

# HYPOGLYCEMIA AND PSYCHOPATHOLOGY: A METHODOLOGICAL REVIEW

Stephen C. Messer\*  
Tracy L. Morris\*  
Alan M. Gross

*The University of Mississippi*

**ABSTRACT.** *In this article, the authors review the available medical and psychological literature relating hypoglycemia and psychopathology. Issues surrounding the proper assessment of hypoglycemia are discussed. The research suggests that many persons carrying the popular diagnosis of hypoglycemia do not meet stringent diagnostic criteria. However, these inaccurately diagnosed individuals often exhibit psychiatric symptomatology, particularly somatization and depression. Also, many persons exhibiting low blood glucose levels do not report symptoms. The evidence supports a relationship between low and/or rapidly declining blood glucose levels and transient cognitive, affective, and somatic symptoms. The limited evidence does not support a relationship between hypoglycemia and panic disorder, major depression, aggression, or somatizing personality features. Implications for the clinician are discussed.*

A problem encountered in the assessment of psychopathology is the accurate identification of co-existing medical conditions that may be contributing to the patient's current complaints. Persons with medical disorders often evidence associated psychopathology. High rates of psychiatric disturbance have been identified in patients with cancer (Derogatis et al., 1983), regional enteritis (Helzer, Chammas, Norland, Stillings & Alpers, 1984), endstage renal disease (Hong, Smith, & Valerius, 1982), and diabetes (Lustman, Griffith, Clouse, & Cryer, 1986). Conversely, it is not unusual for psychiatric patients to exhibit medical problems. For

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\*Share primary authorship.

Correspondence should be addressed to Alan Gross, Department of Psychology, University of Mississippi, University, MS 38677.

example, Koranyi (1979) found that 43% of 2090 psychiatric clinic clients were concurrently diagnosed with a physical illness such as diabetes mellitus, lupus erythematosus, and pancreatitis.

One medical disorder which may present with psychological symptoms is *hypoglycemia*. Hypoglycemia is a commonly encountered and readily treated metabolic disturbance occurring in both fasting and well-fed persons (Fishman, Hoffman, Klausner, & Thaler, 1985). Hypoglycemia refers to a physiological state characterized by a low blood glucose level. The range of potential accompanying symptoms is broad, from palpitations and anxiety to confusion and coma. However, at moderately low blood glucose levels, pronounced individual differences in symptom provocation are suggested. Some factors capable of precipitating hypoglycemic reactions include drug overdose, alcoholism, insulin-secreting tumors, hepatic insufficiency, and carbohydrate ingestion.

Hypoglycemia and its symptoms have been the topic of much popular press coverage. Reports often assert that hypoglycemic states are linked with disordered behavior, including panic attacks, depression, hyperactivity, aggression, and schizophrenia. Although low blood sugar has been linked to transient symptoms of nervousness, trembling, irritability, impaired concentration and the like (Hale, Margen, & Rabak, 1982; Hare, 1986; Holmes, Hayford, Gonzalez, & Weydert, 1983; Schweizer, Winokur, & Rickels, 1986; Taylor & Rachman, 1987), evidence is scant regarding these more extreme claims. Professionals debate even the definition of hypoglycemia.

The purpose of this paper is to review the literature on hypoglycemia and psychopathology. Due to the limited research available, this review is largely a descriptive, methodological, and exploratory discussion. Several facets of hypoglycemia and psychopathology will be addressed. First, hypoglycemia as a medical syndrome is described. Since diagnostic practices rank as an extremely important issue in hypoglycemia, the assessment of hypoglycemia will be dealt with at some length. Next, evidence for an association between hypoglycemia and psychological symptomatology and disorder is explored. Lastly, some suggestions for future research regarding hypoglycemic conditions and behavioral correlates are provided.

## HYPOGLYCEMIA

### *Normal Regulation of Glucose Levels*

Blood sugar levels are maintained and regulated through complex homeostatic processes. The liver functions as the organ maintaining appropriate plasma glucose levels (euglycemia) between meals. Elevated plasma levels of glucose, amino acids, and lipids return to baseline within 8 hours after a meal. The body requires active glucose production during extended fasting since the liver provides at most a 24-hour supply of glycogen. To manufacture glucose, the liver depends upon the availability of nutrients, such as amino acids, and a proper hormonal balance between insulin and glucagon. Therefore, hypoglycemia may occur (a) when adequate substrates are not ingested or presented to the liver, (b) with hepatic dysfunction, and (c) due to hormonal imbalance (Fishman et al., 1985).

### *Signs and Symptoms*

The signs and symptoms of hypoglycemia may be categorized into two basic

groups: (a) adrenergic, and (b) neuroglycopenic. Adrenergic symptoms characterize the initial symptoms of a hypoglycemic episode and include faintness, weakness, tremulousness, palpitation, hunger, diaphoresis, and nervousness (Berkow & Fletcher, 1987; Hale et al., 1982; Hare, 1986; Taylor & Rachman, 1988). Apparently, as blood sugar levels decrease, counterregulatory hormones (adrenaline, glucagon, cortisol, and growth hormone) are released and trigger the onset of these adrenergic symptoms (Fishman et al., 1985). These symptoms are typically transient responses to a low (or falling) blood glucose level and are alleviated by carbohydrate ingestion. As further elaborated in a later section, somatic symptoms of anxiety may suggest hypoglycemia, but most patients with such complaints are not hypoglycemic (Berkow & Fletcher, 1987).

When the hypoglycemic episode is prolonged and the brain is receiving less than the required 80 mg of glucose per minute, neuroglycopenic symptoms are exhibited (Fishman et al., 1985). These symptoms refer to a pattern of CNS symptoms including headache, confusion, impaired problem-solving and concentration, ataxia, visual disturbances, motor weakness, hallucinations, and bizarre behavior (Hale et al., 1981; Hare, 1986; Holmes et al., 1983). If the low blood glucose is allowed to persist, extensive and permanent neurological damage can result, even coma and death.

