COGNITIVE FUNCTION, AFFECTIVE STATE, AND SOMATIC SYMPTOMS RELATED TO BLOOD SUGAR LEVEL

By

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Abstract

In an attempt to find out whether decreased blood sugar level is associated with impaired cognitive function, adverse emotional changes, or somatic symptoms, 36 subjects who believed or suspected that they had hypoglycemia were given 5-hour glucose tolerance tests (GTTs). After each of the nine blood samples taken during the GTT, the subject's mood, performance on the Serial Sevens Test (SST), and somatic symptom reports were recorded. The subjects reported significantly more negative affect after glucose nadir (the lowest level of blood sugar reached) than before nadir, and endorsed more somatic symptoms after nadir than before nadir. SST performance deteriorated at glucose nadir. All of these effects were more pronounced for subjects with high hypoglycemic index scores than for subjects with low index scores. The index is calculated from the speed and magnitude of the decrease in blood sugar, and the absolute value of the nadir. The impairment in SST performance was greater for subjects who showed rapid decreases in blood sugar than for subjects who showed slow decreases. Dividing subjects by high and low nadirs, large and small magnitudes of decrease, and by large and small decreases below fasting level, did not reveal any differences in symptomatology. It is concluded that changes in mood, reports of somatic symptoms, and inferior performance on a mental arithmetic task are associated with lowered blood sugar levels, especially in subjects with high hypoglycemic index scores.

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Introduction

There have been many claims that changes in cognitive functions, affective states, and somatic symptoms are related to changes in blood sugar level (e.g., Brennan & Mulligan, 1975; Budd, 1981). Most of these claims arise in the literature on hypoglycemia, a condition in which blood sugar, or glucose, drops below normal fasting levels. Some of the psychological symptoms that have been attributed to this decrease in blood sugar level include anxiety and depression (e.g., Brennan & Mulligan, 1975; Budd, 1981), and aggression (e.g., Bolton, 1976; Virkkunen, 1982). Other authors, however, state that hypoglycemia is simply a socially acceptable diagnosis for psychological problems (e.g., Mundy, 1976; Yager & Young, 1974). They claim that the body, in all but rare cases, can adapt to low glucose levels (Cahill & Soeldner, 1974). Neither these proponents of "pseudohypoglycemia", nor the above-mentioned supporters of hypoglycemia as an important cause of psychological problems, offer much empirical support for their claims.

Recently, there has been some better designed research investigating the relationship between blood sugar level and cognitive function, affective state, and bodily symptoms (e.g., Hale, Margen, & Rabak, 1982; Pennebaker et al., 1981; Uhde, Vittone, & Post, 1984). The area, however, has many methodological problems. The present study was conducted in an attempt to overcome some of these problems in methodology and determine some of the psychological effects, if any, of changes in glucose level.

Hypoglycemia

Hypoglycemia literally means low blood sugar. Some authors use the term to refer to the physiological symptom of low blood sugar (e.g., Cahill & Soeldner, 1975), whereas others consider hypoglycemia to be a syndrome,

which includes various psychological and somatic symptoms concurrent with lowered blood sugar (e.g., Budd, 1981). It is to this question of the existence of hypoglycemia as a syndrome that the present thesis is addressed.

The opposite of hypoglycemia, hyperglycemia or high blood sugar, occurs in diabetes when the beta cells of the pancreas do not secrete enough insulin (Silvian, 1977). If, in trying to regulate their glucose levels, diabetics take too much exogenous insulin, they may have an insulin reaction or hypoglycemic episode. The symptoms of such a reaction may include sweating, trembling, increased pulse rate, dizziness, headache, hunger, blurred vision, or fainting (Silvian, 1977). In 1924, Seale Harris noticed that non-diabetics experienced these symptoms at blood sugar levels below 70 mg/dl, without administration of insulin. He labeled this phenomenon hyperinsulinism or hypoglycemia.

Two types of hypoglycemia must be distinguished -- fasting and reactive (Young & Karam, 1983). Fasting hypoglycemia is present when the glucose level is below normal eight or more hours after eating; this is said to be rare and indicative of a serious underlying disorder (e.g., pancreatic tumor). As will be discussed later, there is little agreement as to what constitutes a "normal" blood sugar level, although most would agree that less than 30 mg/dl is abnormal (e.g., Young & Karam, 1983).

Most of the literature deals with reactive hypoglycemia (also referred to as postprandial hypoglycemia), a condition in which glucose rises after eating but then decreases below fasting level 2 to 5 hours later. Blood sugar then returns to fasting level within 8 hours. As with fasting hypoglycemia, there is no conclusive evidence as to how low the blood sugar

level must fall to be considered hypoglycemic. There is some speculation that the level required may be relative to the fasting level of a person. For instance, Cahill and Soeldner (1975) report that patients with inoperable insulin-producing tumors may be asymptomatic with blood sugar levels of 20-30 mg/dl, whereas diabetics with chronic hyperglycemia may show symptoms with blood glucose concentrations greater than 100 mg/dl. No documentation is provided for these claims. With respect to the increase in blood sugar, a sample above 200 mg/dl warrants investigation into the possibility of diabetes (Young & Karam, 1983). Another unclarified issue is whether the responses depend upon what is eaten. The popular literature claims hypoglycemia is caused by overconsumption of refined carbohydrates (e.g., Brennan & Mulligan, 1974; Budd, 1981); however, there is no evidence to support this. Cahill and Soeldner (1975) have pointed out the limitations of testing the responses of patients solely to glucose as is currently done. It is possible that the blood sugar response would vary with different types and amounts of food.

The reactive type of hypoglycemia may be caused by a delayed secretion of insulin in some cases; for instance, one study showed that 32 of 44 hypoglycemic patients exhibited delayed peak insulin responses after ingesting glucose, as compared with 28 normal controls (Hofeldt et al., 1974). Insulin was measured with an immunoreactive technique every 30 minutes during the glucose tolerance test. The insulin response was considered delayed if the time between glucose and insulin peak values was significantly greater than that for normal controls. The mean delay was 8 minutes for normals and 34 minutes for reactive hypoglycemics (peak insulin response occurs after peak glucose level).

During the period of low blood sugar after eating, the symptoms of reactive hypoglycemia are said to occur. The symptoms are divided into two kinds, adrenergic and neuroglycopenic, on the basis of their postulated causes -- increased epinephrine secretion and deficient glucose for nerve cell metabolism, respectively (e.g., Hale et al., 1982; Hofeldt, 1975). When blood sugar rises, insulin is secreted so the body cells may use or store glucose, and so hepatic production of glucose is stopped (Cryer & Gerich, 1985). Hormones counterregulatory to insulin -- glucagon, epinephrine, growth hormone, and cortisol -- are then released to reverse this process and restore homeostasis (Corenblum & Volpe, 1983). Adrenergic symptoms result from this increased epinephrine and norepinephrine, and include sweating, palpitations, tremulousness, weakness, nervousness, irritability, flushing, and hunger (e.g., Berger, 1975; Hofeldt, Dippe, & Forsham, 1972). Neuroglycopenic symptoms result when the central nervous system receives insufficient glucose; these include headache, mental confusion, difficulty concentrating, lethargy, memory loss, blurred vision, dizziness, and bizarre behavior (e.g., Berger, 1975; Hale et al., 1982).

There is disagreement as to which type of symptoms occur in reactive hypoglycemia. Most authors assume that epinephrine-mediated symptoms occur, but while some argue that the effects of hypoglycemia are also caused by neuroglycopenia (e.g., Hale et al., 1982; Permutt, 1976), others believe such symptoms occur only in fasting hypoglycemia (e.g., Hofeldt, 1975; Jefferson & Marshall, 1981). This debate, however, seems premature in light of the fact that there is little empirical evidence for the occurrence of any type of symptom during states of low blood sugar. The more fine-grained analysis of the basis of symptoms in hypoglycemia might prove

more profitable if done after glucose-symptom relationships have been documented. Separating these two types of symptoms may be quite difficult and require sensitive assessment techniques. For instance, either anxiety due to epinephrine secretion, or difficulty concentrating due to neuroglycopenia, could account for poor performance on a timed test.

The test most widely used to diagnose hypoglycemia is the glucose tolerance test (GTT). It is a 5- to 6-hour test in which patients fast for 10 to 12 hours overnight, drink a 50- to 100-gram glucose solution, and have their blood sugar level measured at regular intervals (Budd, 1981; Young & Karam, 1983). Usually, blood sugar is measured on arrival to determine the fasting level, a half hour after ingestion of glucose, and at half-hour or hourly intervals thereafter. The measurement of glucose is often done with laboratory instruments such as the Autoanalyzer or hexokinase method; however, studies have shown the Dextrostix Reflectance meter system's results to correlate .96 to .99 with these others (Ikeda et al., 1978; Jarrett, Keen, & Hardwick, 1970; Stewart, 1976). The Dextrostix system measures glucose in whole blood (i.e., from a finger-prick). A drop of blood is placed on a reagent strip for 60 seconds, and the strip is then washed, blotted and placed in a glucometer -- a machine which provides a digital reading of blood sugar level. With proper calibration, this system is simpler, faster, and more convenient than laboratory methods (Stewart, 1976), and may be accurately used even by juvenile patients (Ikeda et al., 1978). It may be somewhat less accurate than the laboratory methods; for instance, Jarrett et al. (1970) found 11 of 48 dual Reflectance meter readings to differ by more than 10 mg/dl, while only 1 in 13 lab results varied by a similar amount.

Patients often are required to prepare for the GTT by following a

high carbohydrate diet for 3 days prior to the test. This is to prevent a spuriously low blood sugar level being found. Permutt, Delmez, and Stenson (1976) compared the glucose responses of 4 female and 6 male normal subjects to high carbohydrate preparation (300 gm carbohydrate per day), and to carbohydrate restriction (less than 10 gm carbohydrate per day) during the 3 days prior to GTT. They found the carbohydrate-restricted diet led to significantly higher blood sugar levels at 1, 1 1/2, and 2 hours after glucose challenge, and significantly lower blood sugar values at nadir, than the high carbohydrate diet did. The mean glucose nadir was 48 mg/dl for the carbohydrate-restricted and 64 mg/dl for the high carbohydrate diet. It was reported that 6 subjects, when tested after carbohydrate restriction, had nadirs less than 50 mg/dl, and five of these exhibited mild symptoms of hypoglycemia (perspiration, tremulousness, palpitations, anxiety, hunger, and a subjective feeling of mental clouding). How these symptoms were measured is not reported. The authors postulate that patients, especially those who think they are hypoglycemic, may treat themselves with carbohydrate-restricted diets, and subsequently have their misdiagnoses reinforced by the GTT.

Not all researchers agree with high carbohydrate preparation for the GTT. Fabrykant (1955b) argues that patients should maintain their regular diets before the GTT -- the diets with which they are getting hypoglycemic symptoms. He suggests that by increasing the amount of carbohydrate, one may erroneously conclude that some patients have normal glucose responses when, in fact, they may exhibit symptoms and hypoglycemic blood sugar levels when following their usual diets. Both the above researchers (Fabrykant, 1955b; Permutt et al., 1976) do agree, however, that

carbohydrate restriction increases the probability of provoking low blood sugar levels and symptoms in normal subjects. Carbohydrate restriction could, therefore, provide a useful method of documenting the relationship between blood sugar levels and symptoms.

There are some potential problems with the GTT and measurement of blood sugar levels, but at present it is the best test available (Permutt, 1976). Some authors suggest that testing with only one type of glucose (e.g., corn sugar) may not be sufficient, as different people may react to different foods (Philpott, 1978; Worden & Rosellini, 1978). Also, the sampling intervals may be too infrequent. Continuous sampling of blood sugar has shown that there are actually two to four subsequent maxima of lesser magnitude after the first (Burns, Bregnant, Van Peenan, & Hood 1965). With hourly sampling, this could cause confusion in trying to correlate symptoms with blood sugar level. Another possible area of confusion is in the reporting of results. Authors should report whether glucose is measured in whole blood, or plasma or serum. Plasma or serum samples contain 12 to 15% more glucose than whole blood, as there is a higher percentage of water in plasma/serum (Jefferson & Marshall, 1981; Owen, Shuman, Boden, & Hoeldtke, 1983). A blood sugar level of 100 mg/dl in whole blood is equivalent to 115 mg/dl in a plasma sample. Finally, one study found the GTT to have low reproducibility in diagnosing diabetes (McDonald, Fisher, & Burnham, 1965). Three hundred and thirty-four nondiabetic male prisoners volunteered to have six 3-hour GTTs over the period of 1 year. The results showed high within-subject variability. For instance, at 3 hours after glucose, subjects' blood sugar levels varied, on average, within plus or minus 21 mg/dl of their mean over the six tests. This study was concerned with

the diagnosis of diabetes and found that of 29 men with one or more positive diabetic test results, none was diagnosed in all six tests. It could be, but was not tested in this study, that the GTT similarly would not show reproducibility of low blood sugar results in subjects.

There is some disagreement in the literature as to what constitutes a diagnosis of hypoglycemia. The simplest criterion is blood sugar level dropping below a predetermined cut-off point. What this cut-off point should be varies from author to author with values ranging from less than 40 mg/dl (Hofeldt et al., 1972; Young & Karam, 1983) through to less than 70 mg/dl (Budd, 1981). No empirical support is offered for the diagnostic value of these figures. In addition to the blood sugar decrease, most authors believe symptoms should be documented at the time of glucose nadir in order for a diagnosis to be made (e.g., Hale et al., 1982; Hofeldt, 1975; Jefferson & Marshall, 1981; Permutt, 1976). This is important if hypoglycemia is to be established as a syndrome (i.e., psychological and somatic symptoms concurrent with lowered blood sugar), rather than simply as a physiological symptom (i.e., low blood sugar levels).

One set of criteria for diagnosing hypoglycemia has been postulated; it requires a history of hypoglycemic symptoms, a blood sugar value below 40 mg/dl concurrent with such symptoms, and immediate recovery from symptoms if the patient is given glucose (Jefferson & Marshall, 1981; Young & Karam, 1983). Again, no evidence is provided for the efficacy of this diagnostic system. Others have suggested the absolute glucose level is unimportant and that the drop from fasting blood sugar is diagnostic. For example, Bolton (1976) used a decrease of 10-25 mg/dl and Salzer (1966) a drop of 20 mg/dl below fasting blood sugar to diagnose hypoglycemia. These decreases could

occur at any time over the course of a 6-hour GTT; a patient whose fasting blood sugar level was 110 mg/dl and whose blood sugar dropped to 85 mg/dl during the GTT, would be diagnosable even though blood sugar had not gone below a standard cut-off point. No data are provided as to the validity of such drops from fasting blood sugar level in diagnosing hypoglycemia. Similarly, the speed of the fall in glucose level has been suggested as a possible cause of hypoglycemic symptoms (Budd, 1981). For instance, a rapid drop of blood sugar to 80 mg/dl may cause symptoms, whereas a gradual decrease to 60 mg/dl might not. There has been little empirical research on this suggestion. The one study (Johnson, Dorr, Swenson, & Service, 1980) to assess speed of drop found symptoms to be related to lower speeds. Documenting low blood sugar levels during spontaneously arising symptoms would be useful in validating a diagnosis of hypoglycemia (Corenblum & Volpe, 1983; Young & Karam, 1983). This would suggest it was not simply the artificial nature of the GTT that provokes symptoms.

