminoaciduria (50). Children who survive may be dwarfed and mentally retarded (60).

In galactosemics, hypoglycemia commonly follows the ingestion of galactose or substances that yield galactose on digestion, but this may vary (70). Galactosemia is suspected on clinical or genetic bases. It is confirmed by demonstrating defective galactose-1-phosphate-uridyl transferase activity or impaired galactose metabolism with accumulation of galactose-1-phosphate by red blood cells in vitro. Galactose tolerance tests are potentially dangerous and should not be used for diagnostic purposes.

Familial fructose and galactose intolerance

Familial fructose and galactose intolerance is diagnosed by fructosuria, galactosuria, aminoaciduria and occasional slight glucosuria (9). Samols and Dormandy (71) found insulin plasma levels to be extremely high in persons with this condition. The complete diagnostic picture has not been determined, but the mechanism allowing patients to produce, tolerate or require such a high concentration of insulin in the blood may reflect some metabolic abnormality at the tissue level.

TREATMENT OF STIMULATIVE HYPOGLYCEMIA

Treatment of hypoglycemia consists of treating the underlying cause if it is known (3,8,9,11). In many cases, however, there is no recognizable cause for the patient's symptoms. In these circumstances it is practicable to assume that symptoms may a) be caused by reactive hypoglycemia of unusual severity and unknown etiology, b) represent an abnormal sensitivity to physiological fluctuations of the blood glucose level, c) be related to carbohydrate ingestion through its effect on body constituents other than glucose or d) be caused by malnutrition as a result of faulty diet or intestinal absorption (9).

Surgical, hormonal, dietary, pharmacological and psychological treatments are available for treatment of hypoglycemia. Surgical treatment is used for fasting hypoglycemias when a tumor is present. Hormonal treatments have been used to treat fasting forms caused by hypopituitarism and hypoadrenalism. The main objective of dietary and pharmacological treatments is to supply body cells with glucose in as continuous a flow as possible, preventing hyperglycemia that stimulates insulin secretion.

Reactive hypoglycemia

Treatment of reactive hypoglycemia includes diet, drugs, psychotherapy or a combination of these. Dietary treatment is usually the first type of treatment used after diagnosis of reactive hypoglycemia.

Diet. If the symptoms are not severe, treatment consists of a diet high in protein and fat with restricted carbohydrate (4,11,72,73). Hypoglycemia can be controlled by dietary treatment, but not cured. Because carbohydrates serve as a stimulus for insulin secretion and provoke hypoglycemic attacks, they are restricted. High amounts of protein and fat are recommended because the glucose supplied by these nutrients is released to the bloodstream gradually. Thus, there is little stimulation of the beta cells to produce an excess of insulin.

Carbohydrates are usually limited to levels below 100 g (72,73). Krause (4), however, reported carbohydrate levels may range from 50 to 120 g. Robinson (72) stated that most Americans consume diets with 200 to 300 g carbohydrate. The initial diet may be planned with 100 g carbohydrate, with reduction to 50 g if the patient shows no improvement.

The carbohydrate should be given in the form of the more slowly digested starches such as the polysaccharides of cereals, potatoes, flour and rice. Simple carbohydrates found in sugars, jam, jelly, syrup, milk and fruits should be avoided (4,72). Artificial sweetener may be substituted for sugar (73).

Because carbohydrates are severely limited in the hypoglycemic diet, bread and milk will be restricted to include adequate amounts of fruits and vegetables that also contain carbohydrate. Low carbohydrate vegetables and fruits and limited quantities of bread, cereal and potatoes should provide the carbohydrate of the diet. Carbohydrate foods should be measured accurately.

A high protein diet, 90 to 140 g, is recommended for the hypoglycemic diet (4,72). The 1973 recommended dietary allowances (RDA) for protein for the reference woman and man are 46 and 56 g respectively, as determined by the Food and Nutrition Board of the National Research Council (74).

There is no appreciable rise in the blood sugar level following high protein meals even though protein furnishes approximately 50 percent of its weight in available glucose (75). This available glucose is released to the blood stream gradually so there is little stimulation of the pancreatic beta cells. A generous serving of meat, fish, poultry, eggs or cheese must be included in each meal to get sufficient protein.

