Reactive Hypoglycemia

Fred D. Hofeldt

The hypoglycemoses include a large category of distinctly unique entities. Guidelines for a clinical, physiological approach to these disorders is presented. Within this diagnostic spectrum of hypoglycemia lies the reactive hypoglycemic disorders that are characterized by their postprandial onset, adrenergic mediated symptoms, and relatively benign causes. The spectrum of reactive hypoglycemia includes early alimentary-reactive hypoglycemia, late diabetic-reactive hypoglycemia, hormonal deficiency states, and idiopathic hypoglycemia. A new postprandial hypoglycemic disorder, fructose 1-6 diphosphatase, can be added to this list.

The frequent sampling of blood-glucose values in the postprandial state will frequently lead to the finding of a biochemically low blood-glucose value of below 50 mg/100 ml, and these individuals show no hypothalamic-pituitary-adrenal stress to the low blood sugar and do not manifest adrenergic symptoms. Their low blood-glucose value simply reflects the transition in intermediary metabolism between the fed and fasting state and provides a biochemical marker of this event. We refer to this asymptomatic biochemical event as transitional low blood-glucose state. It has no clinical implication and may frequently be confused with the bona fide reactive hypoglycemic disorders.

Using a symptomatic, counter-regulatory model to define hypoglycemia as a bona fide disorder, findings are presented in patients with the varying types of reactive hypoglycemia, and their results are compared to normal controls and to a weight-matched and disease patient controls. Abnormalities in insulin secretion are discussed as relating to the pathophysiology causal in the hypoglycemia. An approach to therapy is presented based upon the classification of the patient as to the type of hypoglycemia and their abnormalities in insulin secretion.

Hypoglycemia attracts the widespread interest of the lay public and has enjoyed great popularity in the lay press. Consequently, many manifestations and unusual features have been attributed to this disorder. Considerable emphasis is now being placed by the medical profession on a more clinical interpretation of the patient’s symptoms in respect to the low blood-glucose determination. In the past, hypoglycemia has been defined biochemically as a blood-glucose level of less than 40 mg/100 ml or plasma-glucose level of less than 50 mg/100 ml. Recent observations stress the interpretation of the low blood glucose in relationship to the patient’s symptoms. The differential diagnosis of the hypoglycemias encompass many diverse diseases.
It is the purpose of this review to discuss reactive hypoglycemia as to its proper perspective and to consider recent developments in relationship to its pathogenesis, diagnosis, and treatment.

**HYPOGLYCEMIC DISORDERS**

Reactive hypoglycemia represents a benign, relatively large category of the hypoglycemias, the causes of which are discrete entities. A clinical, physiological approach to the classification of the hypoglycemias is presented in Table 1. This classification utilizes the patient's initial history to determine if the symptoms are occurring on a pharmacologic basis or are due to deranged body functions.

### Table 1. Classification of Hypoglycemic States

**A. Exogenous causes**

1. Iatrogenic (related to treatment with insulin or oral hypoglycemic agents)
2. Factitious (especially seen in paramedical personnel)
3. Pharmacologic (Ackee nut, salicylates, antihistamines, monamine-oxidase inhibitors, propranolol, phenylbutazone, pentamidine isethionate, phentolamine, alcohol)

**B. Spontaneous hypoglycemia (endogenous metabolic processes)**

1. Fasting state hypoglycemia
   a. Pancreatic disorders
      (1) Islet beta-cell hyperfunction (adenoma, carcinoma, hyperplasia)
      (2) Islet alpha-cell hypofunction or deficiency
   b. Hepatic disorders
      (1) Severe liver disease (cirrhosis, hepatitis, carcinomatosis, circulatory failure, ascending infectious cholangitis)
      (2) Enzyme defects (glycogen-storage disease, galactosemia, hereditary fructose intolerance, familial galactose and fructose intolerance, fructose 1–6 diphosphatase deficiency)
   c. Pituitary—adrenal disorders (hypopituitarism, Addison’s disease, adrenogenital syndrome)
   d. Central nervous system disease (hypothalamus or brain stem)
   e. Muscle (hypoalaninemia)?
   f. Nonpancreatic neoplasms
      (1) Mesodermal (spindle-cell fibrosarcoma, leiomyosarcoma, mesothelioma, rhabdomyosarcoma, liposarcoma, neurofibroma, reticulum-cell sarcoma)
      (2) Adenocarcinoma (hepatoma, cholangiocarcinoma, gastric carcinoma, adenocortiocarcinoma, cecal carcinoma)
   g. Unclassified
      (1) Excessive loss or utilization of glucose and/or deficient substrate (prolonged or strenuous exercise, fever, lactation, pregnancy, renal glycosuria, diarrheal states, chronic starvation)
      (2) Ketotic hypoglycemia of childhood (idiopathic hypoglycemia of childhood)