### **Types and Etiology**

Hypoglycemic syndromes are generally classified into two broad etiologically based categories (see Table 1): (a) *reactive hypoglycemia*, low blood glucose level in the non-fasting state provoked by the administration of exogenous factors such as drugs or carbohydrates; and (b) *spontaneous hypoglycemia*, low blood glucose level in the fasting state resulting from endogenous metabolic processes such as liver disease or pancreatic tumor.

Reactive hypoglycemia following a meal is apparently the most common type (no prevalence data) and is characterized by the onset of symptoms 2 to 4 hours after eating (Berkow & Fletcher, 1987). Reactive hypoglycemia has various etiologies. Hypoglycemia due to delayed insulin response is observed in some mild adult-onset diabetic patients and may be an early sign of diabetes mellitus. Reactive hypoglycemia may also be caused by the administration of excess insulin or by alcohol and other drugs. For example, ethanol (alcohol) suppresses hepatic glucose production. Alcohol accounts for more than one-third of all drug-induced episodes of hypoglycemia (Fishman et al., 1985).

One somewhat controversial form of reactive hypoglycemia, functional hypoglycemia, is triggered following meals, and the etiological mechanisms are unknown. Functional hypoglycemia is an apparently rare medical syndrome despite the large number of patients who carry the diagnosis (Fishman et al., 1985). That is, many persons diagnosed with functional hypoglycemia do not meet traditional, stringent laboratory criteria (more below). Functional hypoglycemia is sometimes referred to as essential, idiopathic, or postprandial hypoglycemia. In general, the diagnosis is assigned when typical hypoglycemic symptoms occur several hours after a meal and a simultaneous blood sugar determination is low. The pathogenesis is unclear, although hypotheses range from increased insulin sensitivity or abnormal release of counterregulatory hormones (Goroll, May, & Mulley, 1987), to a preclinical manifestation of diabetes mellitus or a discordance of insulin release (Fishman et al., 1985).

**TABLE 1. Classification of hypoglycemia**

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- I. Spontaneous (endogenous metabolic processes producing hypoglycemia in the fasting state)
    - A. Due to excess glucose utilization
      - 1. Excess insulin effect
        - a. Insulinoma
        - b. Deficiency of counterregulatory hormones
        - c. Erythroblastosis fetalis
        - d. Neonatal hypoglycemia (infants of diabetic mothers)
      - 2. Other mechanisms increasing glucose utilization:
        - a. Prolonged exercise
        - b. Renal glycosuria
        - c. Pregnancy
        - d. Tumor
    - B. Deficient glucose production
      - 1. Diffuse liver disease
      - 2. Hepatic enzyme defects
      - 3. Pancreatic neoplasms
      - 4. Ketotic hypoglycemia of childhood
  - II. Reactive (following administration of exogenous factors)
    - A. Due to carbohydrate ingestion
      - 1. Excess insulin action
        - a. Alimentary (postgastrectomy) hypoglycemia
        - b. Early diabetes mellitus
      - 2. Mechanism unknown
        - a. Functional hypoglycemia
    - B. Pharmacologic agents
      - 1. Provoking excessive glucose utilization, for example,
        - a. Insulin
        - b. Sulfonylurea
      - 2. Provoking deficient glucose production, for example,
        - a. Alcohol
        - b. Salicylates
        - c. Haloperidol
        - d. Chlorpromazine
    - C. Abnormal response to nutrients (inhibited hepatic glucose output)
      - 1. Fructose-1-phosphate aldolase deficiency
      - 2. Galactosemia
      - 3. Leucine hypersensitivity
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*Note.* Adapted from Berkow and Fletcher (1987).

Spontaneous hypoglycemia in the fasting state is less common than the reactive forms and is associated with a deficit in glucose production (e.g., hepatic disease), or rarely, excessive glucose utilization (e.g., vigorous exercise or pregnancy). Excessive glucose consumption due to insulin overproduction from a pancreatic islet cell tumor or extrapancreatic neoplasm may also cause spontaneous hypoglycemia. Most research has not focused on the spontaneous type of hypoglycemia, apparently due to its lower incidence.

Physiologically, the clinical manifestations of either reactive or spontaneous hypoglycemia represent the direct effect of a decreased glucose availability upon the cells of the nervous system. Severe or prolonged hypoglycemia, apparently uncommon, produces nerve cell changes resembling those of anoxia, as the neurons cannot utilize oxygen without glucose (Elliott, 1964).

### **Diagnosis**

A precise operational definition of hypoglycemia has been difficult to establish. The major problem has been establishing what blood glucose level justifies a "low" designation. Many laboratories consider 65 mg to 70 mg/dL of blood glucose as the lower limit of normal blood sugar (Fishman et al., 1985). However, healthy subjects often maintain much lower blood glucose levels without reporting any symptoms (Anderson & Lev-Ran, 1985; Hofeldt, 1975; Lev-Ran & Anderson, 1981). Nevertheless, the demonstration of relatively low plasma glucose (< 50 mg/dL), concurrent with the signs or symptoms mentioned above, which are relieved by carbohydrate ingestion, are the traditional criteria for diagnosing hypoglycemia (Berkow & Fletcher, 1987). Hypoglycemia occurring within 4 or so hours of a meal or following some other endogenous agent (e.g., drugs) suggests reactive hypoglycemia. Typically, adrenergic-like symptoms are associated more with the reactive than the spontaneous type. Symptoms initiated by a fast, either overnight or longer, suggest spontaneous hypoglycemia.