Total kilocalories for the hypoglycemic diet are based on the RDA for the patient's sex and age group (4). When the total kilocalories are determined, (2,000 for the reference woman), the amount of carbohydrate kilocalories (100 g X 4 kcal/g = 400 kcal) and protein kilocalories allowed (90 to 140 g X 4 kcal/g = 360 to 560 kcal) are deducted from the total kilocalories (74). The difference [2,000 kcal - (760 or 960 kcal) = 1240 or 1040 kcal] is the fat kilocalorie allowance. Thus the fat content of the diet will be high to supply the remaining kilocalories required for the day. Fatty meats, bacon, butter or margarine and mayonnaise will aid in supplying the required fat (73). Cream may be substituted for part of the milk to provide fat.

There is no RDA for fat in the diet. However, Robinson (72) stated that Americans derived up to 40 percent of their calories from fat. Fat in a hypoglycemic diet contributes approximately 50 percent of the daily calories. Because fats are a concentrated source of energy (9 kcal/g), small quantities greatly increase the kilocalorie intake. It is important that the individual on a hypoglycemic diet does not increase his caloric intake beyond his needs or he may become overweight.

A high intake of saturated fats and cholesterol increases the concentration of blood cholesterol and certain lipoprotein fractions. The elevated levels of blood lipids appear to be highly correlated with the incidence of cardiovascular diseases and atherosclerosis (72,75). Appreciable dietary substitution of fats rich in polyunsaturated fatty acids for more saturated fats induces a significant decrease in the plasma cholesterol level in a majority of hypercholesterolemic subjects (75). To avoid the increased likelihood of coronary disease on a high fat hypoglycemic diet, the patient should concentrate on using unsaturated oils and low cholesterol foods or cholesterol-substitute food products that are available.

Luyckx and Lefebvre (37) reported that reactive hypoglycemia is frequently associated with obesity. A characteristic of patients with obesity and hypertriglyceridemia is excessive insulin response to carbohydrate feeding (76). Bierman and Porte (77) reported that excessive insulin secretion may be provoked by obesity and cause an increase in the synthesis of triglycerides. It is now largely agreed, however, that excess insulin is the result, not the cause, of obesity (78). The stimulus for the increased insulin response to carbohydrate ingestion appears related to the insulin insensitivity of overstuffed adipose cells rather than a hormonal stimulus (78). Regardless of whether insulin has a primary or secondary role in the etiology of obesity, it is a link that needs to be studied.

Ketosis may occur in obese persons following a hypoglycemic diet. Hood et al. (79) and Bell et al. (80) found measurable ketosis in obese patients on restricted carbohydrate intake, but rapid reduction in circulating ketones with increases in the dietary carbohydrate level. Worthington and Taylor (81) also reported ketosis in overweight female subjects on a high protein, low carbohydrate diet.

Caution must be exercised to prevent the development of any nutrient deficiency in the hypoglycemic diet. Vitamins and minerals should meet the RDA. Calcium and riboflavin intake may be low because of the limited amount of milk permissible on a low carbohydrate diet. A pharmacological supplement for calcium and riboflavin may be needed to supply the required amount of these substances.

Foods not restricted on the hypoglycemic diet are in table 5. These foods add variety to the diet without adding carbohydrate.

TABLE 5

Foods allowed as desired on a hypoglycemic diet (38)

Gelatin, unsweetened	Coffee	Saccharin
Cranberries, unsweetened	Tea	Spices
Dill pickle, unsweetened	Clear broth	Vinegar
Rhubarb, unsweetened	Herbs	Lemon
Bouillon, fat free	Rennet	Mustard, dry

For absorption from the intestine to be gradual, the daily allowance of carbohydrate, protein and fat is divided into 3 approximately equal meals with 2 or 3 between-meal snacks. The patient may find it useful to carry crackers and a cube of cheese to control neuroglycopenic attacks (73).

Food exchange lists, established by the American Dietetic Association, the American Diabetes Association and the U. S. Public Health Service, provide a quick and reasonably accurate estimation of the nutritive value of any diet (appendix, table 1) (82). An exchange list is a grouping of foods in which specified amounts of all the foods listed are of approximately equal carbohydrate, protein and fat value. Specific foods within the lists may differ slightly in their nutritive value from the averages stated for the group. These differences in composition tend to cancel because of the variety of foods selected from day to day (72). Thus, any food within a given list can be substituted or exchanged for any other food in that list.