Finally, an index has been proposed as diagnostic of hypoglycemia, especially in borderline cases between 50 and 65 mg/dl (Hadji-Georgopoulos, Schmidt, Margolis, & Kowarski, 1980). This is the fall in blood glucose during a 90-minute period before reaching nadir, divided by glucose nadir; for example, a blood sugar level of 60 mg/dl at nadir and one of 120 mg/dl 90 minutes before nadir would yield a hypoglycemic index of 1.0. This criterion takes into account the rate and amount of decrease in blood sugar level. These researchers monitored blood sugar continuously in 28 subjects referred for symptoms compatible with postprandial hypoglycemia. A physician in constant attendance observed and noted symptoms reported by patients during the GTT; symptoms included tremor, perspiration, pallor, tachycardia,

hot flushes, hunger, weakness, and nervousness. No assessment was made of the accuracy or reliability of the physician's observations or the patients' self-reports, nor was it reported whether the physician was blind to glucose levels. Subjects were divided into asymptomatic (n = 16) and symptomatic (n = 12) groups. "Symptomatic" was defined as the occurrence of at least three of the above symptoms, "objectively verified" by the physician at nadir. Unfortunately, details are not given as to how symptoms were measured, and pretests do not appear to have been administered. A cut-off of 65 mg/dl resulted in a 46% false positive rate in diagnosing symptomatic hypoglycemia as defined above, and one of 50 mg/dl yielded 56% false negatives. This indicated that cut-off alone is an insufficient criterion for diagnosing hypoglycemia. Index value greater than 1.0 (0.8 with intermittent rather than continuous sampling), however, was always associated with symptoms, while a value of less than 1.0 was not associated with symptoms. This criterion separated the two groups with no overlap, suggesting rate of fall may be important in producing symptoms of hypoglycemia. Absolute level of blood sugar is also important, in that no subject had symptoms with glucose greater than 65 mg/dl and all had symptoms with blood sugar less than 50 mg/dl. Cross-validation is needed to determine the generalizability of these results.

Hadji-Georgopoulos et al. (1980) also found that the symptomatic subjects had significantly higher plasma insulin levels than the asymptomatic subjects 90 minutes before glucose nadir (described by the authors as "late hyperinsulinism"). Also, there was a correlation of .62 between these insulin levels and the hypoglycemic index scores. These results suggest that the hypoglycemic index reflects the effects on blood sugar level of late

hyperinsulinism.

Lev-Ran and Anderson (1981) observed many patients with elevated hypoglycemic indexes (Hadji-Georgopoulos et al., 1980) who were asymptomatic during GTT. In 102 patients suspected of but not having hypoglycemia, index values ranged between 0.14 and 3.73, with 46 subjects having values greater than 0.8. The range for symptomatic patients was 0.83 to 3.67. Unfortunately, these authors do not report any information on how subjects recorded symptoms. They conclude that the index is of no value in diagnosis of hypoglycemia.

Much confusion exists as to the best diagnostic criteria for hypoglycemia. The research on the hypoglycemic index (Hadji-Georgopoulos et al., 1980) is more productive than that on the other criteria in that the criterion is used in an attempt to discriminate subjects who experience symptoms from those who do not. The problem lies in the unsystematic, nonquantitative way symptoms are documented. Whether the diagnosis of hypoglycemia should be based on absolute cut-off point, size of decrease, speed of drop, or elevated hypoglycemic index, can only be determined by research relating such criteria to objective assessment of symptoms. In the present study, symptoms were measured empirically with no a priori decisions as to which subjects should experience symptoms. After symptoms were documented, the various criteria were tested to determine if they could discriminate between symptomatic and asymptomatic subjects.

The treatment usually suggested for hypoglycemia is a change of diet. Specifically, a reduction in carbohydrates, an increase in protein and fat, and more frequent meals are often recommended (Brennan & Mulligan, 1975; Budd, 1981; Young & Karam, 1983). The rationale behind these

recommendations is that hyperglycemia will be prevented and, therefore, hyperinsulinism -- and resulting hypoglycemia -- will not occur. A high protein diet is advised on the basis that protein yields 50% of its weight as glucose but releases it at a slower rate and over a more prolonged period than does carbohydrate (Conn & Newburgh, 1936). Conn and Newburgh (1936) gave isoglucogenic quantities of protein and carbohydrate to 15 diabetic and 3 normal subjects. The average maximum increase in blood glucose over fasting level was 160 mg/dl after carbohydrate load and 37 mg/dl after protein. The 3 normal subjects had changes of 2, -1, and 16 mg/dl after protein as compared with increases of 42, 97, and 82 mg/dl after carbohydrate. The protein meals, therefore, yielded relatively flat glucose tolerance curves, with little or no hyperglycemia. Conn (1936) then went on to state that a high protein diet will eliminate the symptoms of hypoglycemia. He reported on 3 hypoglycemic patients who evinced similar flat curves in response to protein as the normal and diabetic subjects. One of these patients was instructed to follow a high protein diet and 3 months later reported being symptom-free. Whether or not this patient complied with the prescribed diet was not assessed. Thorn, Quigby, and Clinton (1943) gave isocaloric meals high in protein, carbohydrate, or fat to a normal subject. The high protein meal yielded a flat glucose tolerance curve, "an improved sense of well-being", and no symptoms of hypoglycemia. The high carbohydrate meal was followed by hypoglycemic symptoms (hunger and weakness) in 2 hours, along with a decrease in blood sugar to 69 mg/dl. The high fat meal led to a drop in blood sugar to 71 mg/dl after 5 hours accompanied by milder symptoms of hypoglycemia (hunger). How symptoms were monitored was not reported. To summarize, the claim that protein

prevents the increase in blood sugar caused by ingestion of carbohydrates is based on the responses of 4 subjects. The hypothesis that a diet high in protein will cause a reduction in hypoglycemic symptoms remains virtually untested, being based on only 2 case reports. Controlled research needs to be conducted to determine the efficacy of such high protein diets. The recommendations of high fat diets and more frequent meals in the treatment of hypoglycemia similarly need to be the subject of controlled studies, as there is no evidence of their effectiveness.

The popular literature has advocated many detailed treatments for hypoglycemia (Brennan & Mulligan, 1975; Budd, 1981); for instance, the elimination of caffeine, alcohol, and tobacco is often recommended, as is the use of megavitamins and acupuncture. There is no reliable evidence whatsoever in the literature for the benefits of any of these treatments.

Finally, some authors suggest psychotherapy or sedation will decrease symptoms of hypoglycemia (Fabrykant, 1955b; Rennie & Howard, 1942; Young & Karam, 1983). For instance, Rennie and Howard (1942) state that personality disturbances or neuroses can cause hypoglycemia and that resolving the personality disturbance eliminates the low blood sugar symptomatology. They report on 7 patients hospitalized for symptoms of tension or depression apparently related to ingestion of food; for example, patients reported cravings for food or relief of nervous symptoms after eating. How these 7 cases were selected is not reported. In none of the cases is it shown that psychiatric treatment eliminated symptoms of hypoglycemia. In only one case were symptoms even exhibited during a GTT; this patient reported (by letter) that his condition was improving after being counseled by a psychiatrist, but no repeat GTT was obtained. One case is

reported of a woman who was neither examined nor treated psychiatrically, but whose letters were scrutinized and indicated that her nervous symptoms were psychogenic. The majority of the cases exhibited flat GTT curves (i.e., no appreciable increase or decrease in blood sugar level) during nervous or depressed states, and more normal curves when not distressed. No symptoms were reported during the GTTs. This could generate the hypothesis that psychological distress is correlated with flattened GTT curves, but it does not show that psychotherapy eliminates hypoglycemic symptoms. Also, there are no quantifiable measures of neurotic or hypoglycemic symptoms, and whether patients changed their diets was not assessed.

Fabrykant (1955b) states that sedation or therapy should be given, in addition to dietary treatment, in cases with co-existing neurotic conditions. He suggests that the personality disorder and autonomic imbalance play a part in producing hypoglycemic symptoms by increasing the sensitivity to low blood sugar levels. He provides no data, however, of the effectiveness of such treatments. It is possible that stress could increase a person's susceptibility to hypoglycemia. Cox (1978), on the basis of reviewed experiments, postulates that moderate stress causes decreases in blood sugar level and severe stress causes increases in glucose level. He reports conducting an experiment in which research trainees were assessed during a communications exercise. The exercise was perceived as severely stressful and was accompanied by increases in blood sugar levels. This is in contrast to a group of experienced researchers who did the exercises, but saw them as a relaxing break from their regular work. They exhibited no significant changes in blood sugar levels. Whether stress does predispose one to hypoglycemic reactions, and whether treatment aimed at decreasing stress

would be beneficial in controlling hypoglycemia, remains to be empirically tested.

Popular Literature

The popular literature on low blood sugar contains claims that hypoglycemia can cause many symptoms and disorders (Brennan & Mulligan, 1975; Budd, 1981). For example, one book listed 37 symptoms as a representative selection of the most common symptoms of hypoglycemia (Budd, 1981). Included in this list were: fatigue, irritability, overweight, alcoholism, premenstrual tension, nightmares, heart disease, epilepsy, hyperactivity, anxiety, forgetfulness, migraine, lack of sex drive, depression, panic feelings, excessive smoking, phobias, and suicidal tendencies. Another author wrote of hypoglycemia's role in some cases of insomnia, antisocial behavior, schizophrenia, emotional outbursts, murder, drug addiction, family violence, and juvenile delinquency -- as well as many of those symptoms listed above (Brennan & Mulligan, 1975). The explanation given for the effects of hypoglycemia is that not enough glucose is received by the central nervous system (Brennan & Mulligan, 1975); the possible adrenergic cause of symptoms is not emphasized. Writers such as these claim that hypoglycemia is a disease of epidemic proportions. Budd (1981) reports that 92% of 210 "selected" patients tested showed reactive hypoglycemia; in another part of his book he estimates 10 to 50% of all people are hypoglycemic. No details are provided as to how he arrived at these figures.

The most commonly reported symptoms of low blood sugar are very similar to those of anxiety or depression -- fatigue, tremor, headache, dizziness, nervousness, weakness, sweating, palpitations, irritability, confusion,

blurred vision, hunger, and lightheadedness (e.g., Hale et al., 1982; Hofeldt, et al., 1972; Silvian 1977). This fact, along with the extreme claims made with respect to hypoglycemia in the popular literature, may account for the widespread lay belief in hypoglycemia as a cause of psychological symptoms. Boskind-White and White (1983) report that many of their bulimic patients think they have hypoglycemia. There is also some acceptance of this belief in hypoglycemia as a cause of psychological symptoms in the professional literature. For instance, Wolpe (1982) lists hypoglycemia as a common organic cause of anxiety, and Barlow, O'Brien, and Last (1984) state that the physical symptoms of hypoglycemia may mimic anxiety in agoraphobics. Similarly, Knapczyk (1979) claims that hypoglycemia may cause behavior disorders in children. No data are provided to support any of these statements. As will be shown, there is little empirical evidence on the relationship between blood sugar levels and affective state, cognitive function, or bodily symptoms.

The most researched "effect" of hypoglycemia is aggression. Proponents of a relationship between low blood sugar and aggression state that a change in diet could be an alternative to imprisonment (Fishbein, 1982) and that hypoglycemia could provide a case for temporary insanity in assault, disorderly conduct, homicide, child/wife abuse, embezzlement, larceny, vandalism, arson, slander, or sexual offenses (Lyle, 1979). As reviewed previously, there is no evidence that dietary changes can eliminate the symptoms of hypoglycemia. Whether the preceding crimes could occur as the result of the physiological changes of hypoglycemia cannot be evaluated, as no evidence is provided. One case is reported in the literature of a woman who ran over and killed a person and then not only denied any memory for

the incident, but also lied about what had happened to explain the damage to her car (Bovill, 1973). She was given a GTT which revealed a blood sugar level of 30 mg/dl at 4 hours, during which the patient reported being irritable, unable to concentrate, and drowsy. In another test designed to re-create the dietary events before the accident, she had a glucose level of 42 mg/dl and felt ill and sleepy. With blood sugar less than 50 mg/dl, she could not recite nursery rhymes. Whether she had any memory for the above tests was not assessed, nor is it reported how symptoms were measured or if the patient was blind to her blood sugar level. This woman also had a history of alcohol and amphetamine use and showed partial amnesia for any discussions of the accident. She received a nominal fine for the accident on a defense of having been in a hypoglycemic episode. Bovill (1973) and Lyle (1979) argue that amnesia and decerebration result from hypoglycemia and, therefore, make anyone capable of committing a crime. It remains to be documented, however, whether impairment or losses of memory occur at low blood sugar levels or whether, in such states, people do things (e.g., commit crimes) they otherwise would not. The possibility of malingering would have to be controlled for in such cases.

Another hypothesis is that hypoglycemia interacts with temporal lobe disturbances or brain dysrhythmia (Yaryura-Tobias & Neziroglu, 1975) to cause aggressive or violent behavior. Yaryura-Tobias and Neziroglu (1975) report on 45 subjects with the "behavioral-gluco-dysrhythmic triad," which consists of aggressive behavior, brain dysrhythmia, and glucose intolerance. Subjects treated with diet for the hypoglycemia and diphenylhydantoin or pyridoxine for the dysrhythmia (experimental group) showed greater reductions in aggression scores than did those treated with tranquilizers or either of the

above alone. Subjects were selected by GTT, EEG results and aggression score on a scale designed by the experimenters. Forty-two of the subjects also received other diagnoses, as specified by the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II; American Psychiatric Association, 1968), including schizophrenia (n = 23) and nonpsychotic organic brain syndrome (n = 7). There are serious methodological flaws in this study which preclude the drawing of definitive conclusions. The dependent variable consisted of a 0-4 scale developed and scored by the experimenters. Whether ratings were performed blindly is not reported, and operational definitions were not given for the scale's descriptors (e.g., "assaultive", "outbursts of rage"). The length of treatments is described as 1-4 months but the length for each group is not reported, so treatment groups could have been confounded with length of treatment. Subjects appear not to have been assigned randomly to groups, as there was a very uneven distribution of subjects in each group (experimental group 20, tranquilizers 7, diet alone 7, medication alone 11). Treatment was not administered in a double-blind manner. Finally, whether the treatment had the intended effect of eliminating glucose imbalance and brain dysrhythmia was not assessed, nor was compliance with treatment. Because of the possible preselection of subjects and methodological flaws, any possible contribution of hypoglycemia to aggression cannot be determined on the basis of this study, and yet it is referred to as evidence of a relationship between hypoglycemia and aggression (e.g., Benton, Kumari, & Brain, 1982; Virkkunen, 1984).

Bolton (1976) obtained GTT results on 39 male Qolla Indians who are said to have an "aggressive culture." There was a correlation of .57

between blood sugar levels during GTT and hostility in fantasy scores (Sentence Completion Test, rated blindly). The relationship was that those subjects with moderate hypoglycemia showed more aggression than those with normal blood sugar (decrease 10 mg/dl or less) or severe hypoglycemia (decrease 25 mg/dl or more). No information is given as to why such a curvilinear relationship should exist, and it would seem to indicate that hypoglycemia is not responsible for the aggressive responses. Length of response was confounded with group in that those with moderate hypoglycemia used significantly longer sentences than those in the other two groups. Aggression was not measured during the GTT; therefore, no relation between changes in blood sugar and aggression can be inferred.

Virkkunen and Huttunen (1982) reported on 32 violent offenders with antisocial personality (Research Diagnostic Criteria diagnosis; Spitzer, Endicott, & Robins, 1978), 20 normal control subjects and 24 violent control subjects, all of whom were given GTTs. The antisocial offenders showed greater increase in blood sugar after glucose ingestion, greater decreases in blood sugar at nadir, and took longer to return to fasting level than the control subjects. Virkkunen (1982) also showed that 31 habitually violent offenders with intermittent explosive disorder (DSM-III criteria; American Psychiatric Association, 1980) had similar glucose tolerance curves to 37 antisocial offenders, but that they returned to baseline quicker than the 20 normal control subjects. The greater hyperglycemic response to glucose was not replicated in this study for either violent group; however, the violent offenders did again show lower blood sugar levels at nadir than the normal controls. This is a correlational result and one cannot be sure of the direction of the effect; it could be that being violent changes a subject's

glucose tolerance. Or a third variable, such as alcohol consumption, could cause the hypoglycemic responses in the violent offenders. This is plausible in that almost all the crimes were committed under the influence of alcohol. Also, lower glucose nadirs were related to offenders' loss of memory about violent acts and being rated by their relatives as being aggressive while using alcohol. The other finding was that the antisocial offenders took longer to return to fasting blood sugar levels, while the intermittent explosive disorder offenders returned to baseline more rapidly than did normal subjects. There is no literature on the significance of the time to return to fasting blood sugar level from nadir, and the authors do not attempt to explain this result. Recently, Virkkunen (1984) has reported that reactive hypoglycemia is connected to fire-setting behavior in arsonists. Forty-six percent of the 59 arsonists were hypoglycemic as compared with 17% of 29 normal subjects. Hypoglycemic arsonists were more impulsive, confused, and likely to have used alcohol before the crimes than were nonhypoglycemic arsonists. Again, these relationships are correlational, and alcohol use provides a plausible alternative explanation of the results. All of the subjects in these studies have been male. The studies (Virkkunen, 1982, 1984; Virkkunen & Huttunen, 1982) suggest that hypoglycemia contributes to violent and criminal behavior. It does not seem plausible that low blood sugar is a significant causal factor in violent behavior, which makes it imperative that anyone making such a claim use better methodology (e.g., longitudinal studies).