### **The GTT and Plasma Glucose**

The laboratory technique most widely used to measure blood glucose response to carbohydrate provocation, and therefore to allow identification of reactive hypoglycemia, is the five-hour oral Glucose Tolerance Test (GTT). Following an overnight fast, the GTT procedure entails the ingestion of 75-100 g of glucose dissolved in 300 mL of water. The fasting plasma glucose concentration in normal males typically stabilizes between 70 and 110 mg/dL (Permutt, 1979), rarely dropping below 55 mg/dL. However, more than half of normal women evidence fasting plasma glucose levels less than 50 mg/dL. Plasma glucose levels are determined every 30-60 minutes throughout the test. A normal GTT response curve is characterized by an approximate 50% increase in plasma glucose during the first hour as compared to the fasting level. The glucose level approaches the fasting level at the second hour, and drops to a level of about 65 mg/dL around the third or fourth hour, before returning to the near-fasting level. The plasma glucose level at its low-point is referred to as the plasma glucose *nadir*.

Notably, plasma glucose nadirs of less than 50 mg/dL, without accompanying symptomatology, have been identified in as much as 14% of some healthy samples (Lev-Ran & Anderson, 1981). Moreover, Taylor and Rachman (1988) reported mood and somatic symptoms half an hour after glucose nadir, not at the nadir. In an attempt to develop a more sensitive measure, Hadji-Georgopoulos, Schmidt, Margolis, and Kowarski (1980) proposed the use of a *hypoglycemia index*, defined as the decrease in plasma glucose during the 90 minutes preceding the nadir, divided by the value of the nadir. As Taylor and Rachman (1988) observed, the hypoglycemia index takes into consideration the level of the nadir and the degree and speed of the blood glucose decrement. Some work suggests that the diagnostic

validity of the GTT can be improved by the index alone (Taylor & Rachman, 1988) or the combined use of plasma glucose values plus the hypoglycemia index, especially for moderately low nadirs (Hadjigeorgopoulos et al., 1980). Taylor and Rachman (1988) found no support for the hypothesis that symptoms are greater at lower glucose nadirs. The strongest support was found for the hypothesis that symptoms are greater with higher hypoglycemic index scores. The development of the hypoglycemia index is an important advance and has ramifications for the definition and correlates of reactive hypoglycemia.

### **Summary: Assessment of Hypoglycemia**

As Fishman et al. (1985) stated in regard to hypoglycemia, "our understanding of this condition is obscured by the vagueness of its definition" (p. 257). Without an explicit, consistent, and empirical definition of hypoglycemia, little progress can be expected in understanding the causes and consequences of hypoglycemic conditions. Several problem areas can be identified.

First, the GTT has not been established as a reliable tool for the assessment of reactive hypoglycemia (McDonald, Fisher, & Burnham, 1965). Although values derived from the GTT are regarded as the "gold standard" in the diagnosis of hypoglycemia, many parameters affecting the test (e.g., circadian rhythms, diet, acute or chronic stress) have not been thoroughly investigated. Inadequate levels of carbohydrate in the diet prior to the GTT may produce a diabetic-type (hyperglycemic) response (Conn, 1940), while a carbohydrate excess may provoke a spuriously low glucose level (Permutt, Dalmez, & Stenson, 1976).

Second, individual differences in response to a glucose challenge have resulted in confusion regarding the use of an optimal cut-off score for low blood glucose. Using both a blood glucose nadir criterion (e.g.,  $\leq 50$  mg/dL) and a hypoglycemia index (e.g.,  $\geq 1.0$ ) at this early stage of research seem appropriate. The hypoglycemia index may capture the "process" more accurately than any cut score.

Lastly, the accurate assessment of psychological symptomatology experienced during hypoglycemic states requires attention. Basing diagnostic judgements on informally acquired self-reports is a questionable practice. The utilization of psychometrically sound symptom measures (e.g., *The Profile of Mood States (POMS)*; McNair, Lorr, & Droppleman, 1981) would assist in a more standardized assessment of a clinically significant hypoglycemic syndrome.

### **Treatment of Hypoglycemia**

The treatment of hypoglycemia requires attending directly to the underlying etiology and degree of impairment (see Table 1 for various etiologies). For example, diabetic patients are a group vulnerable to hypoglycemic reactions. Hypoglycemic episodes in the insulin-dependent diabetic patient are usually the result of skipping a meal or failing to titrate the insulin dose downward on a day of vigorous exercise (Fishman et al., 1985). The patient experiencing a mild acute episode will respond quickly to carbohydrate consumption and can be advised to moderate their exercise and consume an adequate diet. A severe hypoglycemic reaction, however, may result in emergency medical care, such as a rapid infusion of 50% dextrose solution. Therefore, the severity of the hypoglycemic reaction will influence whether emergency medical treatment is necessary. Also among diabetic

patients, the administration of sulfonylureas (oral hypoglycemic agents) and beta-blocking medications (e.g., propranolol) for hypertension can cause either spontaneous or reactive hypoglycemic states and therefore must be closely monitored.

Insulin-secreting pancreatic tumors, though very rare, are a common cause of spontaneous hypoglycemia. Therapy typically involves surgical excision of the tumor (Fishman et al., 1985). Hypoglycemia following gastric surgery (e.g., gastrectomy) may be treated with anticholinergic agents to delay gastric emptying and a diet consisting of small multiple feedings. Patients with certain severe illnesses (e.g., liver disease, uremia, tumors) are also prone to hypoglycemic episodes and the prompt identification of the underlying pathology guides treatment.

Dietary management is the treatment of choice for the apparently rare patient with functional hypoglycemia (Reiser & Reiser, 1985). The functional hypoglycemic evidences mild to moderate discomfort and impairment with no identifiable pathophysiology, yet experiences symptoms 2 to 4 hours after eating a meal concurrent with a low blood glucose nadir. The suggested diet includes four to six high protein, low carbohydrate meals per day with restriction of caffeine, nicotine, and alcohol (Goroll et al., 1987). However, no controlled studies were identified testing the efficacy of dietary modification, although some individuals may report an improvement of symptoms. As discussed further below, many persons are probably diagnosed incorrectly with functional hypoglycemia and their symptoms are instead of a psychological origin. For these persons, dietary interventions will not succeed in influencing their discomfort and psychological intervention is warranted.