Table 6 illustrates the calculation of a hypoglycemic diet by the food exchange method. For the reference woman with an energy requirement of 2,000 kcal, the following diet may be prescribed: 120 g protein, 90 g carbohydrate and 130 g fat.

TABLE 6

Determination of food exchange allowances for a hypoglycemic diet (Adapted from 72,83)

Food exchange list	Number of exchanges	Carbohydrate g	Protein g	Fat g	Energy kcal
Milk, whole	2	24	16	20	340
Vegetables					
Group A[1]	2	6	4		40
Group B	1	7	2		35
Fruit	2	20			80
Bread	2	30	4		140
Meat	14		98	70	1050
Fat	8			40	360
Total		87	124	130	2045

[1] For a hypoglycemic diet, group A vegetables are calculated as carbohydrate, 3 g and protein, 2 g per 100 g.

To determine the number of each food exchange allowed, first estimate the amount of milk, vegetables and fruits to be included (72). Allowances are dictated somewhat by the preferences of the patient, but the following amounts are minimum levels that should be included: milk, 2 cups for adults, 3 to 4 cups for children or lactating women; vegetables, group A, 1 exchange, group B, 1 exchange; fruit, 2 exchanges. Fill in the carbohydrate, protein and fat values for the tentative amounts of milk, vegetables and fruits.

To determine the number of bread exchanges, total the carbohydrate value of the milk, vegetables and fruit. Subtract this total from the total

amount of carbohydrate prescribed. Divide the remainder by 15 (the carbohydrate value of 1 bread exchange). Use the nearest whole number of bread exchanges. Fill in the carbohydrate and protein values on the tentative form (90 g - 59 g = 31 g carbohydrate or 2 exchanges).

Next, total the carbohydrate column. If the total deviates more than 3 or 4 g from the prescribed amount, adjust the amounts of vegetables, fruits and bread. A second group A vegetable exchange may be added to the minimum amount of 1 exchange at this point.

To determine the number of meat exchanges, total the protein value of the milk, vegetables and bread. Subtract this total from the amount of protein prescribed. Divide the difference by 7 (the protein value of 1 meat exchange). Use the nearest whole number of meat exchanges. Fill in the protein and fat values.

The number of fat exchanges is found by totaling the fat values for milk and meat. Subtract this total from the amount of fat prescribed. Divide the remainder by 5 (the fat content of 1 fat exchange). Fill in the fat value.

Calculate the kilocalories of the diet by multiplying the protein and carbohydrate content by 4 kcal/g and multiplying the fat content by 9 kcal/g. If the total kilocalorie content is not the prescribed amount, recheck the diet for accuracy of computations. If the kilocalorie allowance agrees with the prescribed amount, divide the daily food allowance into 3 meals with 2 or 3 snacks.

A sample daily menu for a hypoglycemic diet is presented in table 7. The diet was determined by the exchanges allowed in table 6.

TABLE 7

Hypoglycemic diet using the food exchange lists

Food exchange list	Exchanges	Sample menu	Measure	Carbohydrate g	Protein g	Fat g	Energy kcal
		Breakfast					
Fruit	1	Orange	1 small	10			40
Meat	2	Eggs, boiled	2		14	10	150
Fat	1	Margarine	1 tsp			5	45
Fat	1	Bacon	1 slice			5	45
		Coffee, no sugar					
		Snack					
		Eggnog					
Milk	1	Milk	1 cup	12	8	10	170
Meat	2	Eggs	2		14	10	150
		Lunch					
		Open-faced sandwich					
Meat	2	Ham	2 slices, 4½ X 4½ X 1/8 inch		14	10	150
Meat	1	Cheese	1 ounce		7	5	75
Fat	1	Mayonnaise	1 tsp			5	45
Bread	1	Rye bread	1 slice	15	2		70
Vegetable group A	1	Lettuce and tomato salad	½ cup	3	2		20
Fat	1	French dressing	1 Tbsp			5	45
Fruit	1	Honeydew melon	1/8, 7-inch diameter	10			40
		Ice cream					
Meat	1	Egg	1		7	5	75
Fat	2	Cream	2 Tbsp			10	90
		Iced tea with lemon					