There has been one study done with normal subjects in which a correlation was found between mild hypoglycemia and questionnaire measures of aggression in 24 male university students (Benton, et al., 1982). Subjects

were given a GTT, during which they "filled the time" by completing the Buss-Durkee Hostility Inventory, Rosenzweig Picture Frustration Study, Multiple Affective Adjective Checklist, and Lagerspetz and Westman Questionnaire. These measures were used to assess general tendencies toward aggression, not transient changes induced by the GTT. The decrease in blood sugar below fasting was correlated with nine measures derived from the above tests. Significant correlations were found between blood sugar drop and the Buss-Durkee (r = -.41) and one section of the Rosenzweig which measures the ability to "gloss over frustration" (r = .57). The relation was such that higher aggression was related to greater drops in blood sugar. The authors conclude that support was obtained for aggression being associated with decreases in blood sugar; however, this conclusion is premature. The majority of their measures showed nonsignificant correlations with blood sugar. No attempt was made to explain this. Also the significant correlations were significant at the .05 and .01 levels respectively. Considering that nine correlations were computed, the Bonferroni inequality (e.g., Hays, 1981) suggests a .006 level of significance to reduce the possibility that results were due to chance.

It is of interest to note that Benton et al. (1982) also found no correlation between drop in blood sugar and the Anxiety or Depression subscales of the Multiple Affective Adjective Checklist. The checklist, however, was administered only once. It is possible that changes in blood sugar caused changes in transient feelings of anxiety or depression. The checklist administered once, however, would not assess such changes, and even if it were influenced by the blood sugar level of the subject while he was filling it out, the design of the study does not permit analysis of such

an effect.

All of the above studies on aggression represent attempts to correlate general tendencies to be aggressive with the results of a single GTT. A more conclusive approach would be to measure states of aggressiveness or irritability across the course of a GTT at different blood sugar levels.

Migraine headaches have also been studied in connection with hypoglycemia. Wilkinson (1949) reported on 92 patients with migraine who were seen over a 17-month period and routinely given GTTs. Of these, 11 had a headache 0 to 120 minutes after a hypoglycemic glucose nadir (17-46 mg/dl). A diet high in protein and low in carbohydrate would improve or cure the headache only in cases in which the GTT provoked a migraine. No information is provided as to the content of or compliance with the diet. Not all migraine patients with hypoglycemia got a headache, suggesting to Wilkinson that there exists a subset of people with "hypoglycemic headache." In another study (Blau & Cummings, 1966), fasting for 19 hours was found to precipitate headache in 6 of 12 subjects with migraine, whereas normal eating did not. Three more subjects developed migraine after eating following the fasting period. A common symptom noted by the subjects during the 19-hour fast was difficulty concentrating. Blood sugar levels ranged from 41 to 91 mg/dl during the fast, but it cannot be determined by the information reported whether low blood sugar levels were associated with headache or difficulty concentrating.

The study quoted in the popular literature as evidence for hypoglycemia causing fatigue is one by Portis, Zitman, and Lawrence (1950). They found that 43% of 50 executive patients who complained of fatigue had low blood sugar during a GTT. The mean blood sugar level at 3 hours was

56.4 mg/dl, with decreases from fasting level ranging from 5 to 40 mg/dl. Fatigue was not assessed during the GTT. This and the fact that no control group was used preclude any conclusions being drawn from this study. A role for hypoglycemia in schizophrenia has also been suggested (Tintera, 1967). Hypoglycemic-like symptoms were reported to occur frequently in a variety of psychiatric patients, most of whom were not schizophrenic. The article is purely speculative and cannot be used to support hypoglycemia as a causal factor in schizophrenia.

The literature also reports that hypoglycemics have similar personalities. Anthony, Dippe, Hofeldt, Davis, and Forsham (1973) found that 27 of 31 hypoglycemic subjects scored two standard deviations above normal on Minnesota Multiphasic Personality Inventory (MMPI) scales 1 (Hypochondriasis) and 3 (Hysteria), whereas 21 nonhypoglycemic endocrine disordered controls did not. The authors interpret this study as suggesting that hypoglycemia causes personality disorders. It could be, however, that the scores reflect the subjects' reports of multiple symptoms. The MMPI was not intended to measure personality in nonpsychiatric subjects. As will be shown below, other authors have interpreted such correlations as indicative that personality disturbances cause self-diagnoses of hypoglycemia.

Pseudohypoglycemia Literature

There are other writers who espouse the view that a neurotic personality style may cause one to develop pseudo or nonhypoglycemia (e.g., Ford, Bray, & Swerdloff, 1976; Johnson, Dorr, Swenson, & Service, 1980; Mundy, 1976; Yager & Young, 1974). Pseudohypoglycemia refers to people attributing their symptoms to hypoglycemia, when in fact there is no relation between their blood sugar level and symptoms. These authors believe the

symptoms are psychological, and that hypoglycemia provides a socially acceptable medical diagnosis for a person's difficulties. Ford et al. (1976) concluded that hypoglycemia does not cause emotional distress or personality disturbance on the basis of their finding of nonsignificant correlations between degree of hypoglycemia and MMPI scale scores or number of symptoms that subjects complained of in daily life. Such correlations would not be expected, however, as hypoglycemia is thought to cause transient symptoms while many other factors may influence scores on the MMPI and daily symptoms. Considering the results of Anthony et al. (1973) above, one could also infer that there was no correlation between MMPI scores and degree of hypoglycemia because of restricted range effects. If subjects exhibited similar MMPI profiles, there would be insufficient score variation to obtain a significant correlation. Thirty subjects who considered themselves hypoglycemic volunteered for this study and were given GTTs. There were no differences in the MMPI profiles or the psychiatric diagnoses of those who had hypoglycemic GTT results (less than 65 mg/dl, $\underline{n}$ = 18) and those whose results were normal ($\underline{n}$ = 7). Many subjects had hysterical personality patterns ($\underline{n}$ = 14) or depression ($\underline{n}$ = 10). Unstructured psychiatric interviews were conducted blindly with respect to blood sugar results, but apparently not to the nature of the study. A possible confounding factor in the subject population is that in the recruitment procedures subjects were informed that psychological evaluations would be conducted. Similarly, 33% of subjects had received psychiatric treatment in the past. Johnson et al. (1980) found that the average MMPI profiles of 98 subjects referred for GTT differed from the norms of general medical patients; they exhibited a conversion V pattern similar to that found by

Anthony et al. (1973). These authors interpret this pattern as reflecting emotional disturbance in patients referred for evaluation of hypoglycemia. They conclude that such distress is not caused by the hypoglycemia. The basis of this conclusion is the observation of no relation between level of hypoglycemia and MMPI profiles. Again, such a relationship should not be expected, as hypoglycemia is thought to cause transient symptoms. It must first be determined if low blood sugar does in fact cause symptoms. Then the apparent correlation between MMPI profile and referral for assessment of hypoglycemia could be better evaluated. From the literature to date, it cannot be determined if hypoglycemia causes personality disturbances, if certain personalities cause one to have -- or cause one to think one has -- hypoglycemia, or if a third variable causes both hypoglycemia and personality disturbances.

The proponents of pseudohypoglycemia state that there is a danger of overdiagnosing hypoglycemia and, therefore, overlooking other possible psychiatric or organic disorders (Fabrykant, 1955a; Jefferson & Marshall, 1981). This view is often supported by findings of low blood sugar levels in normal subjects. For example, 23% of 123 normal subjects showed a blood sugar level of less than 50 mg/dl during a 5-hour GTT (Park, Kahn, Gleason, & Soeldner, 1972). No information is provided as to how these subjects were selected. It is reported that all of these subjects were asymptomatic at the time of glucose nadir; however, how this was determined is not stated. Hofeldt (1975) reports that 48% of 25 normal subjects showed glucose levels less than 50 mg/dl during GTTs. Similarly, Burns et al. (1965) found 5 of 12 normal subjects to have glucose levels less than 50 mg/dl during continuous sampling of blood glucose during GTTs. Again, how the

subjects were selected is not reported. Hofeldt (1975) reports that no symptoms were associated with the low glucose values obtained in his study; he does not, however, state how this was determined. He does mention strict criteria for reactive hypoglycemia, including the showing of definite symptoms as observed and recorded by a physician or paramedic. Data as to the occurrence of such symptoms -- or indeed what these symptoms were -- are not provided. It is possible that physicians' observations are not sensitive enough to detect symptoms of hypoglycemia. Other authors have claimed that subjects with insulin-producing tumors may adapt to blood sugar levels of 20 to 30 mg/dl (Cahill & Soeldner, 1974). What "adapt to" means, how often this occurs, and how it has been documented are not reported. Levine (1974) reports that gradually lowering the blood sugar level makes it possible to have no symptoms in subjects with glucose values of 5 to 10 mg/dl. No data are provided, making it impossible to evaluate this statement. Lev-Ran and Anderson (1981) gave GTTs to 650 subjects who presented no complaints of symptoms suggestive of hypoglycemia, either before or during the test. No data are presented on the determination of this lack of symptoms. The median nadir was found to be 64 mg/dl; 10% of subjects had nadirs less than 48 mg/dl and 2.5% less than 40 mg/dl. The modal nadir value was 75 mg/dl. Time to reach nadir after glucose ingestion was distributed as follows: 13.4% in 120 minutes, 51.5% in 180 minutes, 29.1% in 240 minutes, and 6% in 300 minutes.

Some authors have suggested that, on average, women exhibit lower blood sugar levels than men. For instance, Merimee (1977) reported that after a 72-hour fast, 0 of 15 men had glucose levels of less than 50 mg/dl whereas 39 of 51 women had such glucose levels (male mean 67.5 mg/dl;

female 41.3 mg/dl). These values were obtained between 36 and 72 hours after the subjects had eaten, therefore, their relevance to the postprandial state is uncertain. The degree of hypoglycemia in women during the GTT has been assessed (Jung et al., 1971); however, there was no male control group. Of 285 women participating in a health survey, 17% exhibited blood sugar levels less than 60 mg/dl, with higher percentages within younger (20-45 years of age) and heavier (greater than 145 pounds) women. Compared with the results of Lev-Ran and Anderson (1981) which were based on 304 men and 346 women, these values do not indicate that women have lower nadirs than men. The number of subjects and percentage for each group were as follows: 122 young nonobese, 19%; 58 young obese, 31%; 43 old nonobese, 2%; 62 old obese, 11%. These authors conclude that glucose nadirs between 41 and 59 mg/dl in young women may simply be a variation of normal, and should not be taken as diagnostic of hypoglycemia so readily as such values in older women would. Simply documenting that 17% of these women had blood sugar levels less than 60 mg/dl, however, is not sufficient; it is possible that these 17% were hypoglycemic and did exhibit symptoms during the GTT. No assessment of such a possibility was made. Reports of low blood sugar levels in normal subjects, without objective documentation of the presence or absence of symptoms (e.g., Cahill & Soeldner, 1974; Hofeldt, 1975; Levine, 1974; Park et al., 1972), do not prove that low glucose values are insignificant.

The proponents of pseudohypoglycemia have also reported a lack of relationship between blood sugar level and symptoms in patients referred for evaluation of hypoglycemia. For instance, Johnson et al. (1980) gave GTTs to 192 patients referred for evaluation of hypoglycemia; 129 of these

patients complained of spells in their daily lives of symptoms such as sweating and shakiness (n = 75), dizziness and lightheadedness (n = 65), or weakness and fatigue (n = 71), whereas the other 63 presented with unremitting symptoms such as fatigue, headache, or depression. Blood sugar was measured hourly during the test as well as at the occurrence of any symptom. Results showed 44 patients with nadirs less than 50 mg/dl (range 34-49 mg/dl), 10 of whom were symptomatic. Fourteen other subjects exhibited symptoms at nadirs greater than 50 mg/dl (range 50-69 mg/dl), and 4 patients with nadirs less than 50 mg/dl displayed symptoms when their blood sugar level was greater than 50 mg/dl. Of the 28 subjects exhibiting symptoms during the GTT, 23 were from the group complaining of spells in their daily lives. These investigators calculated the slopes of the curves to determine if rate of glucose descent was related to appearance of symptoms. They found a faster rate of fall in blood sugar level to be related to the absence of symptoms than to their presence. Within subjects with nadirs less than 50 mg/dl, the rate of descent was 67.9 mg/hour in asymptomatic subjects and 50.8 mg/hour in symptomatic subjects. Corresponding rates were 35 mg/hour and 31 mg/hour in those subjects with nadirs greater than 50 mg/dl. No tests of significance are reported. Finally, blood sugar was measured during the spontaneous appearance of symptoms in 26 subjects; glucose values ranged from 73 to 153 mg/dl (median 89 mg/dl). While this study indicates a lack of relationship between symptoms of hypoglycemia and level of nadir or rate of decrease in blood sugar, the authors' failure to report how symptom-presence was determined, along with a confusing presentation of results without statistical analyses, makes the results difficult to evaluate.

Lev-Ran and Anderson (1981) gave GTTs to 118 patients who suspected, or whose physicians suspected, they were hypoglycemic. Patients recorded time and type of complaints experienced during the test. Sixteen of the patients recorded symptoms at the time of nadir (range 33-48 mg/dl, median 39.5 mg/dl). The other 102 patients either presented no complaints or complained of symptoms that did not correlate with nadirs; their median glucose nadir was 64.3 mg/dl. The authors report the clinical diagnoses of the patients, presumably as support that other disorders are misdiagnosed as hypoglycemia. Of the 16 patients with symptoms at nadir, 5 were depressed and 4 somatizers (having numerous somatic complaints without apparent physical cause). Of the other 102, 14 were healthy, 8 had somatic problems, 39 had bipolar or unipolar mood disorders (depression with and without episodes of mania), and 41 had somatization or anxiety disorders. How these diagnoses were made is not reported. Finally, there were 16 subjects who knew the symptoms of hypoglycemia and when to expect them, and were convinced that they were hypoglycemic. They were given glucose and placebo tolerance tests, under the pretense of comparing two different sweeteners. Both beverages were caffeine-free cola drinks, one with 100 grams glucose and the other with no carbohydrate. The patients could not distinguish between the two. Results showed two subjects who exhibited symptoms only during GTT (nadirs 36 and 38 mg/dl); the other 14 subjects complained of symptoms such as perspiration, palpitations, shaking, back pain, numb toes, chills, pressure in the head, yawning, and difficulty urinating during both tests (glucose median nadir 74 mg/dl; placebo median nadir 93 mg/dl). This study indicates that some patients may be misdiagnosed as hypoglycemic either by themselves or by their physicians. In other subjects,

hypoglycemia appears to exist. More conclusive interpretations could be made if more systematic quantifiable measures were made of subjects' symptoms.

Research on the Relationship between Blood Sugar and Symptoms

The research on both hypoglycemia and pseudohypoglycemia is nonspecific; symptoms are seldom measured and, when they are, method of measurement and which symptoms are measured are not reported. There has been some research done to specifically investigate the relationship between blood sugar levels and cognitive functions, affective states, and somatic symptoms.