## HYPOGLYCEMIA AND PSYCHOPATHOLOGY

Numerous claims have been made concerning the relationship between hypoglycemia and psychopathological symptoms or disorder. Persons diagnosed as hypoglycemic have been described as, "highly nervous . . . emotionally labile" (Berger, 1975), "intense, driven and overly conscientious" (Conn & Pek, 1970), and, "tense, neurotic individuals" (Meloni, 1975). An intriguing hypothesis, especially for those seeking biological explanations of behavior, is that hypoglycemia contributes to the etiology or maintenance of psychopathology. Despite such speculation and anecdotal evidence, few controlled investigations have explored the relationship between hypoglycemia and psychopathology. However, the superficial similarity of hypoglycemic symptoms to complaints often accompanying some behavioral problems and continued reports of a relationship justifies a close examination of the available evidence.

### *Anxiety Disorder*

Symptoms of acute anxiety often occur during hypoglycemic episodes (Clancy & Noyes, 1976; Hare, 1986; Taylor & Rachman, 1988), leading to the suggestion that hypoglycemia is a causal or contributing factor in anxiety disorders (Dietch, 1981; Mackenzie & Popkin, 1983). Several agents have demonstrated an ability to trigger panic attacks in some panic disorder patients (e.g., lactate, caffeine, yohimbine, isoproterenol). The discrete and seemingly unprovoked nature of

panic attacks has likely increased the appeal and fueled the search for various physiological precipitating factors, including hypoglycemia. The possibility that a hypoglycemic reaction could function as a nonspecific stressor, such as the agents noted above, and provoke panic attacks has stimulated several studies.

One approach to the investigation of a hypoglycemic-panic disorder relationship would be to induce panic attacks and assess for concurrent hypoglycemic reactions. Following this logic, Gorman, Martinez, Liebowitz, Fyer, and Klein (1984) induced panic attacks with sodium lactate infusions in 10 patients meeting the DSM-III criteria for panic disorder or agoraphobia with panic. Blood glucose levels were determined at the start of a placebo infusion (sodium chloride), the start of the lactate infusion, and the point of panic with the lactate. All 10 patients had panic attacks during the sodium lactate infusion. However, no subject developed a hypoglycemic blood glucose level during the panic attack. It was concluded that the mechanism of lactate-induced panic was not hypoglycemia.

Consistent with this finding, Schweizer et al. (1986) reported no provocation of panic resulting from insulin-induced hypoglycemia via an insulin tolerance test (ITT). Insulin infusion during the ITT commonly results in low blood glucose levels in healthy subjects, allows an assessment of glucose utilization, and is not a diagnostic measure of reactive hypoglycemia. All 10 panic disorder patients developed low blood glucose levels but no panic anxiety. The subjects reported symptoms of adrenergic hyperactivity yet easily differentiated these symptoms from spontaneous panic. The authors admitted that the experimental context could have inhibited the development of perceived panic and noted that the adrenergic symptoms resulting from the drop in blood sugar could conceivably act as conditioned triggers for panic attacks in the natural environment. Nevertheless, the results are consistent with Gorman et al. (1984) suggesting that hypoglycemia does not provoke panic attacks.

Another approach that has been utilized to study correlates of hypoglycemia is to manipulate blood glucose levels with the GTT and measure corresponding symptom reports among patients diagnosed with an anxiety disorder. Uhde, Vittone, and Post (1984) induced hypoglycemia via the GTT in nine women with Research Diagnostic Criteria (RDC) defined panic and agoraphobic disorders. Six patients completed an anxiety analogue scale at baseline and 3 hours later. All patients completed the Zung Anxiety Scale at baseline only. Eight (89%) of the subjects developed symptomatic hypoglycemia, defined as exhibiting a plasma glucose nadir below 60 mg/dL or a hypoglycemia index above 1.0 with concurrent symptoms. These patients developed both somatic symptoms (e.g., palpitations) and increased levels of generalized anxiety.

In the six patients who completed analogue self-ratings, generalized anxiety increased within 4 hours following glucose ingestion. Patients with the highest measures of baseline anxiety using the Zung scale tended to demonstrate the lowest glucose nadirs ( $r = .65$ ). No patient, however, developed a panic attack as DSM-III defined. Although all patients described their anxiety as qualitatively different from their naturally occurring panic attacks, low blood glucose levels were associated with increased generalized anxiety. These results taken together may suggest a transactional process, with high levels of baseline anxiety predisposing to a hypoglycemic response, which in turn results in increased generalized anxiety.

Moreover, the rate of GTT-induced hypoglycemia in the sample was high

(89%). Though no control group was utilized, a previous investigation reported that only 17% of 285 asymptomatic, healthy women developed comparable blood glucose nadirs (Jung et al., 1971). The authors speculated that their findings may indicate disturbed insulin functioning in panic disorder patients. To support this proposition, they noted that insulin-induced hypoglycemia apparently activates neuropeptides implicated in the neurobiology of anxiety. However, no insulin or neuropeptide measures were obtained to support their hypotheses. Of course, the utilization of a medical comparison group would have clarified the results by allowing assessment of demand characteristics or "placebo" effects concerning symptomatology.

In summary, these few studies suggest that a reactive hypoglycemic episode is neither a necessary nor sufficient condition for the immediate provocation of panic anxiety in those diagnosed as panic disorder or agoraphobia with panic. Although several agents (lactate, caffeine, yohimbine) have been demonstrated to provoke panic attacks among some panic disorder patients, the hypoglycemia findings argue against the notion that a nonspecific stressor, such as hypoglycemia, triggers panic attacks. However, in the one study utilizing the GTT (Uhde et al., 1984), a higher prevalence of symptomatic hypoglycemia was observed among the panic disorder patients than might be expected in a "normal" sample, and low blood sugar levels were associated with increased generalized anxiety. The reliability of this finding and any possible mechanism underlying the relationship between hypoglycemia and panic disorder deserve further study.