TABLE 7 (concluded)

Food exchange list	Exchanges	Sample menu	Measure	Carbohydrate g	Protein g	Fat g	Energy kcal
		Snack					
Bread	1	Graham crackers	2	15	2		70
Fat	1	Cream cheese	1 Tbsp			5	45
		Dinner					
Meat	5	Chopped steak	5 ounces		35	25	375
Vegetable group B	1	Acorn squash	½ cup	7	2		35
Fat	1	Butter for squash	1 tsp			5	45
Vegetable group A	1	Celery and carrot sticks	100 g	3	2		20
		Gelatin, artificially sweetened	½ group				
Milk	1	Milk, whole	1 cup	12	8	10	170
		Snack					
Meat	1	Cheese	1 ounce		7	5	75
Total				87	124	130	2045

While the high protein, low carbohydrate diet is the standard recommendation for treatment of reactive hypoglycemia, it is not effective for all patients (9,72,84). The high protein content of the diet may evoke insulin release in some patients resulting in hypoglycemia (26). Therefore the diet and its possible effects should be fully explained to the patient so further tests can be made if the hypoglycemia persists.

"The Low Blood Sugar Cookbook" (85) is a practical guide for hypoglycemics that includes examples of high protein, low carbohydrate diets using a unit system similar to the food exchange lists. Recipes have been modified to low carbohydrate content. A useful list of brand names of low carbohydrate prepared foods and condiments as well as suggestions for quick protein snacks are given.

Drugs. If a patient does not show improvement with a high protein, low carbohydrate hypoglycemic diet, pharmacological agents should be considered. The sulfonylurea drugs used for diabetics (tolbutamide, chlorpropamide and tolazamide) are paradoxically effective in treating reactive hypoglycemia (14,38). These drugs are effective for diabetic and alimentary reactive hypoglycemias. They reduce the hyperglycemia at the beginning of an OGTT for some patients that causes excessive insulin release (84,86).

Phenformin, a biguanide, is used to treat hypoglycemia by its actions on peripheral tissues. In muscle, glucose uptake is increased, partly as a result of an acceleration of glycolysis (14). Anderson and Herman (38) reported that phenformin reduced excessive insulin secretion in obesity and might be particularly valuable in the therapy of alimentary reactive hypoglycemia. Preliminary results indicate that phenformin plus sulfonylurea drugs are effective in treating diabetic reactive hypoglycemia (87).

Psychotherapy. The neurotic patient with essential reactive hypoglycemia usually responds to sedation, use of mild vagus-depressing drugs and supportive psychotherapy in the treatment of a specific tangible disturbance like hypoglycemia (9,11,54). Psychotherapy is used along with a high protein, low carbohydrate diet. However, the effect of the diet in preventing reactive hypoglycemia for a neurotic person is unsubstantiated.

Value of treatment. The diversity of treatments suggested for hypoglycemics and the contradictory reports of their value may, in part, be attributed to heterogeneity of patients both in cause and severity of the hypoglycemia. Information about hypoglycemic diets is sparse in the literature. Diet manuals may contain a low carbohydrate diet, but the carbohydrate level may be greater than the amount prescribed for a hypoglycemic diet. Study of the relationship of hypoglycemia, obesity and coronary disease is needed because of the high fat in the hypoglycemic diet.

Alcohol-induced hypoglycemia

The hypoglycemia of alcohol ingestion is an acute situation and is best treated by intravenous glucose as soon as possible to restore the blood glucose level to normal (9,11). If this fails to produce immediate and complete recovery of consciousness, it is justifiable to give hydrocortisone intravenously and to infuse glucose constantly until the patient is sufficiently improved to feed himself (9). Even without treatment, most patients recover, although a small proportion die without regaining consciousness. Long-term treatment is the same as that of chronic alcoholism.

It is possible that hypoglycemia is a cause of death in alcoholics found dead without a previous history of ill health and for which no cause is demonstrable at postmortem. Danger exists in regarding the illness as merely alcoholic intoxication and allowing the patient to "sleep it off".

Such neglect may lead to permanent central nervous system damage and even to death.