In research on feeding behavior (Rodin, Wack, Ferrannini, & DeFronzo, 1985), 20 subjects' insulin and glucose levels were manipulated independently of each other through the use of an insulin/glucose clamp technique. After a 12-hour fast, subjects were randomly assigned to one of four groups: hyperinsulinemia-hyperglycemia, hyperinsulinemia-hypoglycemia, euinsulinemia-hyperglycemia, or saline control. Subjects rated taste, hunger, thirst, warmth, and mood state every 30 minutes for 2 1/2 hours. A 7-point scale anchored with "not at all" and "extremely" was used. Unfortunately, no description is given of what "mood state" was measured. Results showed hyperinsulinemia to be associated with increased hunger and perceived pleasantness of sucrose, independently of glucose level. There were no effects for blood sugar level, and none of the experimental groups had any significant change in perception of thirst, warmth, or mood. The mean low blood sugar level, however, was 71 mg/dl, which may not have been low enough to stimulate any counterregulatory responses.

Some direct research on hypoglycemia has focused on its relationship

to panic attacks (Gorman, Martinez, Liebowitz, Fyer, & Klein, 1984; Uhde et al., 1984). Gorman et al. (1984) induced panic attacks with sodium lactate infusion in 10 patients with panic disorder (DSM-III diagnosis) after an overnight fast. These authors claim that many patients with panic disorder believe hypoglycemia causes their anxiety attacks; however, no information is given as to whether the subjects in this sample held such beliefs. Blood sugar was measured at the start of sodium chloride (placebo) infusion, 30 minutes later at the start of sodium lactate infusion, and at the point of panic. The mean blood sugar levels at start of placebo and start of sodium lactate were 99 and 98 mg/dl, respectively. The mean decrease in blood sugar was 3 mg/dl; the lowest blood sugar level during panic was 81 mg/dl. The rationale behind this study was that low blood sugar should be documented during a person's usual symptoms. However, panic disordered patients' attacks are not induced by sodium lactate infusion outside of the laboratory, so the generalizability of this effect is equivocal. As the authors point out, this study does not prove that hypoglycemia never contributes to panic. Approaching the question in a different manner, Uhde et al. (1984) gave nine patients with panic disorder GTTs after a 9-hour fast. The patients' mean nadir was 52.1 mg/dl. These subjects also rated their anxiety and somatic complaints. The Zung Anxiety scale was completed by all subjects at baseline, and an anxiety analogue scale was completed by six subjects at baseline and 3 hours after glucose challenge. All subjects had glucose nadirs less than 62 mg/dl; the mean time to nadir was 4.3 hours. Results indicated that all subjects experienced either an exacerbation of anxiety (8 subjects), or two or more somatic symptoms (7 subjects) within 3 to 5 hours after glucose challenge. The symptoms assessed were hunger,

lightheadedness, diaphoresis, and palpitations. It is unclear how these ratings were obtained, as they do not coincide with the administration of the Zung or the analogue scale. Also no information is given as to why only six subjects completed the analogue scale. The authors note that in these six patients, scores on the analogue scale significantly increased within 4 hours after glucose ingestion. There was a correlation of .65 between baseline Zung scores and glucose nadir (subjects with highest baseline anxiety tended to develop lowest nadirs). These researchers also calculated the hypoglycemic index (Hadji-Georgopoulos et al., 1980) and found the seven subjects with index scores greater than 1.0 had both somatic symptoms and increased generalized anxiety; the two subjects with low index scores (0.13 and 0.64) did not develop both symptom types. None of the subjects in the study had a panic attack, which is interpreted by the authors as evidence that hypoglycemia is an unlikely cause of panic attacks. It is possible, however, that the symptoms experienced by these subjects during the GTT could be interpreted differently in the natural environment, and develop into a full-blown panic attack.

Symptom-glucose correlations have been looked at in diabetics (Cox, Gonder-Frederick, Pohl, & Pennebaker, 1983; Pennebaker et al., 1981). Thirty insulin-dependent diabetics completed a 19-item 7-point symptom checklist prior to measuring their own blood sugar levels seven times a day for 6 to 10 days (Pennebaker et al., 1981). All subjects were hospitalized for the duration of the experiment. Between-subjects analyses yielded only one significant correlation -- high fatigue was related to high glucose levels. However, one correlation significant at the .05 level out of 19 possible correlations would be expected by chance alone. Within-subjects analyses

were then conducted on each subject's 19 glucose-symptom correlations, a correlation of plus or minus .40 being considered meaningful. Each of the 19 symptoms was related to blood sugar level for at least one subject, and 80% of the subjects had at least one significant correlation (average 3.2 significant correlations). Nine of the symptoms were associated with low blood sugar (less than 80 mg/dl) for some subjects and high blood sugar (greater than 110 mg/dl) for others. This overlap shows the idiosyncratic nature of these relationships.

The following is a list of symptoms which showed an association only with low blood sugar and occurred in 10% or more of the subjects: trembling, pounding heart, lightheaded, sweating, fast pulse, hungry, and sleepy. It is unfortunate that the actual range of blood sugar values considered "low" is not reported. While a cut-off point of 80 mg/dl would not be expected to yield symptoms on the basis of the hypoglycemia literature, it could be that within a diabetic population such a value would be quite low relative to normal levels. The mean blood sugar level during this study was 150.9 mg/dl. These researchers point out the importance of doing within-subjects analyses because of the individual differences in symptom-glucose relationships. These differences could reflect different physiological responses or selective attention to certain response systems (Pennebaker et al., 1981). The results reported are correlational and, therefore, direction of causality cannot be determined. It is possible that manipulating blood sugar level would yield between-subjects relationships.

In an extension of this research (Cox et al., 1983), 23 of the above subjects recorded their symptoms and blood sugar levels at three intervals (in hospital, and approximately 6 and 8 months after discharge) to assess

reliability of the relationships. During each interval, symptoms and glucose were measured for 7 to 10 days, for a total of 40 recordings per interval. In the hospital, subjects completed a checklist of 24 symptoms; at home, the checklist was reduced to 10 symptoms. Subjects rated five hypoglycemic and five hyperglycemic symptoms, three each of which were the same for all subjects and two individually selected. The three standards for hypoglycemia were trembling, lightheadedness, and weakness; the three for hyperglycemia were dry nose, eyes or mouth, sweet taste, and salivation. The mean reliability coefficients for the three intervals (0 to 6 months, 6 to 8 months, 0 to 8 months) were .51, .28 and .27 respectively; these test-retest correlations varied both within and between subjects. The six standard symptoms showed more reliability than the individually selected ones. Possible reasons for the decreased reliability at 8 months include decreased motivation, physiological changes, and changes in diet or control of diabetes. The 0 to 6 month reliability is quite impressive given the change in assessment device and the correlational nature of the recordings.

Other research on diabetics has focused on training patients to estimate their blood sugar levels (Gross, Magalnick, & Delcher, 1985). It was found that giving feedback as to the accuracy of estimates decreased the magnitude of nine diabetics' errors by 46%. How these patients were able to improve their estimates was not assessed. While the training did not improve metabolic control, it is of interest that subjects reported being better able to prevent minor episodes of hypoglycemia. Perhaps giving feedback on symptom-glucose relationships, as was done by Pennebaker et al. (1981), could improve upon the benefits of this training.

Insulin tolerance tests are another method of manipulating blood sugar

levels. Russell and Rix-Trott (1975) measured the performance of 13 hospitalized patients with either obesity or possible pituitary disorder at baseline blood sugar levels (Session 1) and, 3 days later, after insulin challenge (Session 2). No information is given as to the condition of subjects during Session 1 (i.e., fed or fasted), and blood sugar was not measured at this time. Blood sugar levels during Session 2 were 67 to 101 mg/dl before insulin and 24 to 90 mg/dl (median 29-48 mg/dl) during the 30 minutes of testing 30 minutes after insulin administration. Abilities tested on both days were as follows.

1. Motor coordination: moving 24 pegs into holes in 15 seconds
2. Visual organization: choosing shapes that make a square
3. Word recognition: choosing 20 words previously seen on a list
4. Word recall: reciting 10 words on a list from memory
5. Reverse Digit Span: reciting recalled numbers backwards
6. Nufferno Reasoning Test: determining next letter in sequence.

Results showed that relative to Session 1, Session 2 was associated with decreased performance on the pegboard task, fewer words recalled, and increased time to solve reasoning problems. Visual organization, word recognition, reverse Digit Span, and performance on the reasoning problems were not affected. One potential problem with this study is the possibility of order or practice effects. The investigators took care to remove this possibility with the pegboard task by determining in a preliminary test how many trials were necessary to eliminate the effect of practice. They administered two extra trials to subjects in the study before the baseline trial. With the other tasks, equivalent forms were used, the equivalency of which was predetermined by administering the two forms to a group of 10

subjects, 3 days apart. However, the two forms' order of presentation was counterbalanced, which served to conceal any effect of order. This criticism is of less importance in that the results obtained were in the opposite direction from that which would be predicted on the basis of practice effects. Future research, however, should take into account effects of practice, fatigue, or order of presentation. The results of this study are inconclusive since it cannot be determined whether the performance changes were the result of decreased or fluctuating blood sugar levels, as glucose varied between 24 and 90 mg/dl over the course of the 30-minute testing period after insulin injection. Also to be determined by future research is whether the resulting performance decrements would also be obtained in GTTs or with hypoglycemic or normal subjects.

Another study eliminated this problem of fluctuating glucose levels by using an artificial insulin/glucose infusion technique which held glucose level within 4.3% of targeted levels (Holmes, Hayford, Gonzalez, & Weydert, 1983). These authors measured 12 diabetic university students' performance on various tasks at blood sugar levels of 60 (low), 110 (control), and 300 (high) mg/dl. The sequence of testing at the three blood sugar levels was counterbalanced, and subjects were blind as to their glucose concentration. The study consisted of three 2-hour periods; the initial 1 1/2 hours of each was used to establish the desired blood sugar level and the last half hour for testing. The following tasks were completed by subjects at each of the three blood sugar levels.

1. Digit Supraspan: 12 trials to learn 9 digits
2. Rey Auditory Verbal Learning: 5 trials to repeat 15 words
3. Matching Familiar Figures Test: accuracy and latency

4. Delayed reaction time: key press to red light after white warning light, with short (2-4 second) and long (6-8 second) interstimulus intervals
5. Benton Visual Retention Test: copy geometric designs
6. Nelson Denny Reading test: read passage and answer questions
7. Mathematical computation: speed recall of rote math facts.

Analyses showed that visual reaction time (task 4) was slowed at low and high blood sugar levels (as compared to the control level), but especially at low blood sugar with the longer interstimulus interval. Low blood sugar was also related to a decrease in the number of simple addition problems completed in 1 minute (task 7); accuracy was not affected. These two results were significant at the .05 level; none of the other tasks showed significant differences. The experiment-wise error rate suggests that these results could have been obtained by chance alone, as at least 10 variables were assessed. These authors speculate that the results obtained could indicate that abnormal glucose levels interfere with speed of responding, or with automatic but not inferential tasks. Clearly, replication is needed to determine if these are reliable effects of altered blood sugar levels. As well, future research could determine the generalizability of the results to hypoglycemic subjects. It could be that, if such effects were present in hypoglycemic subjects, blood sugar levels lower than 60 mg/dl would be needed to produce them.

Finally, Hale et al. (1982) have investigated whether postprandial hypoglycemia is associated with a neuroglycopenic symptom -- mental confusion. Sixty-seven subjects completed Serial Sevens Tests at half-hour intervals throughout a GTT. No information is given as to the composition

of this subject group except that they were receiving GTTs at a medical center. Subjects were divided into two groups: 29 who had glucose nadirs less than 60 mg/dl and 38 who had nadirs greater than 60 mg/dl. The start number of the Serial Sevens Test was changed with each trial, and the score computed was a time index score, or the time to do 14 subtractions at nadir minus the best previous time. Thus, a positive score represents a regression in performance. Results indicated that those subjects whose nadirs were less than 60 mg/dl experienced a greater regression in Serial Sevens performance at nadir (21.83 seconds) than did subjects with nadirs greater than 60 mg/dl (5.05 seconds). No data are presented as to whether the two groups differed in overall proficiency at Serial Sevens. Also, it would be interesting to know if a within-subjects analysis would yield significance. The authors conclude that mental confusion, and by extension, symptoms of neuroglycopenia, occur in postprandial hypoglycemia. However, it could be that the regression in subjects' performance was caused by anxiety or inattention. Further research is needed to determine what deficit does occur with hypoglycemia, the best predictor of such a deficit (e.g., cut-off or rate of fall), and what subjects the results generalize to.

Pilot Study

To investigate the effect of changes in blood sugar level on cognitive performance, affective state, and somatic symptoms in normal subjects, and to gain familiarity with the measures and procedures of blood sugar research, a pilot study was conducted. Twenty-two subjects were tested. There were no inclusion criteria, but subjects were excluded if they were diagnosed hypoglycemics or diabetics. The mean age of the subjects was 27 years; there were 12 women and 10 men. Most of these subjects were psychology

graduate students.

Blood sugar was measured with a glucomenter, using the Dextrostix Reflectance meter system described earlier. The tests given were the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971), Serial Sevens Test (Hayman, 1942; Ruesch, 1943), Maze, Digit Span (Wechsler, 1945, 1981), and a symptom scale. The POMS provides scale scores for six states: tension, depression, anger, vigor, confusion, and fatigue. In a Serial Sevens Test, the subject counts backwards aloud by sevens. The Maze consists of a box of wavy numbered lines the subject follows to their cells on the right. In Digit Span, the subject repeats rows of numbers the experimenter reads. Finally, the symptom scale requires subjects to check the levels of sensations -- trembling, pounding heart, flushed face, lightheaded, sweating, fatigue, hungry, weakness, tense, sleepy, irritable, headache, mental confusion, blurred vision, and dizziness -- they are experiencing. These items were derived from the research literature.

The design of the study was a 2 x 2 between-within-subjects Latin Square. The conditions were blood sugar level (low, high) and group (low first, high first), with the variable time of testing (Time 1, Time 2) being nested in the Latin Square. All subjects fasted for 12 hours overnight before the experiment. In the low-first condition, subjects were tested first on arrival with low blood sugar, and then again a half hour after drinking a 75-gram dextrose solution, at high blood sugar. In the high-first condition, subjects were first tested a half hour after the drink and were then tested 1 hour after the first testing at lowered blood sugar. These two conditions were necessary to counterbalance for possible order or practice effects. This design allows for analysis of the effects of blood sugar level, group,

and time of testing.

The overall mean fasting blood sugar level was 75 mg/dl (range 66-82 mg/dl), and the overall level a half hour after dextrose was 135 mg/dl (range 83-185 mg/dl). The mean value 1 hour after the increase occurred was 93 mg/dl (range 68-121 mg/dl).

A criterion was needed to determine which subjects had experienced a significant change in blood sugar level (low vs. high). The range of changes in blood sugar level achieved was 7 to 112 mg/dl. It was decided to exclude those subjects who experienced an absolute change more than one standard deviation below the mean change. The mean change was 52 mg/dl and the standard deviation was 30; therefore, four subjects were eliminated, as their blood sugar level changed less than 22 mg/dl. This left 10 subjects in the low-first group (5 female, 5 male), and 8 subjects in the high-first group (4 female, 4 male). Their mean age was 28 years.

A repeated measures t-test was then performed on the remaining scores of the 18 subjects. The mean overall low glucose measure was 81 mg/dl; the mean high level was 141 mg/dl; these values were significantly different ($t(17) = -9.63$, $p<.001$). This ensured that the manipulation was successful. Between the two conditions (low first, high first) t-tests were done on low blood sugar and high. The two groups did not differ with respect to high blood sugar level ($t(16) = 0.74$, $p = .470$), however, the difference between the two groups' low blood sugar readings was significant ($t(16) = -4.15$, $p<.005$). The means were 74 mg/dl in the low-first condition, and 90 mg/dl in the high-first condition.

Finally, repeated measures ANOVAs were conducted for the dependent variables. For the symptom scale, subjects received a score on each of the

15 items (0-10), as it could not be assumed to be a cohesive measure. The Serial Sevens and Maze were scored for both time and number of errors. This resulted in 27 dependent variables. Many of the self-report measures, however, were not endorsed by many of the subjects. It was decided not to analyze variables on which half or more of the subjects had no scores. This left 13 variables. A probability level of .05 is inappropriate when analyzing so many variables, as it is the probability of a Type I error in one comparison. Therefore, the Bonferroni inequality was calculated, resulting in a corrected probability level of .002. The analyses then resulted in no significant differences whatsoever (see Table 1).