Unfortunately, no studies were identified that tested the relationship between hypoglycemia and other anxiety disorders. Since limited evidence suggests a relationship between baseline anxiety level, a hypoglycemic response to the GTT, and resultant generalized anxiety level, future research might investigate these relations in a generalized anxiety disorder sample. To speculate, chronically anxious persons may develop a tendency, possibly due to chronic stress and diet, to respond to carbohydrate loads in a hypoglycemic fashion with concomitant adrenergic symptoms. These hypoglycemic symptoms could in turn exacerbate their chronic anxiety and initiate a vicious cycle of subjective distress. Such speculative hypotheses await further investigation.

### ***Affective Disorder***

An association between major depression and altered glucose utilization is well documented (Heninger, Mueller, & Davis, 1975; Mueller, Heninger, & McDonald, 1968; Wilkinson, 1981). For example, some diabetic patients evidence elevated blood sugar levels during a depressive episode (Finestone & Weinwe, 1984). A blunted hypoglycemic response and diminished glucose utilization has been demonstrated during an ITT or GTT (Mueller et al., 1968). This finding has been interpreted as indicating a functional state of insulin resistance in depression.

For example, in a recent well-controlled investigation (Winokur, Maislin, Phillips, & Amsterdam, 1988), 28 patients meeting DSM-III criteria for major depression and 21 healthy volunteers completed GTTs. Measurements obtained included serum glucose, insulin, and glucagon. Depressed patients demonstrated small but significantly higher basal glucose levels, greater cumulative glucose responses, and larger cumulative insulin responses after the GTT. Put simply, following the GTT, serum glucose concentrations remained elevated longer in the depressed sample

and the mean cumulative glucose response of the depressed patients was twice that of the controls. Interestingly, the depressed group's glucose response curve had not yet attained the nadir after 5 hours.

The authors concluded that their findings, consistent with those from several other investigations (Brunswick, Fazer, Koslow, & Casper, 1988; Wright, Jacisin, Radin, & Bell, 1978), suggest impaired glucose utilization and the presence of a functional state of insulin resistance during major depression similar to that found with non-insulin-dependent (Type II) diabetes. As a matter of fact, insulin induced hypoglycemia via the ITT may be more sensitive to hypothalamic-pituitary-adrenal (HPA) abnormalities and a better discriminator of major depression than the dexamethasone suppression test (DST) (Meller, Kathol, Jaeckle, Grambsch, & Lopez, 1988). Therefore, the available evidence suggests a state of hyperglycemia, rather than hypoglycemia, in depressed samples. These findings suggest the presence of a generalized biological disturbance in some patients with major depression. Future studies should attempt to further elucidate influential factors (e.g., diet, carbohydrate craving) and mechanisms underlying these relationships and assess their validity among bipolar and dysthymic patient samples.

### ***Somatization and "Neurotic" Personality Traits***

Several authors have hypothesized a relationship between hypoglycemia and "neurotic" personality characteristics (Harris, 1936; Rennie & Howard, 1942). However, empirical evidence is again limited and does not strongly support these claims.

For example, Anthony, Dippe, Hofeldt, Davis, and Forsham (1973) identified 37 previously diagnosed hypoglycemic patients. Sixteen of the patients had been diagnosed as hypoglycemic based on GTTs with a blood glucose nadir below 40 mg/dL. Ten were admitted to the study because of isolated low blood glucose values plus symptoms suggestive of hypoglycemia. Eleven were admitted due to symptoms alone. Subjects were administered a GTT and re-classified according to blood glucose nadir, plasma cortisol (11-OHCS) response to the nadir, "well-defined symptoms in daily life," and symptoms at time of low blood glucose. Varying etiological factors characterized the hypoglycemic groups (diabetic (29%), alimentary (22%), other (6%) or functional (42%)). The Minnesota Multiphasic Personality Inventory (MMPI) was completed by the hypoglycemic subjects and by a comparison group of 21 patients with various endocrine disorders but without hypoglycemic symptoms. Notably, the comparison group was not administered GTTs.

Hypoglycemic subjects scored more than two standard deviations above the MMPI standardization sample means on scales 1 and 3 (*T* score of 74 and 77, respectively). No other scale means were less than a *T* score of 70. Scales 1, 3, 7, and 8 were significantly higher in the hypoglycemic as compared to the mixed endocrine group. Anthony et al. (1973) concluded that hypoglycemic patients manifest MMPI scores compatible with significant "hypochondriacal" and "hysterical" personality features. Of course, elevated scores on these scales may merely reflect the endorsement of the large number of items indicative of "physical" symptomatology consistent with hypoglycemia and not necessarily suggesting personality problems. The authors note that the issues of confounding and potential relationships between personality disorder and hypoglycemia are matters warranting further inquiry.

A comparable study reported no association between reactive hypoglycemia and personality deviance as measured by the MMPI (Ford, Bray, & Swerdloff, 1976). GTTs differentiated 30 volunteers suspected of hypoglycemia into three major groups: reactive hypoglycemia (blood glucose nadirs below 65 mg/dL,  $n = 18$ ), normal ( $n = 7$ ), and diabetic ( $n = 5$ ). Sixty percent of the MMPI protocols were interpreted as disordered (clinical scale  $T$  score above 70). The average profile suggested the "conversion V" syndrome characterized by denial, repression, and somatization. Forty-eight percent of the hypoglycemic patients demonstrated this profile compared with 22% of the nonhypoglycemic group (a nonsignificant difference). The hypoglycemic and nonhypoglycemic groups were not significantly different on any of the MMPI scale scores.