Recurrent attacks of hypoglycemia from alcohol ingestion are relatively few. Intervals up to 4 years between episodes have been recorded (88). The ease with which hypoglycemia can be provoked by alcohol in susceptible subjects suggests that they experience hypoglycemic attacks more often than their hospital admission records reveal (89).

Hereditary fructose intolerance

The only effective treatment for HFI is to eliminate fructose from the diet (32). Intravenous glucose may be given to treat acute symptoms caused by hypoglucosemia as when a patient inadvertently eats food containing fructose. Some patients, as they become older, can tolerate a small but increasing amount of fructose (9). Table 8 gives a fructose free diet.

Galactosemia

Management of patients with galactosemia is to eliminate galactose from the diet (9,32). If treatment with a low galactose diet is begun early, the patient's mental and physical health should be normal, but visual difficulties caused by cataracts remain common (60).

Milk sugar (lactose) must be removed from the diet because it yields galactose during digestion. Holzel (90) indicated that several of the low galactose formulas were not devoid of oligosaccharides containing galactose. Gitzelmann and Auricchio (91) reported that soybean formulas were generally safe for galactosemic infants.

In older children avoidance of milk sugar is more difficult because many foods contain unlabeled lactose. Thus, candies and compounded foods, especially bread, sausage and frankfurters, must be rigidly excluded unless the exact composition is known. Table 9 lists a galactose free diet.

TABLE 8

Fructose-free diet (32)

Food	Foods to use	Foods to omit
Milk	Milk and milk products	None
Meat, fish, poultry, cheese	Beef, veal, lamb, pork, chicken, fish, turkey, cheese	Ham, bacon, lunch meats and other meats in which sugar is used in processing
Eggs	Eggs	None
Vegetables	Asparagus, cabbage, cauliflower, celery, green beans, green peppers, lettuce, spinach, wax beans	All other vegetables
Potato or substitute	White potatoes, macaroni, noodles, spaghetti, rice	Sweet potatoes
Fruits	None	All fruits and fruit juices
Bread	No bread, soda crackers or saltines	Any bread or crackers
Cereal	Cooked or ready-to-eat cereals	Sugar-coated cereals
Fat	Butter, margarine, oil, home-made mayonnaise or French dressing made without sugar	Mayonnaise, salad dressings made with sugar
Desserts	Dietetic jello, dietetic ice cream, dietetic puddings	All desserts containing sugar, such as cake, pie, cookies, candy, puddings, jello, ice cream, sherbet and others. Any dessert with honey, fruit or fruit juices
Miscellaneous	Vegetable juices (no tomato), coffee, tea, soups from allowed vegetables, sugar substitute, dietetic beverages	Catsup, chili sauce, carbonated beverages, sugar, honey, syrup, jam, jelly, preserves, other sauces

TABLE 9

Galactose-free diet (32)

Food	Food to use	Food to omit
Milk and milk products	None	All milk of any kind, cheese, ice cream, sherbets, food containing milk or milk products
Meat, fish, fowl	Beef, chicken, turkey, fish, lamb, veal, pork, ham	Creamed or breaded meat, fish or fowl, luncheon meats, hot dogs, liver sausage, meats containing milk or milk products, organ meats
Eggs	Eggs	None
Vegetables	Artichokes, asparagus, beets, green beans, wax beans, broccoli, celery, cauliflower, corn, chard, cucumber, eggplant, kale, lettuce, greens, okra, onions, parsley, parsnips, pumpkin, rutabagas, spinach, squash, tomatoes	Sugar beets, peas, lima beans, soybeans, any vegetable in which lactose has been added during processing, legumes, creamed, breaded or buttered vegetables
Potatoes and substitutes	White potatoes, sweet potatoes, macaroni, noodles, spaghetti, rice	Any creamed, breaded or buttered, French fried potatoes or instant potatoes if lactose or milk has been added during processing
Breads and cereals	Any that do not contain milk or milk products	Prepared mixes such as muffins, biscuits, waffles, pancakes; some dry cereals, instant cream of wheat, dry cereals with added skim milk powder or lactose, breads and rolls made with milk, crackers

TABLE 9 (concluded)