2. Postprandial hypoglycemia (reactive of fed state)
   a. Reactive to glucose
      (1) Alimentary hypoglycemia (includes patients with previous GI surgery, peptic-ulcer disease, disordered GI motility syndromes, and asymptomatic GI disease)
      (2) Diabetes mellitus
      (3) Hormonal (includes hyperthyroidism and deficient reserve syndromes of cortisol, epinephrine, glucagon, thyroid hormone, and growth hormone).
      (4) Deficient early hepatic gluconeogenesis (fructose 1–6 diphosphatase deficiency)
      (5) Idiopathic
   b. Reactive to other substrate (fructose, leucine, galactose)

**C. Transitional low blood-glucose state ("nonhypoglycemia")**

**D. Pseudohypoglycemia (chronic leukemias with WBC generally in excess of 300,000)**

metabolism (spontaneous hypoglycemia). If the former considerations can be excluded, then the diagnosis depends upon determining whether the symptoms occur in the fasting or fed state and whether the symptoms are of a neuroglycopenic or adrenergic type. The classification preserves part of older terminology while stressing a clinical approach to patient evaluation. The exogenous or pharmacologic causes of hypoglycemia are drug-related and represent iatrogenic and patient overdosage, factitious drug usage, and drug side effects. Conn and Seltzer have coined the term spontaneous hypoglycemia to represent a large category of hypoglycemic disorders due to deranged endogenous metabolic processes. These can be further divided into the fasting and fed state hypoglycemias. Fasting hypoglycemia represents a chronic problem that develops in the fasting state and generally presents with neuroglycopenic symptoms of either psychiatric or neurologic manifestations. Alterations in thought processes or consciousness is seen with these disorders, and the causes of the hypoglycemia are generally serious or life-threatening disorders. In contrast to this, reactive hypoglycemia represents an acute onset of hypoglycemia that is related to the rapid fall in blood glucose into stress levels, and it is the secondary catecholamine release which in turn provokes the symptoms. These disorders occur postprandially, consciousness is preserved, spontaneous recovery is the rule, and the diseases are not considered life-threatening. Thus, depending upon the cause of the hypoglycemia, two cardinal types of symptoms may arise. The careful assessment of the symptoms in relationship to the fasting or fed state allows for an initial differential diagnosis as to the possible underlying etiologies. The postprandial hypoglycemias or fed-state hypoglycemias include alimentary hypoglycemia, diabetes mellitus, hormonal hypoglycemia, deficient early hepatic gluconeogenesis, and idiopathic-reactive hypoglycemia. Idiopathic-reactive hypoglycemia is the preferred terminology over the older terminology of “functional hypoglycemia” when the cause of the reactive hypoglycemia remains undetermined.

If one considers all biochemically low blood-glucose states to represent hypoglyemic disorders, then an asymptomatic biochemical hypoglycemic category exists that has been alluded to in recent publications as “nonhypoglycemia.” We have preferred the terminology, transitional low blood-glucose states, for this group of patients in order to distinguish them from patients with clinically significant disease.