Two factors make a comparison of these findings with the Anthony et al. (1973) results difficult. First, the criteria for the diagnosis of hypoglycemia in the Ford et al. (1976) investigation appears relatively nonstringent ( $< 65$  mg/dL is fairly liberal, especially without hypoglycemia indexes), allowing the possibility that the Ford sample represented a basically nonsevere hypoglycemic group. Second, the extremely small comparison sample in the Ford study resulted in statistical power so low as to deem the results limited.

These two studies weakly support an association between reactive hypoglycemia and elevated MMPI scores indicative of numerous physical complaints. The validity of the conversion or somatizing profiles evidenced by these samples is questionable due to the overlap of MMPI items regarding physical symptoms and hypoglycemic symptomatology. To put it simply, the MMPI elevations may be tapping hypoglycemic and not personality pathology. Future studies might partial out or control for those redundant items that may be confounding any interpretation of the findings. Analyses of MMPI subscale scores as well as the use of additional measures of symptoms, personality, and social skills may allow for a more refined test of a hypoglycemia-personality relationship.

Several investigations have examined the clinical psychiatric characteristics of individuals suspected of hypoglycemia. Anderson and Lev-Ran (1985) evaluated 135 patients previously diagnosed elsewhere as hypoglycemic. A low blood sugar level was defined as a GTT plasma glucose nadir of less than 39 mg/dL. Symptoms were diagnosed on the basis of reported hunger, perspiration, palpitation, piloerection, and circumoral numbness coinciding with GTT nadirs (even if above 39 mg/dL), absent at other times, and quickly relieved by carbohydrates. Hypoglycemic indexes were not utilized due to previous findings by the authors (Lev-Ran & Anderson, 1981) indicating poor differentiation of symptomatic and asymptomatic groups using the 0.8 criterion. In addition to the GTTs, postprandial plasma glucose levels were determined with unspecified methods. Lastly, the patients were evaluated with clinical psychiatric interviews prior to their GTTs.

Of the 135 patients, only four (3%) were found to be "true" reactive hypoglycemics, defined by (a) low blood glucose levels, (b) concurrent with symptoms, plus (c) symptoms reported as typically experienced postprandially. Eleven patients (8%) were symptomatic following glucose load, but not following meals. Five subjects (4%) demonstrated low blood glucose but not symptoms during the GTT.

Of the 115 remaining patients who did not meet the investigators criteria for hypoglycemia, 94 (82%) met the criteria for a psychiatric disorder. Clinically significant depression was diagnosed in 43 (37%) of the subjects. Thirty percent of this depressed group had conditions requiring treatment that the investigators believed could have directly contributed to symptomatology, including factitious

thyrotoxicosis, migrainous and tension headaches, coccidioidomycosis, and functional bowel syndrome. Fifty-one of the patients (44%) were characterized as somatizers. In this subgroup, GTT nadirs ranged from 41 to 113 mg/dL, with only 5 patients exhibiting plasma glucose levels below the 10th percentile.

Anderson and Lev-Ran (1985) concluded by noting the high prevalence (82%) of psychiatric conditions, mainly depression and somatization, among those suspected of, but not evidencing, strictly defined hypoglycemia. However, the study utilized a conservative blood glucose criterion and did not use the hypoglycemia index or standardized measures of symptomatology.

Similarly, 192 patients undergoing endocrine evaluations for suspected hypoglycemia with GTTs evidenced no apparent relationships between hypoglycemic symptoms and plasma glucose nadirs or a slope measure of rate of glucose fall (Johnson, Dorr, Swenson, & Service, 1980). However, the presentation of the results were difficult to interpret and statistical reporting was limited. MMPIs were completed by half of the sample and mean *T* scores on scales 1 and 3 were approximately 70. Unfortunately, the MMPI correlations or comparisons with blood glucose nadirs or slopes were not reported.

To summarize, the scarce data regarding the personality correlates of reactive hypoglycemia are methodologically weak and confusing. A relationship has been demonstrated in a single study (Anthony et al., 1973) between a diagnosis of reactive hypoglycemia and a conversion MMPI profile but the confounding of hypoglycemic symptoms and MMPI physical disorder items prevents interpretation. On the other hand, one study (Anderson & Lev-Ran, 1985) suggests an association between somatization, depression, other physical conditions and those complaining of but *not* testing positive for reactive hypoglycemia. Only further well-defined research will clarify any potential personality correlates of those evidencing "true" and "false" hypoglycemia.

### ***Antisocial and Aggressive Behavior***

The search for biological correlates of antisocial personality disorder and aggressive behavior has focused on such factors as resistance to punishment, low anxiety, neurological deficits, and behavioral genetics. More recently, several studies have appeared exploring the relationship between hypoglycemia and aggressive behavior and its disorders.

For example, Virkkunen (1984) examined hypoglycemia in 59 arsonists hospitalized for psychiatric examination, 27 offenders diagnosed as intermittent explosive disorder (IED), and 29 male psychiatric nurses. All offenders had been incarcerated for approximately 6 months and were thus alcohol-free during measurements. Participants received GTTs and the arsonist group was further categorized as hypoglycemic ( $n = 27$ ) or nonhypoglycemic ( $n = 32$ ). Results indicated that significantly more (46%) of the arsonists had a hypoglycemic value (defined as  $< 3.0$  mmol/L = 54 mg/dL) as compared with 17% of the nurses. Hypoglycemia among the arsonists was associated with alcohol-related behavioral problems. For example, 100% of the hypoglycemic arsonists reported a temporary lack of memory during the fire compared with 33% of the nonhypoglycemic arsonists; 100% of the hypoglycemic arsonists described themselves as sometimes aggressive when drinking as compared to 25% of the nonhypoglycemic arsonists.