Food	Food to use	Food to omit
Fats	Oils, bacon, shortenings, dressings that do not contain milk or milk products	Margarine, butter, cream, cream cheese, dressings containing milk or milk products
Soups	Clear soups, vegetable soups that do not contain peas or lima beans, consommes	Cream soups, chowders, commercially prepared soups that contain lactose
Desserts	Water and fruit ices, jello, angel food cake, homemade cakes, pies, cookies from allowed ingredients	Commercial cakes, cookies and mixes, custard, pudding, ice cream made with milk, anything containing chocolate
Fruits	All fresh, canned or frozen that are not processed with lactose	Any canned or frozen that are processed with lactose
Miscellaneous	Nuts, peanut butter, popcorn (unbuttered), pure sugar candy, jelly or marmalade, sugar, Karo, carob powder, chewing gum, olives	Gravy, white sauce, chocolate, cocoa, toffee, peppermints, butterscotch, caramels, molasses, candies, instant coffee, powdered soft drinks, monosodium glutamate, some spice blends

Labels should be read carefully and any products that contain milk, lactose, casein, whey, dry milk solids or curds should be avoided. Lactate, lactic acid, lactalbumin and calcium compounds do not contain lactose.

Familial fructose and galactose intolerance

Fructose and galactose intolerance occurs upon ingestion of either fructose or galactose. The only therapy documented is to remove these sugars from the diet (9).

SUMMARY

Spontaneous hypoglycemia is a disturbance of glucose homeostasis that can be caused by a number of factors involving the liver or the endocrine or nervous systems. Clinically, spontaneous hypoglycemia is classified as fasting or stimulative.

Fasting hypoglycemia occurs in a fasting state and is caused by a tumor or dysfunction of the liver or endocrine glands; it is progressive and can be fatal. Stimulative hypoglycemia occurs 2 to 4 hours after carbohydrate ingestion. The reactive types of stimulative hypoglycemia are the most common forms of spontaneous hypoglycemia and can be caused by vagal overstimulation, gastrectomy, latent diabetes or excessive intestinal glucagon release. Symptoms are usually mild and disappear spontaneously. However, other types of stimulative hypoglycemia, i.e., alcohol-induced and those caused by inborn errors of metabolism can be fatal.

Because of the short duration of reactive hypoglycemic attacks, the patient is usually not seen by a doctor during the attack. Therefore, tests are administered to provoke hypoglycemia for diagnosis. The 6 hour oral glucose tolerance test is the only provocative test that is satisfactory in diagnosing reactive hypoglycemia but its results should be interpreted with care.

Alcohol-induced hypoglycemia is diagnosed by neuroglycopenia with hypoglycemia accompanied by alcoholemia and sometimes by acidosis. Plasma insulin assay may be necessary to differentiate between alcohol-induced hypoglycemia and hyperinsulinism, a fasting hypoglycemia. Stimulative hypoglycemia caused by the inability to digest fructose or galactose evokes a neuroglycopenic reaction following ingestion of the appropriate hexose.

Treatment of hypoglycemia is that of the underlying cause, if known. Surgical, hormonal, dietary and psychological treatments are available. Surgical and hormonal treatments are used in fasting types of spontaneous hypoglycemia.

Dietary treatment is usually the first type of treatment used after diagnosis of reactive hypoglycemia. A diet high in protein and fat with restricted carbohydrate is prescribed. Food exchange lists can be used for calculation of the diet. Dietary treatment for fructose and galactose intolerance types of stimulative hypoglycemia consists of removing the hexose causing the metabolic problem from the diet.

If a patient does not show improvement with a hypoglycemic diet, sulfonylurea drugs may be used. Phenformin has been used alone and with the sulfonylureas to treat reactive hypoglycemia. The neurotic patient with essential reactive hypoglycemia usually responds to vagus-depressing drugs and supportive psychotherapy along with a hypoglycemic diet.