HISTORICAL DEVELOPMENTS IN REACTIVE HYPOGLYCEMIA

In 1924, Harris presented five cases of reactive hypoglycemia. He postulated that there exists a counterpart to diabetes mellitus, or hypoinsulinism, that represents hypoglycemia caused by hyperinsulinism or dysinsulinism. Harris had observed symptoms in patients similar to those occurring with an insulin reaction in insulin-treated diabetic patients. He correlated these symptoms with a lowered blood-glucose value of below 70 mg/100 ml. In his initial publication, he observed low blood-pressure readings in all but two of the nondiabetic patients who had symptoms of reactive hypoglycemia and postulated that there may be an association between the altered insulin secretions and abnormalities in secretory disorders of the thyroid, pituitary, or adrenal gland. He advocated
treating the disorder with a low-carbohydrate diet and frequent small feed-
ings.\textsuperscript{31-33} Subsequent to this, a number of investigators reported their experience with this disorder.\textsuperscript{34-37} Varying interpretations of hypoglycemia were proposed. Some authors defined hypoglycemia as a drop of 20 mg/100 ml or more below the fasting blood sugar level during a 6-hr glucose-tolerance test. A condition of "relative" hypoglycemia was diagnosed if the drop in blood glucose was 10\%--20\% below the fasting blood-glucose level.\textsuperscript{38-39} Later, more critical investigators\textsuperscript{17,20,23,40,41} defined hypoglycemia as occurring when the blood glucose was around 40 mg/100 ml. The number of terms applied to reactive hypoglycemia have added to the confusion. These include functional hyperinsulinism, essential hypoglycemia, functional hypoglycemia, dysinsulinism, hypoglycemic fatigue, insulinogenetic hypoglycemia, and relative hypoglycemia. Simultaneously, a number of testimonials and articles began to appear in the lay\textsuperscript{42-45} and medical literature\textsuperscript{36,37,46,47} documenting the very vagueness of the condition. Reactive hypoglycemia was attributed as causal or related to such diverse diseases as acute rheumatic fever,\textsuperscript{47} asthma,\textsuperscript{48} hayfever,\textsuperscript{49} peptic ulcer,\textsuperscript{50} gastrointestinal nonspecific complaints,\textsuperscript{34,51,52} and seizures.\textsuperscript{35,55} Likewise, the disease came to encompass a host of vague symptom complexes\textsuperscript{10,15,36,37,39,51,53} and was described in association with hypocalcemia.\textsuperscript{53} The psychiatric literature related hypoglycemia to life situations, emotions, tension, depression, neurosis, and asthenic syndromes and to a condition of pernicious inertia.\textsuperscript{39,54-62} Subsequently, reactive hypoglycemia became associated with a number of disease states that included behavioral disturbances, criminal behavior, alcoholism, allergies, rheumatoid conditions, neurological disturbance, neurocardiac disturbances, and asthenic syndromes. Inasmuch as the symptom complex included the majority of the available patient complaints, it became a fashionable and popular disease for the lay public and physicians alike. Numerous articles continue to appear in the popular lay journals that add to its popularity. It is in this setting that the establishment of a hypoglycemic society emerged. Varying forms of treatment have been advocated including special diets, frequent feedings, avoidance of caffeine, fructose-levulose diet, injection of calcium glycerylphosphates, adrenal extracts, and vitamin preparations. The elegant assessment of spontaneous hypoglycemia by Conn and Seltzer\textsuperscript{12} organized medical thought along the lines of considering hypoglycemia as being caused by discrete disease entities. The array of ill-defined medical reports and the increasing popularity of reactive hypoglycemia in the public's mind, has led the American Diabetes Association and the American Medical Association to issue a joint statement on the necessity of critical evaluation of hypoglycemic states and to discourage the usage of the biologically inactive adrenocortical extracts as therapy for these disorders.\textsuperscript{1,12}

Interestingly, patients with bona fide reactive hypoglycemic states may manifest an abnormal personality profile as determined by the Minnesota Multiphasic Personality Inventory (MMPI).\textsuperscript{63} These patients' personality profiles are characterized by hypersomatization and hypochondriacal complaints. This variation of the neurotic triad is frequently perplexing to physicians. Also, the nonspecific symptoms of reactive hypoglycemia can be seen in a host of paroxysmal disorders that present as adrenergic-mediated syndromes to include anxiety neurosis, seizure disorders, pheochromocytoma, carcinoid syndrome,
reactive hypoglycemia, hyperthyroidism, cardiac arrhythmias, dumping syndrome, and beta-adrenergic hyperresponsive state (De Costa's syndrome). Thus, the very vagueness of these disorders, the widely reported associated disease processes, and the abnormal psychodynamics of reactive hypoglycemic patients present a perplexing diagnostic enigma for the physician. A cautious approach to diagnosis is appearing in lay\textsuperscript{44,65} and medical publications.\textsuperscript{6-9}