It could be argued that if no effects of blood sugar level in a normal population were hypothesized, making the probability level more stringent would be misleading. Therefore, the results were also analyzed with a probability level of .05. This analysis as well yielded no effects for blood sugar level. There were a few order and group effects (see Table 2). On the POMS, there was a trend for subjects to be more tense at the time of first testing than at second testing ($F(1, 16) = 5.30$, $p<.05$). Subjects also tended to be more fatigued at Time 1 than Time 2 ($F(1, 16) = 7.05$, $p<.05$). On the analogue scale, the high-first group was significantly more hungry than the low-first group ($F(1, 16) = 13.16$, $p<.005$).

This pilot study indicates that normal subjects' cognitive performance, affective state, and somatic symptoms are very resilient to the changes in blood sugar level achieved. It appears likely, subject to confirmation, that the popular literature contains exaggerations of the dependence of psychological functioning on blood sugar level. This experiment does not, however, show psychological functioning to be unimpaired at hypoglycemic

Table 1

Mean Scores for Blood Sugar Conditions

Task	Blood sugar condition	
	Low (M=81mg/dl)	High (M=141mg/dl)
Profile of Mood States:		
Tension	5.2	4.9
Fatigue	5.7	5.4
Vigor	17.5	17.2
Confusion	5.6	5.6
Symptom scale:		
Hunger	4.6	3.6
Fatigue	2.0	1.5
Sleepy	1.6	1.7
Weakness	1.6	1.3
Tension	1.2	1.1
Cognitive tasks:		
Digit Span	5.6	5.3
Maze time	58.9	58.1
Serial Sevens time	51.4	51.4
Serial Sevens errors	0.8	0.7

Note. Figures based on N=22. Time scores are in seconds.

Table 2

Effects for Order and Group

POMS Tension

	Low blood sugar	High blood sugar	Overall mean
Low first	5.4	4.1	4.8
High first	4.9	6.0	5.4
Overall mean	5.2	4.9	

POMS Fatigue

	Low blood sugar	High blood sugar	Overall mean
Low first	6.5	4.6	5.6
High first	4.6	6.4	5.5
Overall mean	5.7	5.4	

Symptom -- Hunger

	Low blood sugar	High blood sugar	Overall mean
Low first	3.5	2.0	2.7
High first	6.1	5.7	5.9
Overall mean	4.6	3.6	

Note. Figures based on N=22.

levels. None of the blood sugar values reached in the low-blood-sugar condition was low enough to be considered hypoglycemic by any relatively stringent criterion. It is possible that, had there been more time, and the blood sugar level had decreased further, there would have been symptoms in the high-first group. Clearly, research is needed which involves systematic measurement of cognitive performance, affective state, and somatic symptoms over the entire course of the GTT.

Summary

As has been discussed, there are many methodological problems in the research on the relationship between blood sugar level and cognitive function, affective state, and bodily symptoms. For example, much of the hypoglycemia research consists of uncontrolled case reports of selected patients. Conclusions on aspects of the physiology of hypoglycemia were based on 3 specially selected patients (Permutt et al., 1973), and Cahill and Soeldner (1974) quoted these results as evidence that people who erroneously complain of hypoglycemia have physiological responses similar to those of normal subjects. Tintera (1967)'s account of 16 case histories of patients with non-schizophrenic-like symptoms is quoted as evidence of the relationship between hypoglycemia and schizophrenia. Claims for the effectiveness of high protein diets in the treatment of hypoglycemia are based on the glucose curve responses to protein of 3 subjects, and the positive response of 1 of these patients to a high protein diet (Conn, 1936). Data from case reports are suggestive and may generate hypotheses, but definitive research requires well-controlled studies.

Comparing the glucose tolerance curves of subjects with a preexisting disorder with those of normals creates another methodological problem

characteristic of studies in the hypoglycemia literature. As was discussed earlier with respect to the research on violent offenders (e.g., Virkkunen & Huttunen, 1982), such relationships are correlational, and therefore, direction of causality cannot be determined. Similarly, the influence of a third variable cannot be ruled out. Also, this type of research does not indicate whether changes in blood sugar level are related to changes in psychological symptoms. Chronic problems are correlated with hypoglycemic results, but whether the transient symptoms are induced during the GTT is not reported. For example, Portis et al. (1950) state that hypoglycemia causes fatigue on the basis that some subjects complaining of chronic fatigue evinced hypoglycemic GTT results; however, they did not assess whether subjects were tired during the GTT. Similarly, Benton et al. (1982) found a relationship between questionnaire measures of aggression and hypoglycemia but did not attempt to measure aggressive feelings or irritability at different levels of blood sugar during the GTT. A complaint of a symptom in everyday life and a low blood sugar finding on a GTT do not establish a causal relationship between the two.

The research on personality has yielded a correlation between conversion V MMPI profiles and hypoglycemia (Anthony et al., 1973; Johnson et al., 1980); however, whether hypoglycemia causes personality changes, or a certain personality type is prone to develop or complain of hypoglycemia, remains in question. The findings of glucose-symptom relationships in diabetic patients are also correlational (Pennebaker et al., 1981). Subjects rated their symptoms and then measured their blood sugar. It could be that the blood sugar level causes changes in the symptoms, but it is also plausible that the symptoms cause the glucose level to change, or that a

third variable changes both. For example, Cox (1978) reported on findings that stress can alter blood sugar level. In order to determine what changes in psychological functioning low blood sugar levels cause (if any), one must manipulate blood sugar and measure symptoms. Using such a paradigm, one could still compare the effects upon different groups of subjects. Such research could prove interesting in illuminating some of the possible chronic end results of having transient hypoglycemic reactions.

There is a lack of objective criteria in the hypoglycemia research, most often for symptoms but sometimes also for hypoglycemia itself. For example, Fishbein (1982) used responses to a Symptomology Exam and a Food Frequency questionnaire to classify subjects as hypoglycemic or nonhypoglycemic; no physiological measures of blood sugar were taken. Her measure of symptoms related to hypoglycemia was the Hoffer-Osmond Diagnostic test -- described as a quick and easy test to diagnose schizophrenia (Fishbein, 1982). Clearly, the validity of such measures can be seriously questionned. Other researchers report that symptoms were or were not related to low blood sugar levels but do not describe how these symptoms were measured (e.g., Anthony et al., 1973; Johnson et al., 1980). One is left to assume that the occurrence of symptoms was determined by experimenter observation or statements of patients.

A further problem with the measurement of symptoms is that observation of subjects' symptoms often is not blind, leaving room for bias and expectancy effects. Nurses who knew whether patients were receiving glucose or placebo observed symptoms in one study (Lev-Ran & Anderson, 1981), and experimenters who knew which groups subjects were in rated aggressiveness of patients before and after various treatments

(Yaryura-Tobias & Neziroglu, 1975). Similarly, many subjects may be familiar with the popular literature and know when and what symptoms they should show (Hofeldt, 1975). This is what may have been demonstrated in Lev-Ran and Anderson's (1981) study in which a placebo substance gave rise to complaints of symptoms in 14 out of 16 subjects. One solution to these problems is to have random double-blind experiments with glucose and saline tolerance tests (Cahill & Soeldner, 1974). There are ethical problems with such an approach in that subjects, who are giving at least 5 hours of their time, would have to be deceived or simply accept the fact that they may receive a test which will tell them nothing about their responses to glucose. Otherwise, this method would yield a very powerful test of the relationship between blood sugar level and symptoms.

In addition to having observers blind to blood sugar levels, symptoms should be measured in a more systematic and quantifiable way than they often are at present. For example, in one study (Lev-Ran and Anderson, 1981) patients recorded the time and type of complaint -- in some unspecified fashion -- that they were experiencing during their GTTs. If a patient in this study reported anxiety at a certain blood sugar level, one could not discern whether the symptom was related to glucose level, as there is no previous rating of symptoms with which to compare. Symptoms should be monitored at regular intervals to determine if they change with changes in blood sugar level. Also, symptoms must be measured in a quantifiable way; reporting symptoms as present or absent may not get at changes that are occurring along a continuum. And if subjects are at all confused or lacking in concentration during the GTT, the researcher may need to use objective criteria to determine effects the subject may not notice (Permutt, 1976).

The use of the Serial Sevens test by Hale et al. (1982) is a good example of a direct measure of symptoms. Finally, if at all possible, measures of known reliability and validity should be employed.

While blood sugar level provides an objective and quantifiable measure of the independent variable, there still remains the problem of an agreed upon criterion for hypoglycemia. Various cut-off points (e.g., Hofeldt et al., 1972), decreases in blood sugar level from fasting (e.g., Bolton, 1976), and the hypoglycemic index (Hadji-Georgopoulos et al., 1980) have been used to designate hypoglycemia. Researchers in the future should concentrate on objectively documenting symptoms during the GTT, in order to validate the existence of hypoglycemia as a syndrome. Such research should allow any findings to be related to the various criteria that have been proposed in order to assess their validity.

A final problem sometimes encountered in the blood sugar research is the possibility of order effects. Some investigators have shown an awareness of this possibility and attempted to deal with it (e.g., Holmes et al., 1983; Russell & Rix-Trott, 1975); however, the majority have not. One solution to this problem is to counterbalance the order in which subjects are tested under each level of blood sugar. Unfortunately, this option is not viable if one is manipulating blood sugar during the GTT; the physiological response is such that high blood sugar always precedes low blood sugar. When measuring performance on tasks, one might predict that performance would improve with practice -- or deteriorate with fatigue. It is therefore imperative to determine the nature of the order effect with respect to the dependent variable employed in one's study. This could be done with a control group that is simply tested on the dependent measures over a time

period congruent with the GTT. This method, however, does nothing to remove the effects of practice from the experimental group. If there was an effect such that performance improved with number of trials, this could obscure any effect of low blood sugar to impair performance. The effect would have to be very powerful to overcome the opposing force of the practice effect. An alternative would be to conduct a preliminary study to determine the number of trials over which the order effect is appreciable. If, for instance, there is no further change in performance after five trials, subjects could be given five trials of the task prior to the GTT, thereby eliminating the practice effect. A possible problem with this strategy is ensuring equivalency of effects between the preliminary group and the group receiving the GTT. For this purpose, a saline placebo group would be most informative, as setting, blood sampling, and hospital procedures would be similar across groups.

The problem of order effects differs slightly with respect to the self-report of such symptoms as anxiety, trembling, palpitations, weakness, irritability, fatigue, and lightheadedness. Again, the necessity of empirically determining the nature of the effects becomes apparent in that one could reasonably predict effects in either direction. For instance, fatigue could decrease over time if subjects are more tired on arrival at the experiment first thing in the morning. Or, fatigue could increase with time if the subject becomes bored with the procedures. In the case of symptoms such as these, one could not conceivably rule out the effects with a preliminary study in which subjects simply rated their symptoms over a time period similar to the GTT. Subjects would have to be involved in a similar medical

situation to determine the effect of order -- if any -- upon these variables. A saline placebo group could eliminate this threat to internal validity.

Given the methodological problems in the area, one cannot say that changes in blood sugar level have been shown to have any reliable effects. There is some suggestive evidence, however, that given sound methodology, some symptoms might be shown to be reliably related to low blood sugar levels. The following symptoms are attributed to low blood sugar with great regularity: tremor, nervousness, weakness, sweating, palpitations, confusion, irritability, lightheadedness, fatigue, flushed face, headache, blurred vision, dizziness, and hunger (e.g., Hale et al., 1982; Hofeldt et al., 1972; Kwentus, Achilles, & Goyer, 1982; Levine, 1974). The frequency of reports of these symptoms is suggestive of a relationship; however, little research has been conducted to address the measurement of these symptoms in a systematic way. Such symptoms (i.e., anxiety, lightheadedness, hunger, diaphoresis, palpitations) were measured in only one study (Uhde et al., 1984) and, unfortunately, insufficient information was presented as to which symptoms occurred and the magnitude of change in them. Also, this study employed a small sample of 9 patients with panic disorder, the representativeness of which cannot be judged. The study, nevertheless, is indicative of an exacerbation of anxiety and somatic symptoms at glucose nadir. The only other study involving systematic measurement of such symptoms did so in diabetic patients over the course of their daily activities (Pennebaker et al., 1981); it found trembling, pounding heart, lightheadedness, sweating, fast pulse, hunger, and sleepiness to be related to low blood sugar level.

The other more methodologically sound studies in the area have shown low blood sugar (relative to normal levels) to be related to increased

reaction time and decreased number of additions calculated in 12 diabetics (Holmes et al., 1983); impaired performance on a pegboard task, fewer words recalled, and increased time to solve problems in 13 obese or suspected pituitary-disorder patients (Russell & Rix-Trott, 1975); and impaired performance on the Serial Sevens Test in 29 subjects with glucose nadirs less than 60 mg/dl during a GTT (Hale et al., 1982). A problem with these results is determining why performance is impaired on the tasks. It is plausible that any of such symptoms as anxiety, mental confusion, fatigue, or weakness could account for such performance deficits. While such behavioral measures of symptoms are necessary, it is imperative that self-report measures of specific symptoms also be given to gain a better understanding of the mechanism behind the changes in performance.

In summary, the main sources of possible error in this area are uncontrolled case studies, lack of objective dependent measures, unverified criteria for hypoglycemia, experimenter and subject expectancy, and order/practice effects. These problems make it difficult to determine the relationship between blood sugar level and psychological symptoms on the basis of the published evidence. To overcome some of these problems, the present study included an assessment of the occurrence of symptom changes, by self-report and performance measures, at regular intervals over the 5-hour course of the GTT. The only other investigator to measure a symptom during the GTT (Hale et al., 1982) used a between-subjects design; however, a within-subjects design was chosen for the present study. In this way, an a priori decision about which subjects would or would not experience symptoms was avoided. Various possible predictors of which subjects would become symptomatic were tested, however. These included the magnitude of

the decrease in blood sugar, the speed of the decrease in blood sugar, the size of the decrease below fasting blood sugar level, glucose nadir, and the hypoglycemic index score.

The main aim of the study was to determine whether changes in blood sugar level are associated with changes in cognitive function, affective state, or somatic symptoms. The second aim was to determine which indices of blood sugar levels/changes, if any, are predictive of psychological change. The following hypotheses were advanced.

1. Lowered blood sugar levels are associated with impaired cognitive performance, adverse emotional changes, and somatic symptoms (including increased heart rate).
2. The cognitive impairment, adverse emotional changes, and somatic symptoms will be greater:
   (a) the greater the magnitude of the drop in blood sugar
   (b) the more rapid the decrease in blood sugar
   (c) the greater the drop in blood sugar from fasting level
   (d) the lower the absolute level of blood sugar
   (e) the higher the hypoglycemic index score (Hadji-Georgopoulos et al., 1980).

Method

In order to test the hypotheses, the following data were needed: blood sugar levels, mood state, cognitive performance, and somatic symptom presence. Blood sugar level was manipulated with the procedures of the glucose tolerance test. Subjects fasted overnight and ingested a 75-gram glucose solution the following morning at the experiment. This causes blood

sugar to rise and subsequently fall. Blood sugar samples were taken and measured in mg/dl at regular intervals throughout the GTT.

Mood state, cognitive performance, and somatic symptom presence were also assessed at these intervals during the GTT. Mood state was defined by scores on the Profile of Mood States (POMS; McNair et al., 1971). Cognitive performance was defined by performance on the Serial Sevens Test (SST; Hayman, 1942; Ruesch, 1943), a test in which subjects are given a number from which they must count backwards by sevens. Somatic symptom presence was defined by scores on the Somatic Symptom Scale. Also, one somatic index -- heart rate -- was measured with a Sanyo Model HRM-97E digital electronic pulse meter.

Subjects

Thirty-six subjects (26 female and 10 male) who believe or suspect that they have hypoglycemia participated in the experiment. They were recruited by notices posted in the community. Subjects were between 21 and 66 years of age ($\underline{M}$ = 32.4 years), and had between 12 and 21 years of education ($\underline{M}$ = 15.5 years). Eight of the subjects were nurses.