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APPENDIX

TABLE 1

FOOD EXCHANGE LISTS (72,82)

Food exchange	Measure	Weight	Carbohydrate	Protein	Fat	Energy
		g	g	g	g	kcal
Milk	8 ounces	240	12	8	10	170
Vegetables—A	100 g	100	3	2	—	20
Vegetables—B	½ cup	100	7	2	—	35
Fruit	Varies	—	10	—	—	40
Bread	Varies	—	15	2	—	70
Meat	1 ounce	30	—	7	5	75
Fat	1 tsp	5	—	—	5	45

List 1—Milk exchanges
Per exchange: carbohydrate, 12 g; protein, 8 g; fat, 10 g

	Measure	Weight
		g
Milk, whole (plain or homogenized)	1 cup (8 ounces)	240
Milk, skim, liquid*	1 cup	240
Milk, evaporated	½ cup	120
Milk, powdered whole	3 to 5 tablespoons**	35
Milk, nonfat dry*	3 to 5 tablespoons**	35
Buttermilk (from whole milk)	1 cup	240
Buttermilk (from skim milk)*	1 cup	240

* Because these forms of milk contain no fat, 2 fat exchanges may be added to the diet when they are used; or 1 exchange of these forms of milk may be calculated as carbohydrate 12 g, protein 8 g, fat 0 g.

**The amount of milk powder to use depends upon the brand used; read package directions for the equivalent for 1 cup liquid milk.

List 2—Vegetable exchanges
Group A—Per exchange: carbohydrate, 3 g; protein, 2 g; fat, 0 g

Asparagus
Beans, string, young
Broccoli***
Brussels sprouts
Cabbage
Cauliflower
Celery
Chicory***
Cucumbers
Escarole***
Eggplant
Greens***
beet
chard, Swiss
collard
dandelion
kale
mustard
spinach
turnip
Lettuce
Mushrooms
Okra
Pepper***
Radish
Sauerkraut
Squash, summer
Tomatoes***
Watercress***

Group B—Per exchange: carbohydrate, 7 g; protein, 2 g; fat, 0 g

Beets
Carrots***
Onion
Peas, green
Pumpkin***
Rutabaga
Squash, winter***
Turnip

*** These vegetables have high vitamin A value. At least one serving should be included in the diet each day.

List 3—Fruit exchanges
Per exchange: carbohydrate, 10 g; protein and fat, 0 g
Fruits may be used fresh, cooked, canned or frozen, unsweetened

	Measure	Weight
		g
Apple	1 small, 2-inch diameter	80
Applesauce	½ cup	100
Apricots, dried	4 halves	20
Apricots, fresh	2 medium	100
Banana	½ small	50
Blackberries	1 cup	150
Blueberries	2/3 cup	100
Cantaloupe+	¼, 6-inch diameter	200
Cherries	10 large	75
Dates	2	15
Fig, dried	1 small	15
Figs, fresh	2 large	50
Grapefruit+	½ small	125
Grapefruit juice+	½ cup	100
Grape juice	¼ cup	60
Grapes	12	75
Honeydew melon+	1/8, 7-inch diameter	150
Mango	½ small	70
Nectarines	1 medium	80
Orange+	1 small	100
Orange juice+	½ cup	100
Papaya	1/3 medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	½ cup, cubed	80
Pineapple juice	1/3 cup	80
Plums	2 medium	100
Prunes, dried or fresh	2 medium	25
Raisins	2 tablespoons	15
Raspberries	1 cup	150
Strawberries+	1 cup	150
Tangerine	1 large	100
Watermelon	1 cup diced	175

+ These fruits are rich sources of ascorbic acid. At least one exchange should be included in the diet each day.

List 4—Bread exchanges
Per exchange: carbohydrate, 15 g; protein, 2 g; fat, 0 g

	Measure	Weight
		g
Bread	1 slice	25
biscuit, roll (2-inch diameter)	1	30
muffin	1 medium	35
cornbread	1½-inch cube	35
Cereal, cooked	½ cup	100
Cereal, dry	3/4 cup	20
Crackers, graham	2	120
oyster	20 (½ cup)	20
saltines (2 inches square)	5	20
soda (2½ inches square)	3	20
round, thin (1½-inch diameter)	6 to 8	20
Flour	2½ tablespoons	30
Grits	½ cup, cooked	100
Ice cream, vanilla (omit 2 fat exchanges)	½ cup	70
Macaroni	½ cup, cooked	100
Matzoth	½ 6½-inch square)	20
Noodles	½ cup, cooked	100
Rice	½ cup, cooked	100
Spaghetti	½ cup, cooked	100
Sponge cake, no icing	1½-inch cube	25
Vegetables		
beans, baked; no pork	¼ cup	50
beans and peas, dried (includes Lima, kidnay, navy beans, blackeyed, split and cow peas, etc.)	½ cup, cooked	100
beans, Lima, fresh	½ cup	100
corn, popped	1/3 cup or ½ small ear	20
corn, fresh	1/3 cup or ½ small ear	80
parsnips	2/3 cup	125
potatoes, white	1 small (2-inch diameter)	100
potatoes, white, mashed	½ cup	100
potatoes, sweet or yam	¼ cup	50