**GLUCOSE HOMEOSTASIS**

The fuel requirements to support body cellular metabolism are met by substrate sources from the diet and endogenous intermediary metabolic processes. The former condition reflects the fed state of body metabolism, and the latter reflects the fasting state of body metabolism that occupies approximately 65\% of a 24-hr period. After ingestion of a meal, carbohydrates, proteins, and fats are enzymatically cleaved within the gut and transported into the portal circulation or lymphatic ducts. The subsequent configuring of the glucose curve depends upon gastrointestinal (GI) pyloric emptying, GI transit time, and rate of digestion and absorption of varying nutrients. The pancreatic beta cell responds to rising blood-glucose levels as an exquisitely intricate glucose-sensing device. The rising blood-glucose value is proportionally sensed with appropriate insulin discharge. This process works in a computer-like fashion inasmuch as intravenous stimuli will cause a rapid release of readily releasable insulin within 1 min following the infusion of tolbutamide, glucagon, glucose, or other stimuli.\textsuperscript{66-74} Likewise, in normal subjects, the configuration of the oral glucose-tolerance test shows simultaneous peaking of glucose and insulin.\textsuperscript{5} The frequent irregular spikes in a glucose curve due to irregular pyloric emptying or glucose absorption are generally accompanied by simultaneous insulin spikes.\textsuperscript{21,75} Furthermore, various gastrointestinal factors that include the gastrointestinal hormones\textsuperscript{72,76-90} (gastrin, pancreozymin-cholecystokinin, enteric glucagon-like substance, secretin, gastric inhibitory polypeptide, and insulin-releasing polypeptide) and the vagus nerve\textsuperscript{91} act in an entero-insular axis for facilitating insulin discharge to the glycemic stimulus. The insulin discharge allows for the peripheral clearance of glucose into glucose-sensitive tissues. The role of insulin on facilitating glucose absorption is controversial.\textsuperscript{92,93} The enteric hormones may also assist in the control of pyloric sphincter function.\textsuperscript{94}

Hepatic extraction of both glucose and insulin is considerable. In the fed state, the elevated blood glucose inhibits hepatic glucose output,\textsuperscript{95} and insulin activates hepatic glycolytic enzymes and decreases gluconeogenic enzymes.\textsuperscript{96-100} As plasma-glucose levels fall, hepatic glucose output increases. At some point in the summation of these two events, a biochemically low blood-glucose value may be reached.

**TRANSITIONAL LOW BLOOD-GLUCOSE STATES**

Numerous investigators have commented upon the occurrence of biochemically low blood sugars observed during a 5-hr glucose-tolerance test. Burns et al.\textsuperscript{101} using continuous plasma-glucose monitoring, showed that approximately 42\% of normal subjects demonstrated blood-glucose nadirs that were below 50 mg/100 ml. Cahill and Soeldner\textsuperscript{4} have described similar findings.
in 23% of a normal population. Likewise, in 25 patients that we have recently studied, approximately 48% had blood-glucose levels below 50 mg/100 ml and had no symptoms associated with the low blood-glucose value. Similarly in these patients, we found no evidence of a pathophysiological hypothalamic stress mechanism as manifest by a plasma-cortisol rise following the blood-glucose nadir. Blood-glucose values as low as 35 mg/100 ml have been reported by Cahill and Soeldner in asymptomatic patients, and we have seen a number of patients with blood-glucose values below 40 who have remained asymptomatic. This condition of the biochemically low blood-glucose values not associated with symptoms has added considerable confusion to the interpretation of previous studies. The misattributions of the physicians in overdiagnosing reactive hypoglycemia most likely occurs because of the frequency with which these low blood-glucose values normally occur in the postprandial state. Inasmuch as the vague symptoms that have been described in association with reactive hypoglycemia are known by a knowledgeable reading public, the physician often performs a 5-hr glucose-tolerance test and may misattribute the significance of the glucose nadir to this disease process.

**BONA FIDE REACTIVE HYPOGLYCEMIA**

During insulin-induced hypoglycemia, the blood sugar falls rapidly to low levels, and there is a timely catecholamine discharge with adrenergic-mediated symptoms and an appropriate rise in other counter-regulatory hormones to defend against and remove the hypoglycemic stress. These counter-regulatory hormones include glucagon, epinephrine, growth hormone, and cortisol. A falling blood sugar alone into nonstressful hypoglycemic levels will stimulate a rise in growth hormone. Plasma cortisol, during the late part of a glucose-tolerance test, will not rise into stress levels unless there has been a significant hypothalamic-pituitary-adrenal stress. Approximately 5 yr ago, we began a long-term study using strict criteria to assess reactive hypoglycemic disorders. Using a symptomatic, counterhormonal regulatory model to define hypoglycemia as a bona fide disorder, we have reported our findings in 70 patients with reactive hypoglycemia. Patients were only included in the study if they showed definite symptoms during the test period as observed and recorded by a physician or paramedic. In addition, the hypoglycemia symptoms must occur coincident with the glucose nadir, and there must be evidence of activation of a hypothalamic-pituitary-adrenal stress mechanism as manifest by a significant rise in plasma cortisol following the glucose nadir. Hypoglycemic patients were compared to normal control subjects and to weight-matched and disease-matched patient controls to determine if abnormalities in insulin secretion were present to account for the reactive hypoglycemia. Patients with alimentary hypoglycemia had symptoms and low blood-glucose values occurring early in the course of the glucose-tolerance test, with symptoms occurring between 2 and 3 hr after glucose administration. These patients showed excessive insulin discharge when compared to normal controls and to disease-matched controls who had undergone similar gastrointestinal surgical procedures. Similar observation has been made by others in alimentary-reactive hypoglycemia.