Virkkunen concluded that a reactive hypoglycemic tendency appears to be

associated with fire-setting behavior. However, apparently no symptom reports were obtained from the subjects during the GTT, making a diagnosis of hypoglycemia in its complete sense unwarranted. Most importantly however, is the potential confound between alcohol abuse, antisocial behavior, and hypoglycemia. That is, the data seem more accurately to suggest relationships among alcohol abuse, hypoglycemia, and arson mediated through antisocial behavior patterns.

In a similar investigation, Virkkunen (1986) studied 33 male, habitually violent and impulsive offenders and 13 controls by means of the GTT and insulin measurements. Both in intermittent explosive disorder and in violent antisocial personality, there was a tendency for low blood sugar nadirs. Virkkunen has obtained comparable results using similar samples in other studies (Virkkunen, 1982; Virkkunen & Huttunen, 1982), often utilizing the same "normal" control group, not utilizing the hypoglycemia index, and not controlling for the potentially critical confounding variable of alcohol consumption and associated disturbed dietary habits. To even attempt a meaningful correlational analysis of blood sugar levels and violence, future research must control for the effects of alcohol abuse. For example, a violent but non-alcoholic comparison group would be required to tease out any association between hypoglycemia and aggressive/violent behavior.

In an investigation of blood glucose values and aggression in college students, Benton, Kumari, and Brain (1982) administered GTTs to 20 male undergraduates without a history of aggressive behavior or abnormal glucose metabolism. Dietary preparation information was not included. Dependent measures were responses to several self-report measures of aggression. Significant correlations were found between blood glucose values and scores on a hostility inventory as well as a frustration measure, suggesting increased aggression with lower blood glucose.

The authors concluded that hypoglycemia is associated with a tendency to act, and to approve of acting, in an aggressive manner. Questions can be raised concerning the validity of the dependent measures as indicators of "aggression." Possibly, the subjects responding with lower blood glucose values were experiencing mild hypoglycemic symptoms of irritability and hunger and these could have contributed to higher "aggression" scores. That is, the findings may provide evidence for the expected correlation between hypoglycemia and hypoglycemic symptoms, not evidence for a hypoglycemia and aggressive attitude/behavior relationship.

In summary, the few available hypoglycemia-aggression studies suffer from major methodological limitations, including confounded variables and the inadequate definition of hypoglycemia, precluding any conclusions regarding a hypoglycemia and aggression or impulsivity link. Future research appears warranted, nevertheless, in that hypoglycemic symptomatology might conceivably act as an exacerbating factor in the elicitation of irritable behavior over the short term.

### *Some Methodological Issues and Future Directions*

A first methodological issue in the investigation of hypoglycemia and psychopathology is the proper operationalization of the independent variable of interest: low blood sugar or hypoglycemia. The major limiting factor in the available evidence is the questionable reliability and validity of the GTT and its associated diagnostic criteria. Studies have not consistently reported on conditions or charac-

teristics that may influence a GTT response such as dietary preparation for the test administration (Ford et al., 1976; Virkkunen & Huttunen, 1982) and gender differences in GTT patterns. Various blood glucose diagnostic criteria have been used, ranging from 39–64 mg/dL (Anthony et al., 1973; Ford et al., 1976). Similarly, the hypoglycemia index has not been used in several investigations (Ford et al., 1976; Virkkunen, 1984, 1986). The absence of a rate of fall (or increase?) measure is crucial since the absolute drop in blood glucose level is potentially less important than an individualized measure for change in sugar level, such as that provided by the hypoglycemia index. Moreover, a moderate number of subjects may not demonstrate “typical” GTT response curves (e.g., flat or M-shaped curves, late blood glucose peaks, etc.; Taylor & Rachman, 1988), and these subjects should be analyzed separately.

Diagnosing hypoglycemia has been inconsistent due to the various criteria utilized in many studies. The diagnosis of hypoglycemia requires that three criteria be met: a reliably documented low blood glucose level (e.g., < 50 mg/dL) and/or high rate of fall measure (e.g., > 1.0) such as the hypoglycemia index, distressing symptom presentation functionally related to glucose level, and symptom relief following carbohydrate ingestion (Goroll et al., 1987). However, symptom reports are typically collected in an unstandardized fashion (Anthony et al., 1973; Ford et al., 1976; Gorman et al., 1984). Baseline symptom measures are usually not reported. Functional relationships between glucose levels and symptom reports are not demonstrated. Carbohydrate-induced symptom relief is not specifically reported to have occurred. Symptom presentation may not be restricted to measures concurrent with the nadir, but may also appear in the index period or even at postnadir readings (Taylor & Rachman, 1988).

Several questions must be addressed to further elucidate possible hypoglycemia-psychopathology relationships. First, does low blood sugar or a rapid drop in blood sugar produce psychological symptoms, and if so, what level or degree of blood sugar change elicits such symptoms and what is their duration? Second, what are the mechanisms (e.g., cortisol, adrenergic, ketone responses, certain foods) that mediate a potential blood sugar-symptom effect? Third, is hypoglycemia concurrently related with any form of psychological disorder? Fourth, assuming a relationship is found, how is hypoglycemia related to the disorder (i.e., does hypoglycemia precipitate symptoms, exacerbate symptoms, or contribute to symptom maintenance or duration)? Fifth, does hypoglycemia predispose persons to psychological disorder or vice versa? And sixth, what are the potential mechanisms by which hypoglycemia could mediate psychological disorder (e.g., conditioning, sensitization, cognitive labeling of arousal)?

To address the above and similar questions, several lines of inquiry seem necessary. Of course, true experimental designs to demonstrate the psychological effects of fluctuating and rebounding blood sugar levels are essential. A randomized double-blind experiment with glucose tolerance tests and placebo would be highly useful. These experimental designs are essential for the demonstration of an unequivocal blood sugar-symptom relationship. Such an experimental design with “normal” subjects would clarify the magnitude of effect of blood sugar changes within the normal range on behavior. Experiments using previously diagnosed hypoglycemic subjects would demonstrate the importance of degree of blood sugar change and resultant degree of symptomatology. Lastly, experimental investigations using homogeneous samples of subjects with stringently defined psychological disorders would address the influence of hypoglycemia on short-

term symptom provocation, exacerbation, or maintenance.