List 5--Meat exchanges
Per exchange: carbohydrate, 0 g; protein, 7 g; fat, 5 g
Measures and weights are for cooked meat

	Measure	Weight
		g
Meat and poultry (medium fat)		
(beef, lamb, pork, veal, liver, chicken, turkey, etc)	1 ounce	30
cold cuts (bologna, liver sausage, luncheon loaf, boiled ham, salami, etc.)	1 slice, 4½-inches square, 1/8 inch thick	45
frankfurter (9 per pound)	1	50
Fish		
cod, haddock, halibut, herring, etc.	1 ounce	30
crab, lobster, salmon, tuna	¼ cup	30
clams, oysters, shrimp	5 small	45
sardines	3 medium	30
Cheese, cheddar	1 ounce	30
cottage	¼ cup	45
Egg	1	50
Peanut butter++	2 tablespoons	30

++Limit to 1 exchange daily or adjust for carbohydrate. Deduct 5 g carbohydrate for each additional exchange.

List 6--Fat exchanges
Per exchange: fat, 5 g, protein and carbohydrate, 0 g

	Measure	Weight
		g
Butter or margarine	1 teaspoon	5
Bacon, crisp	1 slice	10
Cream, light, 20 percent	2 tablespoons	30
Cream, heavy, 35 to 40 percent	1 tablespoon	15
Cream cheese	1 tablespoon	15
French dressing	1 tablespoon	15
Mayonnaise	1 teaspoon	5
Nuts	6 small	10
Oil or cooking fat	1 teaspoon	5
Olives	5 small	50
Avocado	1/8, 4-inch diameter	25

SPONTANEOUS HYPOGLYCEMIA: ITS ETIOLOGY, DIAGNOSIS AND DIETARY TREATMENT

by

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AN ABSTRACT OF A MASTER'S REPORT

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Spontaneous hypoglycemia can be caused by a number of factors involving the liver or the endocrine or nervous systems. Clinically, spontaneous hypoglycemia is classified as fasting or stimulative.

Fasting hypoglycemia occurs in a fasting state and is caused by a tumor or dysfunction of the liver or endocrine glands; it is progressive and can be fatal. Stimulative hypoglycemia occurs in the postprandial state following carbohydrate ingestion. The reactive hypoglycemias are the most common forms of spontaneous hypoglycemia and can be caused by vagal overstimulation, gastrectomy, latent diabetes or excessive intestinal glucagon release. Symptoms are mild and disappear spontaneously. However, other types of stimulative hypoglycemia, i.e., alcohol-induced and those caused by inborn errors of metabolism, can be fatal.

Because of the short duration of reactive hypoglycemic attacks, the patient is usually not seen by a doctor during the attack. Therefore, tests are administered to provoke hypoglycemia for diagnosis. The 6 hour oral glucose tolerance test is the only provocative test that is satisfactory in diagnosing reactive hypoglycemia but its results should be interpreted with care.

Alcohol-induced hypoglycemia is diagnosed by neuroglycopenia with hypoglycemia, alcoholemia and sometimes acidosis. Stimulative hypoglycemia caused by the inability to digest fructose or galactose, evokes a neuroglycopenic reaction following ingestion of the appropriate hexose.

Treatment of hypoglycemia is that of the underlying cause if known. Surgical and hormonal treatments are used in fasting types of hypoglycemia. Dietary treatment is used for reactive hypoglycemias. A diet high in

protein and fat with restricted carbohydrate is prescribed. Dietary treatment for fructose and galactose intolerance types of hypoglycemia consists of removing the hexose causing the metabolic problem from the diet. If a patient does not show improvement with a hypoglycemic diet, sulfonylurea drugs or phenformin may be used. The neurotic patient with essential reactive hypoglycemia usually responds to vagus-depressing drugs and supportive psychotherapy along with a hypoglycemic diet.