The subjects' weight was normal, being, on average, within 0.08% of ideal body weight (Howard, 1985; Metropolitan Life Insurance Company, 1959). Weights ranged from 16% below to 38% above ideal, with 24 subjects weighing less than ideal and 12 subjects weighing more than ideal. Only 3 subjects participating were obese (defined as being more than 20% above ideal body weight).

Twenty-one of the subjects had been diagnosed in the past as being hypoglycemic, and 13 subjects reported a family history of diabetes. There were 9 married subjects and 27 who were single, separated, or divorced. Six

of the subjects were cigarette smokers. Informed consent was obtained in writing from each subject.

Independent Variable

The variable being manipulated was blood sugar level. It was of primary interest to observe subjects after their blood sugar level had fallen to glucose nadir (i.e., the lowest level of blood sugar reached). In order to accomplish this, the GTT was used. All testing was carried out at the Diabetes Specialty Centre, Shaughnessy Hospital, Vancouver, British Columbia (Director: Dr. K. Dawson).

Subjects fasted for 12 hours before they arrived at the Centre; for example, a subject starting the GTT at 9 a.m. would not eat anything after 9 p.m. the night before (drinking water was allowed). Subjects started the experiment between 8:00 and 10:00 a.m. During the GTT, subjects first had their blood sugar level measured in the fasting state, and then ingested a 75-gram glucose solution (Glucodex). Blood sugar level was then measured at regular intervals over a 5-hour period; that is, 45, 120, 150, 180, 210, 240, 270, and 300 minutes after glucose ingestion. The usual response to this manipulation is an increase in blood sugar level within the first 45 minutes, followed by a decline to fasting or lower blood sugar levels after 2 to 5 hours. Finally, if blood sugar level has dropped below fasting level, it gradually returns to fasting level.

Glucose Analysis. Blood sugar samples were taken via finger pricks and placed in a Vacu-container containing sodium fluoride as an anticoagulant. The samples were analyzed in a YSI 23A Glucose Analyzer (Yellow Springs Instrument Company, Yellow Springs, Ohio 45387), which provides a digital display of blood sugar level in mg/dl. The YSI was

re-calibrated each day and after any blood sugar value greater than 200 mg/dl. This instrument analyzes blood sugar via glucose oxidase immobilized between two membranes (Chua & Tan, 1978; Spencer, Sylvester, & Nelson, 1978). Glucose diffuses through the first membrane and reacts with the glucose oxidase to produce hydrogen peroxide proportional to the glucose concentration. This hydrogen peroxide then diffuses through the second membrane to a hydrogen peroxide-sensitive electrode.

The YSI is used in laboratories to analyze glucose level. Its glucose values correlate .997 with the Beckman Glucose Analyzer (Chua & Tan, 1978), and .999 with the TEKIT SFG Enzyme-Chromogen-Buffer (Paul, 1978). Spencer et al. (1978) found no significant differences between glucose values obtained with the YSI and the Du Pont aca, instruments that are used routinely in laboratories.

As a test of the YSI, blood sugar samples from 26 diabetic patients who attended the the Clinic were analyzed on the YSI and by the hospital's laboratory (capillary samples for the YSI and venous serum samples for the lab). A correlation of .959 was found between the two methods. It should be noted, however, that these pairs of values differed in absolute value. The serum values ranged from 24.3% higher than the YSI value to 35% lower than the YSI value (13 values were higher and 13 values lower than the YSI's). There were 16 values within plus or minus 10% of each other and 20 values within 15% of each other. These data show that there is a lot of variation between the different methods of glucose analysis ,and therefore, caution should be exercised in interpreting absolute values of blood sugar. Cut-off levels observed in one setting with one method of glucose analysis may not generalize to other settings or instruments.

Predictor Variables. In order to test which parameters are associated with greater symptomatology, the following values were calculated for each subject:

1. Magnitude of drop in blood sugar -- defined as peak glucose value minus glucose nadir
2. Speed of fall in blood sugar -- defined as the drop in blood sugar between peak and nadir, divided by the time between peak and nadir, yielding score in mg/h
3. Drop from fasting blood sugar level -- defined as glucose value in fasting state minus glucose value at nadir
4. Lowest absolute level of blood sugar or glucose nadir -- defined as lowest level of blood sugar achieved after ingestion of glucose
5. Hypoglycemic index score (Hadji-Georgopoulos et al., 1980) -- defined as the drop in glucose during the 90 minutes preceding nadir, divided by glucose nadir.

Dependent Measures

Profile of Mood States. The Profile of Mood States (POMS; McNair et al., 1971) is a self-report instrument consisting of 65 words or phrases describing feelings people have. Subjects are instructed to read each word carefully, and then indicate how they "are feeling right now". This is done by placing a mark on a 5-point scale appearing to the right of each descriptor; the scale is labeled as follows: 0 "not at all", 1 "a little", 2 "moderately", 3 "quite a bit", and 4 "extremely". Filling in the scale takes approximately 3 to 5 minutes.

The POMS is intended to rapidly assess transient fluctuating affective states. From the scale, six factor scores are derived: tension-anxiety,

depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. The sum of these scales (with vigor negatively weighted) provides a total mood disturbance score.

The POMS is reliable, sensitive to change, and a valid measure of mood states (Eichman, 1978). Its scales show acceptable reliability, with KR-20 values ranging from .84 to .95. Validity studies have been conducted, showing the POMS to be sensitive to changes in mood after psychotherapy, drug trials, and emotion-inducing conditions such as viewing films and speaking in public.

Serial Sevens Test. The Serial Sevens Test (SST) is a task in which subjects are given a number and instructed to count backwards by sevens from it (orally) until told to stop. For instance, given the number 100, a subject would count aloud 93, 86, 79, 72, 65, 58, 51, 44, 37, 30, 23, 16, 9, 2. The test is scored as the time taken to complete 14 subtractions. Subjects were instructed to say the entire number and be as accurate as possible. Number of errors was also recorded.

In the present study, there were 11 different SST starting numbers to prevent simple memorization of responses; the numbers used were 211, 258, 296, 329, 376, 382, 436, 459, 493, 543 and 589. These numbers were chosen so that the well-known multiples of seven (7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77) would not appear. The order of presentation of the various start numbers was randomized to rule out any systematic influence of possible differences in difficulty level of the various starting points. Subjects were given two pretrials on the SST before commencing the experiment to eliminate or attenuate the effect of improvement with practice.

Preliminary Study. A preliminary study was conducted to determine how many pretrials should be administered. Fifteen psychology graduate students (9 women and 6 men; mean age 26.9 years) completed six SSTs over the course of an hour. While the results of this exercise may not generalize to a GTT, it does provide an estimate of the practice effect. The start numbers used were: 589, 493, 296, 543, 382, and 211; they were presented in a different order to each subject. A repeated measures analysis of variance was conducted on the data using time of testing or trial as the variable of interest (i.e., first SST completed versus second versus third and so on). This ANOVA was significant ($F(5, 70) = 7.62$, $p<.0001$), therefore, multiple comparisons were conducted via the Tukey HSD method. The critical difference was 7.79. The mean times (in seconds) to complete the 14 subtractions over the six trials were: 50.07, 43.93, 40.20, 40.33, 36.67, and 36.13. Using the critical difference, Trial 1 took significantly longer than Trials 2 to 6, and Trial 2 took significantly longer than Trial 6. No other comparisons were significant. It was therefore decided to administer two trials of the SST before starting the experiment.

A repeated measures analysis of variance was also conducted to compare the time taken to complete the SST using the various start numbers. This ANOVA was also significant ($F(5, 70) = 2.37$, $p<.05$), and Tukey's HSD yielded a critical difference of 8.95. The mean times to complete the SST were: 37.73 for Item 1, 44.93 for Item 2, 43.00 for Item 3, 44.60 for Item 4, 38.73 for Item 5, and 38.33 for Item 6. None of these times was significantly different from any of the others, indicating fairly equivalent difficulty levels amongst the items.

The SST is described as a quickly applicable test of intellectual efficiency (not capacity) and mental impairment (Hayman, 1942). Test-retest reliability coefficients are reported as .89 to .91 (Hayman, 1942). Hayman (1942) reports that factors interfering with mental efficiency are reflected in the response to the SST. Ruesch (1943) found the SST to be the most sensitive of various tests evaluated at demonstrating impairment after head injury.

Somatic Symptom Scale. A scale was developed to measure various somatic symptoms that are said to occur during hypoglycemia. The symptoms assessed are: trembling, pounding heart, flushed face, lightheadedness, sweating, hunger, weakness, headache, blurred vision, dizziness, and nausea. Five symptoms included on the symptom scale during the pilot study (i.e., fatigue, tension, sleepiness, irritability, and mental confusion) were eliminated as their content overlapped with that of the POMS. "Nausea" was added because nurses reported it to be frequently experienced by subjects during the GTT. Subjects are instructed to place a mark on the dashed line to indicate how they are feeling "right now". The dashes are not numbered, but were scored from 0 to 9. The far-left dash is labeled "not at all", and the far-right dash "a great deal" or "extremely" as appropriate to the adjective being rated.

The 11 descriptors were chosen on the basis of their frequent appearance in the literature. Many other such symptoms (e.g., shakiness, nervousness) were not included on the scale, as their content is covered on the POMS. No established instrument was found which would assess the 11 symptoms included on the Somatic Symptom Scale.

Pulse Meter. Subjects had their heart rate measured with a Sanyo Model HRM-97E digital electronic pulse meter. A photo-electric pulse sensor is clipped to the subject's ear lobe. The meter displays heart rate in beats per minute every second; it is sensitive to rates between 38 and 200 beats per minute.

In the present study, a subject's heart rate score was calculated as the average of six readings taken 10 seconds apart. In this way, a more reliable measure was obtained, as the effects of point in the respiration cycle were randomized (Porges, McCabe, & Yongue, 1982). Also, the subjects' activity level was kept constant during each of the repeated heart rate measures in order to decrease extraneous variability due to differences in activity. Heart rate was measured after the other tests in the battery, rather than before as activity before testing sessions could vary.

Currently, there is no research evidence available which could be used to predict the pattern of change in heart rate over a 5-hour period. In the present study, the hypothesis was that heart rate will increase at the time of glucose nadir. A recent review (Linden & McEachern, 1985) showed heart rate to be very stable during adaptation periods, especially when subjects were certain about what procedures they would be participating in. Under conditions of uncertainty, decreases in heart rate of 2 or 3 beats per minute were observed during 15-minute adaptation periods. Heart rate is reported to increase in response to stressors such as mental arithmetic (Siddle & Turpin, 1980), but this response habituates with repeated presentations of the stressor (Linden & McEachern, 1985). From these findings, it was hypothesized that heart rate would decrease or remain stable during a 5-hour period in which subjects repeatedly complete the same tasks. That is, the

hypothesized increase in heart rate during the GTT is opposite to that which might be expected over time alone.

Procedure

A repeated measures design across 9 time points was used. Subjects who believe or suspect that they have hypoglycemia were recruited to participate in a study on the effects of changes in blood sugar level. The nature of the experiment was explained and informed consent was obtained before participation.

After fasting for 12 hours overnight, subjects arrived at the hospital and were seated in a reclining easychair. Demographic data -- sex, age, years of education, height and weight -- were collected, and the two pretrials of the SST were administered. Subjects then had their first blood sugar sample taken (fasting blood sugar level), and completed the the first set of tests. Next, they ingested a 75-gram glucose solution (Glucodex). Subsequently, blood sugar was sampled and tests were given at the following times after glucose ingestion: 45, 120, 150, 180, 210, 240, 270, and 300 minutes, for a total of 9 measurement periods. Each time, the order of measures was: blood sugar sample, Somatic Symptom Scale, SST, POMS, heart rate; this battery of tests took between 5 and 10 minutes to complete.

Between testing periods, subjects sat, read, and/or went for short strolls. Eating and drinking (except water) were not allowed. Subjects and the experimenter were blind with respect to blood sugar levels throughout the study, but were aware that a GTT was being conducted, and that symptoms might occur. A medical student operated the YSI Glucose Analyzer. After the last set of measures was taken, subjects had something

to eat and went home. They were contacted, within 1 week, to have their results explained and any questions answered.

Results

As stated above, in order to test the hypotheses of this study, the following data were collected: blood sugar levels, Profile of Mood States (POMS) scores, Serial Sevens Test (SST) performance, Somatic Symptom Scale (SSS) scores, and heart rate. Measures were obtained on each of these variables over the course of the GTT. This resulted in nine measurement points (fasting and 45 minutes; 2, 2.5, 3, 3.5, 4, 4.5, and 5 hours post-glucose ingestion). The point of most interest was that at which subjects' blood sugar was lowest (glucose nadir). Because nadir occurred at different times for different subjects, conducting the analyses across these nine time points would not adequately test the hypotheses. Therefore, for the main analyses, the following five measurement points were used: 1 hour before nadir, 1/2 hour before nadir, nadir, 1/2 hour after nadir, and 1 hour after nadir. These will be referred to as ONEBEF, HALFBEF, NADIR, HALFAFT, and ONEAFT.

In order to assist in evaluating the results and their interrelationships, a brief summary of the results will be presented before explaining the details of the analyses. Subjects reported more mood disturbance and somatic symptoms after glucose nadir than before nadir, with the highest level of symptoms being reported half an hour after nadir. Performance on the mental arithmetic task was poorest at glucose nadir. The above effects were strong, or present, for only a subset of the subjects. In particular, subjects with high hypoglycemic index scores exhibited symptom increases,

whereas subjects with low hypoglycemic index scores did not. To a lesser extent, subjects with rapid speed of fall in blood sugar, large magnitude of drop in blood sugar, large decreases below fasting blood sugar level, and low glucose nadirs, also showed greater increases in symptoms than subjects with less abnormal blood sugar responses. There were no differences between these groupings of subjects with respect to heart rate.

The dependent measures used in this study yielded 20 scores: 6 POMS scale scores, 11 SSS items, SST time, SST errors, and heart rate. It was desirable to decrease this number of dependent variables in order to reduce the experiment-wise error rate and increase the reliability of the measures.

Scores on the 6 POMS scales at NADIR (tension, depression, anger, vigor, fatigue, and confusion) were correlated and subjected to principal components analysis. The correlation matrix showed that the 6 scores were highly intercorrelated (see Table 3). The principal components analysis yielded only one factor, which accounted for 62% of the variance, again indicating highly intercorrelated variables (see Table 4). For these two reasons, it was decided to use the sum of the 6 scale scores (with vigor negatively weighted) as a measure of overall mood disturbance. This will be referred to as POMS-Total.

In a similar manner, scores on the 11 SSS items at NADIR (trembling, pounding heart, flushed face, lightheaded, sweating, hungry, weak, headache, blurred vision, dizzy, and nauseous) were correlated and subjected to principal components analysis. These items were strongly intercorrelated, as shown in the correlation matrix (see Table 5). The principal components analysis yielded two factors, accounting for 59% and 11% of the variance,

Table 3

POMS Scale Intercorrelations

	Tension	Depression	Anger	Vigor	Fatigue
Tension	1.000				

Depression	.707	1.000			
	p=.000	--------			
Anger	.467	.570	1.000		
	p=.002	p=.000	--------		
Vigor	--.359	--.510	--.367	1.000	
	p=.017	p=.001	p=.015	--------	
Fatigue	.555	.484	.280	--.520	1.000
	p=.000	p=.002	p=.051	p=.001	--------
Confusion	.838	.694	.534	--.470	.698
	p=.000	p=.000	p=.000	p=.002	p=.000

Note. Figures based on N=35; scores at nadir.

Table 4

POMS Scale Principal Components Analysis

Factor	Eigenvalue	Percent of Variance
1	3.73205	62.2
2	.78350	13.1
3	.69512	11.6
4	.40550	6.8
5	.25684	4.3
6	.12699	2.1

Factor Matrix:

	Factor 1
Confusion	.91382
Tension	.85375
Depression	.84889
Fatigue	.75146
Anger	.66771
Vigor	-.66102

Note. Figures based on N=35; scores at nadir.