Survey, cross-sectional, or correlational studies of hypoglycemia are much more limited. Designs such as that of Anthony et al. (1973) and Ford et al. (1976), in which hypoglycemics are identified and comparisons with nonhypoglycemics are performed on criterion measures such as the MMPI reveal only contemporaneous correlations. This does not mean that such studies are useless. With appropriate subject selection, adequate comparison groups, and valid measures, correlational studies can provide suggestive information. Comparison groups with a major medical disorder may not be appropriate due to the high prevalence of psychiatric disorder often evidenced (Lustman et al., 1986). Both hypoglycemic and control subjects should be screened for alcohol abuse, heavy carbohydrate intake, ingestion of hypoglycemic agents, or early-stage diabetes. A strong correlational study must establish a "dose-response" relationship (i.e., an association between symptom scores and blood glucose levels or index values). Moreover, significant correlations among pre-GTT, GTT-induced, and post-GTT symptoms (e.g., anxiety, depression) may suggest a reciprocal or transactional relationship among psychiatric symptomatology and hypoglycemia (e.g., Uhde et al., 1984). This potential reciprocal relationship in which psychiatric condition influences reactive hypoglycemia, and vice versa, deserves a closer analysis. Lastly, assuming a hypoglycemia-disorder relationship could be found, any causal relation could be tested by treating the hypoglycemic condition and observing any concomitant diminution of disorder.

Investigations of a predisposing role for hypoglycemia and later psychopathology would require prospective studies. Of course, a formal, expensive, longitudinal study is premature without a reasonable supply of previously obtained supporting evidence. A compromise design might involve some form of follow-up study. For example, subjects recently diagnosed as hypoglycemic could be assessed for psychopathology and followed-up at later dates to ascertain changes in emotional adjustment.

One last design, the single-case experimental design, could be effective in demonstrating a functional relationship over the short- or long-term, between blood glucose level and psychological symptoms or disorder. In single-case studies, manipulating blood sugar through diet, intravenous administration of glucose, insulin, or placebo, and assessing symptom provocation or exacerbation might be informative, especially in the elucidation of individual differences. Here again, normal, hypoglycemic, or psychologically disturbed individuals are potential subjects in such research.

Finally, behavioral characteristics and environmental conditions that might predispose to hypoglycemia such as physical illness, dietary habits (e.g., carbohydrate binging and craving), smoking and drug use, acute and chronic stress (and associated neuroendocrine changes), trait anxiety, self-focused attention, and interoceptive "conditionability" warrant inclusion in future studies of hypoglycemia and psychopathology. Potential relationships discovered could be conceptualized as a transactional process whereby personal characteristics and environmental conditions are reciprocally involved in the evolution of behavior. For example, persons evidencing trait anxiety and experiencing chronic stress may eat nonnutritiously and crave carbohydrates, setting the occasion for hypoglycemic responding with associated symptoms of trembling and the like, which are experienced intensely due to the anxious person's heightened activation, slow habituation, and

responsivity to somatic changes, ultimately providing opportunities for the further conditioning of anxiety responses.

### CONCLUSIONS: HYPOGLYCEMIA AND PSYCHOPATHOLOGY

A definitive answer concerning the relationship between hypoglycemia and psychopathology is elusive due to the lack of well-controlled studies in the area. Our review has found evidence to support a relationship between low blood sugar level or rapid drop in blood sugar and transient cognitive, affective, and somatic symptoms. Little support for hypoglycemia as a covariate of more persistent and pervasive psychopathology was discovered. To oversimplify somewhat, hypoglycemia is related to transient psychological *symptoms*, but the relation with *disorder* has not been reliably demonstrated. However, at this early stage of research into the links between blood glucose levels and behavioral conditions, methodological problems abound.

Moreover, hypoglycemia test results are often negative among those previously diagnosed or complaining of hypoglycemia. Many persons (as high as 82%; Anderson & Lev-Ran, 1985) complaining of reactive hypoglycemia, but testing negatively or inconsistently under more stringent conditions, exhibit psychiatric symptomatology, especially somatization and depression.

How might the clinician formulate and manage the client reporting hypoglycemic-like symptomatology? Patients presenting with symptoms suggestive of hypoglycemia (or any physical disorder) should be referred for a medical evaluation, including an endocrinological work-up, if necessary. Generally, neuroglycopenic (e.g., headache and confusion) or adrenergic (e.g., sweating and palpitations) symptoms occurring consistently before breakfast, after exertion, or 2 to 4 hours after eating, may be suggestive of hypoglycemia. The patient diagnosed with hypoglycemia will require medical and/or dietary treatment depending on etiology. The psychologist can offer assistance in managing stress and anxiety associated with a medical intervention and changes in lifestyle resulting from treatment. For those patients requiring dietary modification, the clinician can provide support and guidance in self-management techniques.

Patients with a thorough, nonremarkable medical examination and a history of ineffective but well-implemented dietary modifications, are likely not exhibiting "true" hypoglycemia. Rather, their symptoms may be a function of somatization, depression, anxiety, or personality disorder. A meticulous assessment should provide direction for an appropriate psychological and/or psychiatric intervention. The clinician should nevertheless remain alert over the course of therapy to changes in the client's physical condition and make the necessary medical referral.

In sum, there is no evidence to suggest that hypoglycemics are at risk of behavioral disorder. More importantly, many persons carrying the diagnosis of hypoglycemia probably do not exhibit the "true" syndrome. They may be seeking a physiological explanation for their difficulties, and likely exhibit difficulty with psychological interpretations of their presenting complaints. For these individuals "hypoglycemia" is a useful explanation, since a wide variety of complaints may be attributed to the "disorder."

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