Diabetic patients (n = 16) showed hyperinsulinism and delayed insulin secre-
tion when compared to normal controls, but showed no significant change in amount or time of peak insulin secretion when compared to weight and disease-matched diabetic controls. Other investigators have also noted the delayed insulin secretion in diabetic-reactive hypoglycemia. The abnormality in diabetic-reactive hypoglycemia may represent an abnormal oscillation of the mechanism controlling blood glucose as related to the glucagon-insulin system, to variations in hepatic glucose uptake and output or to variations in peripheral insulin sensitivity.

Hormonal hypoglycemic patients (n = 5) showed altered carbohydrate tolerance with excessive and delayed insulin secretion. In four of the patients in whom hypothyroidism was present, thyroid-hormone replacement alone corrected the abnormality of hypoglycemia and glucose intolerance and returned the insulin secretory pattern to normal.

Forty-four patients with idiopathic-reactive hypoglycemia were compared to normal controls and to weight and disease-matched patient controls. Abnormality in insulin secretion could be found in the majority of these patients. This abnormality consisted of a delay between peak time of insulin secretion when compared to the absorptive glucose peak. There was a statistically significant delay when these values were compared to the control groups. In this group of idiopathic patients, 12 showed no delay in glucose-insulin peak times. Three of these patients had hyperinsulinism to account for the hypoglycemia, and in nine patients, there appeared to be no abnormality in insulin secretion to account for the hypoglycemia. This observation has led us to investigate hepatic gluconeogenic mechanisms that occur early in the fasting state. We have subsequently studied 14 randomly selected idiopathic patients and have identified five adult patients with a partial fructose 1-6 diphosphatase enzyme deficiency. Although this type of hypoglycemia occurs postprandially and masquerades as reactive hypoglycemia, in reality it heralds the onset of fasting state. An interesting patient in this category was a mother who had reactive hypoglycemia and a partial deficiency of this enzyme in biopsy tissue from the gut and liver. In subsequent studies of family members, her daughter was found to have a complete deficiency of the enzyme causing a ketotic form of hypoglycemia of childhood. Previous studies with folic acid have demonstrated glycolytic and gluconeogenic enzyme induction. On folic-acid therapy, elevations of the enzyme activity on repeat biopsy and amelioration of hypoglycemic symptoms occurred in these family members.

THERAPY

Once the diagnosis of bona fide reactive hypoglycemia has been established, then appropriate therapy can be initiated. The practical diagnosis of reactive hypoglycemia can be established in most clinics or laboratories on the basis of a 5-hr oral glucose-tolerance test with blood-glucose sampling at half-hour intervals and the patient keeping a symptomatic diary during the test. If the patient relates the timely onset of symptoms with a recorded blood-glucose nadir, and in particular, if the patient has a blood glucose drawn at an intermediate time when symptoms are maximal, the diagnosis of reactive hypoglycemia can be made. The measurements of plasma cortisol after the hypoglycemia nadir
has been a convenient research tool to utilize as objective laboratory evidence for hypoglycemic stress. Our studies measuring plasma cortisol have been performed with an indwelling venous catheter and saline infusion to minimize the stress of venapuncture. It is anticipated that if cortisol measurements are drawn without such precautions erroneous information might be obtained. Subsequently, we do not recommend the casual drawings of plasma cortisols unless these research sampling precautions are taken.