Table 5

SAS Item Intercorrelations

	SAS1	SAS2	SAS3	SAS4	SAS5	SAS6	SAS7	SAS8	SAS9	SAS10
1	1.000									

2	.709	1.000								
	p=.000	--------								
3	.670	.727	1.000							
	p=.000	.000	--------							
4	.691	.606	.515	1.000						
	p=.000	.000	.001	--------						
5	.510	.520	.670	.392	1.000					
	p=.001	.001	.000	.010	--------					
6	.325	.278	.193	.447	.198	1.000				
	p=.028	.053	.133	.004	.128	--------				
7	.735	.664	.519	.864	.439	.416	1.000			
	p=.000	.000	.001	.000	.004	.006	--------			
8	.531	.601	.530	.661	.418	.373	.565	1.000		
	p=.001	.000	.001	.000	.006	.014	.000	--------		
9	.365	.494	.621	.536	.421	.313	.432	.783	1.000	
	p=.016	.001	.000	.000	.006	.033	.005	.000	--------	
10	.604	.806	.655	.760	.482	.365	.777	.676	.575	1.000
	p=.000	.000	.000	.000	.002	.016	.000	.000	.000	--------
11	.391	.623	.705	.467	.641	.110	.470	.564	.607	.608
	p=.010	.000	.000	.002	.000	.264	.002	.000	.000	.000

Note. SAS1/1=trembling; SAS2/2=pounding heart; SAS3/3=flushed face; SAS4/4=lightheaded; SAS5/5=sweating; SAS6/6=hungry; SAS7/7=weak; SAS8/8=headache; SAS9/9=blurred vision; SAS10/10=dizzy; SAS11/11=nauseous

respectively. The data are factorially complex, however, with items often loading highly on both factors (see Table 6). This factorial complexity and the large percentage of variance accounted for by one factor suggest that these are one-factor data. Also, such factors may not be stable due to the small number of subjects for factor analysis. For these reasons, and the correlation matrix results, the SSS items were summed to provide a total somatic symptom score (SSS-Total).

Finally, the SST errors score was not used because it correlated highly with the SST time score (r = .473, p = .002), and showed very little variation (range of scores: 0 to 6 errors). This left four dependent measures to be used for the main analyses: POMS-Total, SSS-Total, SST-Time, and heart rate.

Sample

Blood sugar was manipulated via the procedures of the GTT, which cause blood glucose to rise, fall to nadir, and return to fasting level. The mean blood sugar levels over the course of the GTT are presented in Table 7. One subject could not complete the GTT as she had a migraine headache. Of the remaining 35 subjects, it was noted that not all exhibited the typical response to the GTT. In particular, 2 subjects had flat curves, 5 subjects had M-shaped curves, and 2 subjects had their peak blood sugar level at 2.5 hours (versus the usual 45 minutes). It was decided to exclude these 9 subjects from the analyses as the manipulation had not produced the expected changes in blood sugar level and, therefore, it was unclear whether or when symptoms could be expected to occur. A flat curve was defined as one in which the increase in blood sugar was less than 20 mg/dl, and the overall fluctuation in blood sugar was less than 30 mg/dl. An M-shaped

Table 6

SSS Item Principal Components Analysis

Factor	Eigenvalue	Percent of Variance
1	6.51681	59.2
2	1.22952	11.2
3	.91051	8.3
4	.66730	6.1
5	.43763	4.0
6	.41691	3.8
7	.27744	2.5
8	.22333	2.0
9	.13419	1.2
10	.10936	1.0
11	.07702	.7

Oblimin-Rotated Pattern Matrix:

	Factor 1	Factor 2
Nauseous	.94447	--.15149
Flushed face	.89183	.00637
Sweating	.82788	--.10580
Pounding heart	.65725	.32118
Blurred vision	.65477	.16908
Dizzy	.53537	.50412
Headache	.51985	.41665
Hungry	--.22312	.82449
Lightheaded	.26125	.76019
Weak	.27645	.73654
Trembling	.40592	.53183

Note. Figures based on N=35; scores at nadir.

Table 7

Means (Standard Deviations) for Blood Sugar Level

Group	Fasting	45min	2h	2.5h	3h	3.5h	4h	4.5h	5h
Original Sample (N=35)	85.8 (10.4)	148.0 (35.9)	113.7 (21.9)	98.2 (23.1)	82.2 (20.3)	74.3 (15.0)	71.8 (12.4)	74.0 (12.0)	74.2 (11.9)
Typical Response Sample (n=26)	87.1 (9.7)	159.8 (30.3)	117.8 (21.0)	100.0 (22.5)	79.0 (18.8)	71.3 (13.1)	69.0 (10.4)	71.9 (11.0)	73.7 (11.2)

Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
Original Sample (n=28)	111.3 (23.6)	82.4 (15.3)	61.5 (9.4)	72.3 (11.5)	76.9 (11.8)
Typical Response Sample (n=22)	114.2 (21.8)	81.7 (13.5)	59.3 (7.3)	69.4 (7.6)	73.6 (9.1)

Note. Mean blood sugar levels in mg/dl for original sample (i.e., entire sample tested) and typical response sample (i.e., sample after subjects with unexpected GTT curves removed). Top shows means across the nine sampling times of the GTT. Bottom shows means for 1 hour before nadir, 1/2 hour before nadir, nadir, 1/2 hour after nadir, and 1 hour after nadir.

curve was defined as one in which blood sugar increased more than 10 mg/dl after beginning to fall, and then fell again (i.e., there were two peaks and drops). The mean blood sugar levels for the 26 subjects for whom the manipulation was successful are also presented in Table 7. This curve has a higher peak and a lower nadir than the curve based on all 35 subjects.

As has been described, the main analyses were conducted across five time points; that is, at 1 hour before nadir (ONEBEF), 1/2 hour before nadir (HALFBEF), nadir (NADIR), 1/2 hour after nadir (HALFAFT), and 1 hour after nadir (ONEAFT). The mean blood sugar levels for these measurement points are shown in Table 7. Subjects' nadirs occurred between 2.5 and 5 hours after glucose ingestion: 4 subjects at 2.5 hours, 9 subjects at 3 hours, 7 subjects at 3.5 hours, 8 subjects at 4 hours, 1 subject at 4.5 hours, and 6 subjects at 5 hours. This resulted in a further reduction in sample size for the main analyses as 7 subjects had no data for HALFAFT and/or ONEAFT (due to their nadirs occurring at 4.5 or 5 hours). Thus, the main analyses were based on the 22 subjects for whom the manipulation was successful and for whom there were data available for all 5 measurement points. (It should also be noted that ONEBEF actually represents 1.75 hours before nadir for those subjects with nadir at 2.5 hours).

Tests of the Primary Hypothesis

A multivariate approach was taken to the analyses of this study. All MANOVAs reported utilized the Wilk's Lambda test statistic with the standard F-approximation. Significant MANOVAs were further analyzed via ANOVAs to determine which dependent measures showed significant changes. All such ANOVAs were conducted with Bonferroni-corrected probability levels to decrease the chance of Type I error (i.e., .05 divided by the number of

dependent measures). Finally, multiple comparisons were conducted on the significant repeated measures ANOVAs (via the Tukey HSD method, .01 level of significance) to determine which levels of the independent variable the symptoms were significantly different between.

The main hypothesis of this study is that lowered blood sugar levels will be associated with impaired cognitive performance, adverse emotional changes, and somatic symptoms. To test this hypothesis, a repeated measures MANOVA was conducted on the four dependent measures (POMS-Total, SSS-Total, SST-Time, heart rate) across the five measurement points (ONEBEF, HALFBEF, NADIR, HALFAFT, ONEAFT). This MANOVA was significant ($F(16, 235.88) = 4.39$, $p<.0001$), therefore, repeated measures ANOVAs were conducted (with corrected probability levels of .0125). The means for the four dependent variables are presented in Table 8. The effect for POMS-Total was significant ($F(4, 80) = 7.85$, $p<.0001$), with subjects reporting significantly more mood disturbance at HALFAFT than at ONEBEF or HALFBEF. The SSS-Total effect was also significant ($F(4, 80) = 9.03$, $p<.0001$). Subjects reported significantly more somatic symptoms at NADIR, HALFAFT, and ONEAFT than at ONEBEF; only symptoms at HALFAFT were significantly greater than those at HALFBEF. Thus, for both POMS-Total and SSS-Total, scores were highest half an hour after nadir.

The ANOVA for SST-Time was significant ($F(4, 80) = 3.42$, $p<.0125$); however, none of the multiple comparisons reached significance. It is informative to compare the pattern of SST-time means in Table 8 with that of the pilot subjects tested for this study (see Table 9). Similarly, it is useful to compare the pattern in Table 8 with the first five trials (two practice trials, fasting, 45 minutes, 2 hours) of subjects in the present study

Table 8

Means (Standard Deviations) for POMS-Total, SSS-Total, SST-Time, and Heart Rate Across Five Measurement Points

Measure	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	16.27 (36.17)	18.55 (33.21)	29.55 (33.88)	34.27 (39.64)	31.23 (37.05)
SSS-Total	16.46 (18.00)	19.18 (17.90)	26.59 (19.73)	29.59 (22.77)	27.45 (21.24)
SST-Time	52.86 (16.56)	51.50 (17.33)	60.27 (24.95)	57.96 (25.57)	52.09 (20.39)
Heart rate	65.40 (8.36)	63.29 (8.50)	63.97 (9.60)	61.28 (7.75)	62.03 (8.09)

Note. Figures based on n=21.

Table 9

Comparison SST-Time Means (Standard Deviations)

Time	Pilot Subjects (n=15)	Time	Present Sample (N=35)
1	50.07 (21.24)	Practice 1	71.94 (36.31)
2	43.93 (17.88)	Practice 2	66.65 (26.74)
3	40.20 (17.23)	Fasting	61.91 (29.72)
4	40.33 (15.14)	45min	57.91 (23.49)
5	36.67 (13.59)	2h	57.41 (22.07)
6	36.13 (13.48)	2.5h	55.38 (20.95)
		3h	57.35 (20.93)
		3.5h	59.56 (28.44)
		4h	60.09 (26.46)
		4.5h	62.68 (34.71)
		5h	56.50 (27.20)

Note. Mean SST-Time performance in seconds of pilot and present subjects with scores arranged by order of trials. Compare with SST-Time means in Table 8, where scores are arranged by time of nadir.

(i.e., before any subject had reached nadir; see Table 9). The pilot subjects and the present subjects (when scores were analyzed by time of testing) showed an improvement in performance across trials. Conversely, when scores were analyzed on the basis of blood sugar response (i.e., by time of nadir), the present subjects showed a deterioration in performance at nadir.

Finally, the ANOVA for heart rate was also significant ($F(4, 80) = 10.00$, $p<.0001$). Multiple comparisons showed heart rate at HALFAFT and ONEAFT to be significantly less than at ONEBEF. Also, heart rate at HALFAFT was significantly less than that at NADIR.

In order to get a preliminary idea of which symptoms were the most affected by the GTT, repeated measures MANOVAs were conducted on the 6 POMS scales and the 11 SSS items. The MANOVA on the POMS was significant ($F(24, 276.81) = 1.88$, $p<.01$). Subsequent ANOVAs (corrected probability .0083) were significant for tension ($F(4, 84) = 8.98$, $p<.0001$) and confusion ($F(4, 84) = 4.93$, $p<.002$) (see Table 10). Multiple comparisons indicated that subjects reported significantly more tension at HALFAFT and ONEAFT than at ONEBEF, while only tension at HALFAFT was reported significantly more than at HALFBEF. No comparisons were significant for confusion. The MANOVA on the SSS was also significant ($F(44, 285.06) = 2.35$, $p<.0001$). The ANOVAs, with corrected probability levels of .0045, showed significant effects for trembling ($F(4, 84) = 13.94$, $p<.0001$), pounding heart ($F(4, 84) = 4.19$, $p<.004$), hungry ($F(4, 84) = 22.01$, $p<.0001$), and weak ($F(4, 84) = 5.82$, $p<.0004$). Means for these effects are presented in Table 11. Subjects reported significantly more trembling at HALFAFT and ONEAFT than at ONEBEF and HALFBEF; significantly more pounding heart at HALFAFT than at ONEBEF and HALFBEF; and significantly more weakness

Table 10

Effects for 6 POMS Scales

Scale	Means (Standard Deviations)				
	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
Tension (p<.0001)	3.73 (5.27)	3.82 (5.26)	6.86 (7.15)	9.46 (8.85)	7.77 (7.84)
Depression (p=.2158)	6.05 (9.08)	6.05 (7.54)	7.18 (8.25)	8.18 (9.74)	7.14 (8.62)
Anger (p=.1568)	2.91 (7.39)	3.05 (6.46)	3.73 (5.69)	4.23 (6.06)	4.68 (7.95)
Vigor (p=.0202)	11.18 (7.03)	10.86 (6.83)	8.41 (5.69)	8.36 (6.57)	8.46 (5.47)
Confusion (p<.002)	4.68 (5.83)	4.82 (6.01)	7.09 (6.57)	7.32 (6.54)	6.73 (6.20)
Fatigue (p=.0107)	10.09 (8.14)	11.68 (8.01)	13.09 (8.16)	13.45 (8.29)	13.18 (8.49)

Note. Figures based on n=22. ANOVA probability reported in brackets beneath scale names.

Table 11

Effects for 11 SSS Items

Item	Means (Standard Deviations)				
	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
Trembling (p<.0001)	0.64 (1.09)	0.86 (1.64)	2.09 (2.16)	3.36 (2.90)	2.50 (2.41)
Pounding heart (p<.004)	0.55 (1.10)	0.59 (1.01)	0.91 (1.11)	1.36 (2.11)	0.95 (1.53)
Flushed face (p=.0053)	0.45 (1.14)	0.50 (1.34)	1.23 (1.80)	1.55 (2.44)	1.32 (2.32)
Lightheaded (p=.1235)	2.41 (2.84)	2.64 (2.74)	3.32 (2.93)	3.14 (2.80)	2.96 (2.55)
Sweating (p=.0067)	0.45 (1.14)	0.55 (1.50)	1.36 (2.32)	1.96 (2.92)	1.32 (2.46)
Hungry (p<.0001)	3.00 (2.62)	4.36 (2.80)	5.50 (3.07)	6.05 (3.12)	6.00 (2.99)
Weak (p<.0004)	2.59 (2.68)	2.91 (2.78)	3.91 (2.83)	4.05 (2.72)	3.91 (2.72)
Headache (p=.0628)	2.05 (2.66)	2.18 (2.68)	2.55 (2.79)	2.41 (2.67)	3.00 (2.81)
Blurred vision (p=.8730)	1.27 (2.25)	1.27 (2.25)	1.36 (1.89)	1.32 (1.84)	1.55 (1.99)
Dizzy (p=.1090)	1.68 (2.40)	1.96 (2.48)	2.46 (2.67)	2.59 (2.74)	2.32 (2.53)
Nauseous (p=.2522)	1.36 (1.79)	1.36 (1.94)	1.91 (2.35)	1.82 (2.22)	1.64 (2.28)

Note. Figures based on n=22. ANOVA probability reported in brackets beneath item names.

at HALFAFT than at ONEBEF. Thus, for these three symptoms, subjects reported higher levels half an hour or an hour after nadir than an hour or half an hour before nadir. For hunger, a slightly different trend was apparent. Subjects did report significantly more hunger at HALFAFT and ONEAFT than at HALFBEF, but they also reported significantly less hunger at ONEBEF than at any of the four other measurement points.

Tests of the Subsidiary Hypotheses

The subsidiary hypotheses of this study are that the cognitive impairment, adverse emotional changes, and somatic symptoms will be greater: (a) the greater the magnitude of the drop in blood sugar; (b) the more rapid the decrease in blood sugar; (c) the greater the drop in blood sugar from fasting level; (d) the lower the absolute level of blood sugar; and (e) the higher the hypoglycemic index score. Subjects received a score for each of these five predictor variables. The variables will be labeled MAGNITUDE, SPEED, DROPFASTING, LOWPOINT, AND INDEX. Table 12 shows the correlations among the five predictors.