The backbone of successful management of reactive hypoglycemia is the diet. A 100-g carbohydrate diet, isocaloric (25 calories per kilogram body weight) with six equal feedings with avoidance of refined carbohydrates will be successful in the majority of cases. Some authors report a beneficial effect by the restriction of caffeine-containing beverages and alcohol. Alcohol utilizes important gluconeogenic NAD substrate for its metabolism, depresses the activity of important gluconeogenic enzymes, and limits alanine substrate availability. An occasional case may show worsening on the low-carbohydrate, high-protein diet. Since there is an aminogenic influence on insulin secretion, this could potentially aggravate the reactive hypoglycemia in some patients. However, the concurrent protein stimulation of glucagon release could offset the effects of insulin. Our studies on hepatic gluconeogenesis have shown that in patients with the fructose 1-6 diphosphatase deficiency there is characteristically a worsening of symptoms when stressed with a low-carbohydrate (ketogenic) diet. These patients, in order to maintain blood-glucose levels early in the fasting state, must call on adrenergic mechanisms to release glycogen stores. Similarly, an occasional patient will develop intolerant symptoms while on the low-carbohydrate, weight reduction Stillman or Atkins diet. These patients may well show similar hepatic enzyme defects. In this special low-carbohydrate intolerant subgroup, the stress of any ketotic diet is avoided and dietary carbohydrates are increased to 150 g or greater. We are presently conducting studies on the therapeutic effectiveness of folic acid (15 mg/day) in these patients with beneficial results.

In patients with diabetic reactive hypoglycemia, treating the diabetic state as clinically significant disease with weight reduction and oral agents such as DBI or sulfonylureas may ameliorate the hypoglycemia. In patients with alimentary hypoglycemia, frequent small feedings with the use of sedatives, tranquilizers, and anticholinergic agents may be beneficial. An unusual group of patients with alimentary hypoglycemia with characteristic biochemical features, namely, a lag glucose curve with hyperinsulinism, but who lacks a clinical history of previous gastrointestinal surgery or GI symptoms have been reported to have a beneficial response to DBI. Others have reported on the usefulness of DBI in obese idiopathic-reactive hypoglycemic patients. Our own experience with DBI in alimentary-reactive hypoglycemic patients who have undergone previous gastrointestinal surgery is that of a worsening of their disease process. One such typical patient (E. B.) studied before and after DBI treatment is presented in Fig. 1 and Table 2. This patient was studied on a selfselected 100-g carbohydrate breakfast. Some investigators have criticized studies in reactive hypoglycemic patients as being
biased by the nature of the refined oral glucose challenge that is a "non-physiologic stimulus." Subsequently, we have studied a number of patients on a selfselected breakfast and have demonstrated similar findings, as we have seen when patients are studied with the standard oral glucose-tolerance test. Comparison of acute DBI studies with control studies in patient E. B. shows increased insulin discharge following the meal (260% increase) and, after long-term DBI therapy of a 2-mo duration, the patient showed a characteristic aggravation of her symptoms, further increase in insulin levels (600% increase over basal study), and worsening of the hypoglycemic nadir. We have been impressed that the occasional patient with hyperinsulinism and alimentary reactive hypoglycemia may receive some beneficial effects with diphenylhydantoin (Dilantin®). Further studies are in progress to assess the usefulness of this
## Table 2. Special Studies in Patient AB

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agent in the other varieties of hypoglycemia, but preliminary results show that it is only useful when hyperinsulinism is present\(^{153}\). However, others\(^{154}\) report a beneficial response of diphenylhydantoin in treatment of patients with reactive hypoglycemia.

If a hormonal deficiency state can be identified in association with the hypoglycemia, then hormone replacement will alleviate the hypoglycemia\(^8,155\). In most patients with idiopathic-reactive hypoglycemia, diet alone suffices; but one should be alerted for the aggravation of symptoms on a low-carbohydrate diet. If this occurs, one should suspect fructose 1-6 diphosphatase enzyme deficiency, and the diet should be increased in carbohydrates. In the group of idiopathic-reactive hypoglycemic patients, inasmuch as a number of them show a delay in insulin secretion, the oral sulfonylureas may be useful in returning the insulin secretory pattern to normal. Others have reported on the usefulness of DBI\(^{151}\) and anticholinergic agents in these patients\(^{12,156}\). As there are certain associated neuropsychiatric features that occur in these reactive hypoglycemic patients, an explanation of the mechanism causal in the hypoglycemia and the use of sedatives or tranquilizing agents may be useful.

**FUTURE**

If future studies in patients with reactive hypoglycemia are carefully characterized to include only patients with clinically significant disease, and if the varieties of reactive hypoglycemia are analyzed according to alimentary, diabetic, hormonal, hepatic, and idiopathic groups comparing obese and nonobese patients separately, then further insight into these disorders can be expected. The frequent occurrence of a transitional low blood-glucose state should alert the physician to look critically for clinically significant disease. The liver plays an important role in intermediary metabolism that occupies the major metabolic event within a 24-hr period. Further studies on hepatic extraction of substrate and activation or deactivation of hepatic enzymes appear most fruitful in selective patients in whom abnormalities in insulin secretion cannot be demonstrated.

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