For the purpose of these analyses, subjects were divided into high and low scoring groups for each of the predictor variables. That is, the 11 subjects with the highest scores on a predictor variable would constitute one group, while the 11 subjects with the lowest scores would comprise another group. Subjects in the high MAGNITUDE group had magnitudes of drops ranging from 101 to 168 mg/dl ($\underline{M}$ = 123 mg/dl), while those in the low MAGNITUDE group had magnitudes ranging from 45 to 89 mg/dl ($\underline{M}$ = 75 mg/dl). High SPEED subjects had rates of drops in blood sugar between 35.6 and 73.1 mg/h ($\underline{M}$ = 48.7 mg/h); low SPEED subjects' rates were between 21.2 and 34.7 mg/h ($\underline{M}$ = 30.3 mg/h). For DROPFASTING, subjects

Table 12

Correlations Between Predictor Variables

	MAGN	SPEED	DROP	LOW	INDEX
MAGNITUDE	1.000				

SPEED	.595	1.000			
	p=.001	--------			
DROPFASTING	.464	.424	1.000		
	p=.008	p=.016	--------		
LOWPOINT	--.090	--.038	--.256	1.000	
	p=.332	p=.427	p=.103	--------	
INDEX	.303	.768	.333	--.399	1.000
	p=.066	p=.000	p=.048	p=.022	--------

Note. Figures based on n=26. MAGNITUDE = magnitude of decrease in blood sugar. SPEED = rate of decrease in blood sugar. DROPFASTING = size of decrease from fasting blood sugar level. LOWPOINT = glucose nadir. INDEX = hypoglycemic index score.

in the high group experienced drops below fasting of 29 to 45 mg/dl (M = 35 mg/dl), while subjects in the low group experienced drops of 10 to 27 mg/dl (M = 22 mg/dl). On the LOWPOINT variable, high subjects had nadirs ranging from 61 to 75 mg/dl (M = 65 mg/dl), while low subjects had nadirs ranging from 48 to 60 mg/dl (M = 53 mg/dl). Finally, subjects in the high INDEX group had index scores between 1.14 and 2.10 (M = 1.44); subjects in the low INDEX group had scores between 0.61 and 1.06 (M = 0.84).

To test the subsidiary hypotheses, the data were analyzed in three ways: (1) 2 x 5 between-within MANOVAs were conducted; (2) Hotelling's tests were computed on residual gain symptom scores; and (3) bivariate correlations were calculated between residual gain symptom scores and predictor variable scores.

The main analyses of the subsidiary hypotheses were conducted via 2 x 5 between-within MANOVAs in which the high and low predictor variable groups formed the two levels of the between-group factor, and the measurement points (ONEBEF, HALFBEF, NADIR, HALFAFT, ONEAFT) formed the five levels of the within-group factor. The interaction between group membership and measurement point was of interest. For the analysis of INDEX, this interaction was significant ($F(16, 223.66) = 2.29$, $p<.005$). Subsequent ANOVAs (corrected probability .0125) were significant for POMS-Total ($F(4, 76) = 4.14$, $p<.005$), SSS-Total ($F(4, 76) = 5.40$, $p<.0008$), and SST-Time ($F(4, 76) = 4.97$, $p<.002$), but not for heart rate ($F(4, 76) = 1.00$, $p = .4131$). The means for these effects are shown in Table 13. Multiple comparisons showed that POMS-Total scores were significantly higher at NADIR, HALFAFT, and ONEAFT than at ONEBEF for the high INDEX group. Similarly, for this group, subjects reported more mood

Table 13

High versus Low INDEX Group Means (Standard Deviations)

Variable	INDEX Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	High	25.90	30.50	49.10	59.40	49.80
		(19.27)	(19.35)	(25.27)	(27.62)	(25.11)
	Low	10.09	7.09	10.82	14.64	18.55
		(46.89)	(41.08)	(32.51)	(37.87)	(39.75)
SSS-Total	High	14.90	19.40	33.20	37.60	34.10
		(8.80)	(11.89)	(18.88)	(20.35)	(19.23)
	Low	19.00	19.73	21.09	23.91	22.91
		(24.20)	(23.21)	(20.40)	(24.19)	(22.81)
SST-Time	High	56.70	57.40	76.10	72.00	62.40
		(18.94)	(20.10)	(27.43)	(27.94)	(24.75)
	Low	50.45	47.27	47.64	47.55	42.91
		(14.76)	(14.04)	(12.90)	(16.92)	(11.05)
Heart rate	High	66.46	63.68	64.58	60.86	62.55
		(8.43)	(7.55)	(10.17)	(7.82)	(7.71)
	Low	64.44	62.93	63.41	61.65	61.55
		(8.59)	(9.64)	(9.51)	(8.04)	(8.76)

Note. Figures based on n=21; 10 subjects with high hypoglcemic index scores and 11 subjects with low hypoglycemic index scores. INDEX = hypoglycemic index score.

disturbance at HALFAFT and ONEAFT than at HALFBEF. No comparisons were significant for the low INDEX group. On the SSS-Total, high INDEX subjects reported significantly more symptoms at NADIR, HALFAFT, and ONEAFT than at ONEBEF and HALFBEF. Again, no comparisons were significant for the low INDEX group. Finally, high INDEX subjects' performance on the SST was significantly poorer at NADIR and HALFAFT than at ONEBEF and HALFBEF. There were no significant comparisons for the low INDEX group.

The interaction between group and measurement point was also significant for SPEED ($F(16, 223.66) = 1.78$, $p<.05$). Subsequent ANOVAs were significant for SST-Time ($F(4, 76) = 5.79$, $p<.0005$), but not for POMS-Total ($F(4, 76) = 2.35$, $p = .0617$), SSS-Total ($F(4, 76) = 2.20$, $p = .0772$), or heart rate ($F(4, 76) = 0.49$, $p = .7401$). Means for these effects are presented in Table 14. Multiple comparisons for SST-Time indicated that high SPEED subjects took longer to do the SST at NADIR and HALFAFT than at ONEBEF and HALFBEF. Performance was also poorer at NADIR than at ONEAFT. No comparisons were significant for the low SPEED group.

The interaction effects for MAGNITUDE ($F(16, 223.66) = 1.07$, $p = .3898$), DROPFASTING ($F(16, 223.66) = 1.28$, $p = .2133$), and LOWPOINT ($F(16, 223.66) = 0.71$, $p = .7846$) were not significant. The means for these effects are presented in Tables 15, 16, and 17.

The between-within analyses indicate whether one group has significant changes on the dependent measure while the other group does not; however, these analyses do not indicate whether the changes themselves are significantly greater in one group than the other. For this reason,

Table 14

High versus Low SPEED Group Means (Standard Deviations)

Variable	SPEED Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	High	20.80	24.10	42.20	50.30	42.20
		(25.36)	(26.34)	(34.10)	(35.88)	(30.33)
	Low	14.73	12.91	17.09	22.91	25.45
		(45.46)	(40.27)	(31.97)	(40.23)	(41.04)
SSS-Total	High	10.70	14.30	27.40	29.60	25.90
		(7.24)	(9.06)	(21.02)	(18.52)	(15.02)
	Low	22.82	24.36	26.36	31.18	30.36
		(23.23)	(23.22)	(20.38)	(27.32)	(26.56)
SST-Time	High	53.60	54.50	74.00	68.60	56.00
		(10.71)	(8.84)	(20.70)	(19.08)	(9.45)
	Low	53.27	49.91	49.55	50.64	48.73
		(21.40)	(23.09)	(23.86)	(28.38)	(27.64)
Heart rate	High	63.31	60.49	61.50	58.74	60.20
		(9.49)	(9.40)	(11.20)	(8.80)	(9.79)
	Low	67.30	65.83	66.21	63.58	63.69
		(7.11)	(7.08)	(7.73)	(6.17)	(6.18)

Note. Figures based on n=21; 10 subjects with high speed of drop in blood sugar and 11 subjects with low speed of drop in blood sugar. SPEED = rate of decrease in blood sugar.

Table 15

High versus Low MAGNITUDE Group Means (Standard Deviations)

Variable	MAGNITUDE Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	High	17.40	20.40	39.20	42.20	37.80
		(21.45)	(25.03)	(32.45)	(37.81)	(31.61)
	Low	17.82	16.27	19.82	30.27	29.45
		(47.43)	(41.70)	(35.42)	(42.53)	(41.51)
SSS-Total	High	13.10	15.60	28.50	28.70	27.70
		(8.40)	(10.50)	(21.16)	(18.11)	(14.60)
	Low	20.64	23.18	25.36	32.00	28.73
		(23.89)	(23.16)	(20.15)	(27.48)	(26.95)
SST-Time	High	51.10	50.60	66.60	61.20	50.80
		(14.98)	(15.71)	(24.36)	(26.22)	(15.29)
	Low	55.55	53.45	56.27	57.36	53.45
		(18.67)	(19.70)	(26.04)	(26.00)	(25.66)
Heart rate	High	63.98	61.06	61.93	59.88	61.14
		(10.54)	(9.88)	(11.94)	(9.26)	(10.09)
	Low	66.69	65.31	65.82	62.55	62.84
		(6.01)	(6.87)	(6.92)	(6.25)	(6.13)

Note. Figures based on n=21; 10 subjects with high magitude of decrease in blood sugar and 11 subjects with low magnitude of decrease in blood sugar. MAGNITUDE = magnitude of decrease in blood sugar.

Table 16

High versus Low DROPFASTING Group Means (Standard Deviations)

Variable	DROPFASTING Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	High	34.67	38.89	47.67	63.00	62.67
		(42.39)	(34.51)	(30.99)	(36.83)	(34.27)
	Low	4.82	2.75	15.08	15.67	11.50
		(26.44)	(24.99)	(31.40)	(29.12)	(18.42)
SSS-Total	High	23.11	28.44	35.56	42.22	43.00
		(22.03)	(20.57)	(18.67)	(24.73)	(23.56)
	Low	12.50	12.92	20.33	21.58	17.17
		(14.07)	(13.60)	(19.44)	(17.79)	(10.93)
SST-Time	High	57.33	54.67	70.56	69.89	60.00
		(20.33)	(22.32)	(31.23)	(32.51)	(27.67)
	Low	50.50	50.17	54.17	51.17	46.33
		(13.69)	(13.67)	(17.83)	(15.84)	(12.21)
Heart rate	High	67.52	65.18	67.00	63.00	63.88
		(8.46)	(7.48)	(8.86)	(7.18)	(7.84)
	Low	63.81	61.87	61.69	59.98	60.64
		(8.29)	(9.26)	(9.85)	(8.21)	(8.32)

Note. Figures based on n=21; 9 subjects with high drop from fasting blood sugar level and 12 subjects with low drop from fasting blood sugar level. DROPFASTING = size of decrease from fasting blood sugar level.

Table 17

High versus Low LOWPOINT Group Means (Standard Deviations)

Variable	LOWPOINT Group	ONEBEF	HALFBEF	NADIR	HALFAFT	ONEAFT
POMS-Total	High	19.55	16.27	26.73	33.36	31.55
		(44.01)	(37.78)	(38.61)	(40.35)	(39.92)
	Low	15.50	20.40	31.60	38.80	35.50
		(28.26)	(31.18)	(31.55)	(41.18)	(34.28
SSS-Total	High	17.27	19.09	25.82	28.18	26.36
		(24.10)	(22.70)	(23.74)	(24.53)	(22.19)
	Low	16.80	20.10	28.00	32.90	30.30
		(9.60)	(12.92)	(16.59)	(22.18)	(21.56)
SST-Time	High	57.09	55.09	59.09	59.82	52.09
		(13.01)	(10.45)	(19.97)	(19.34)	(9.95)
	Low	49.40	48.80	63.50	58.50	52.30
		(20.02)	(23.20)	(30.89)	(32.09)	(29.31)
Heart rate	High	63.30	61.20	62.15	60.15	61.19
		(9.43)	(9.33)	(10.83)	(8.33)	(9.23)
	Low	67.71	65.58	65.96	62.52	62.95
		(6.74)	(7.27)	(8.12)	(7.28)	(6.99)

Note. Figures based on n=21; 11 subjects with high nadirs and 10 subjects with low nadirs. LOWPOINT = glucose nadir (lowest level of blood sugar reached).

Hotelling's tests were conducted on residual gain symptom scores. A dependent measure at NADIR was regressed on the same dependent measure at ONEBEF. The score that would be predicted at nadir (from the ONEBEF score) was then computed. The residual symptom score was computed as the difference between the NADIR score and the predicted nadir score (NADIR minus predicted nadir). Thus, a positive residual score indicates that a subject experienced more symptoms at NADIR than would be predicted from the subject's score at ONEBEF. Conversely, a negative residual score indicates that less symptoms were reported at NADIR than would be predicted from symptoms at ONEBEF. Another advantage of using such symptoms scores is that they have no correlation with the subjects' baseline symptom magnitude (i.e., symptoms at ONEBEF), whereas raw gain scores do show such correlation.

The Hotelling's test for INDEX was significant ($F(4, 16) = 3.51$, $p<.05$). Subsequent t-tests (corrected probability .0125) were significant for POMS-Total ($t(19) = 13.45$, $p<.002$), and SST-Time ($t(19) = 7.86$, $p<.0125$), but not for SSS-Total ($t(19) = 6.72$, $p = .0179$) or heart rate ($t(19) = 0.38$, $p = .546$). The means are shown in Table 18. As can be seen, the significant effects are such that subjects in the high INDEX group show a gain in symptoms at NADIR, whereas the subjects in the low INDEX group do not.

The Hotelling's tests for SPEED ($F(4, 16) = 2.73$, $p = .0659$), MAGNITUDE ($F(4, 16) = 1.75$, $p = .1893$), DROPFASTING ($F(4, 16) = 0.62$, $p = .6522$), and LOWPOINT ($F(4, 16) = 0.56$, $p = .6973$) were not significant. The means are shown in Table 19. It should be noted that for each of these predictor variables, the subjects with the most abnormal blood sugar response (i.e., high SPEED, high MAGNITUDE, high DROPFASTING, low

Table 18

Residual Gain Means (Standard Deviations) for INDEX Groups

Variable	INDEX Group	
	High (n=10)	Low (n=11)
POMS-Total	12.18 (14.88)	--13.73 (17.25)
SSS-Total	7.77 (17.18)	--7.55 (9.05)
SST-Time	10.15 (19.13)	--11.47 (16.20)
Heart rate	--1.44 (3.21)	--0.58 (3.21)

Note. Figures based on n=21. INDEX = hypoglycemic index score.

Table 19

Residual Gain Means (Standard Deviations) for Predictor Groups

Variable	Group			
	High SPEED (n=10)	Low SPEED (n=11)	High MAGNITUDE (n=10)	Low MAGNITUDE (n=11)
POMS-Total	9.27 (17.92)	--11.08 (18.51)	8.94 (18.28)	--10.78 (18.56)
SSS-Total	5.26 (18.41)	--5.26 (10.36)	4.48 (19.22)	--4.56 (9.76)
SST-Time	11.45 (20.59)	--12.65 (12.29)	6.79 (20.89)	--8.41 (17.98)
Heart rate	--1.36 (3.20)	--0.66 (3.24)	--1.60 (3.14)	--0.44 (3.22)
	High DROPFASTING (n=9)	Low DROPFAST (n=12)	High LOWPOINT (n=11)	Low LOWPOINT (n=10)
POMS-Total	3.89 (20.08)	--5.35 (20.94)	--5.22 (24.03)	2.82 (16.24)
SSS-Total	3.70 (11.66)	--3.22 (17.50)	--1.47 (17.54)	1.09 (13.31)
SST-Time	3.92 (22.21)	--4.99 (19.11)	--7.28 (21.83)	5.55 (17.46)
Heart rate	--0.09 (3.48)	--1.67 (2.86)	--0.69 (2.97)	--1.32 (3.49)

Note. Figures based on n=21. SPEED = rate of decrease in blood sugar. MAGNITUDE = magnitude of decrease in blood sugar. DROPFASTING = size of decrease from fasting blood sugar level. LOWPOINT = glucose nadir.

LOWPOINT) exhibit positive residual POMS-Total, SSS-Total, and SST-Time scores, whereas the other subjects exhibit negative residual scores. That is, subjects with the most abnormal GTT responses report more symptoms than would be predicted from their baseline, whereas subjects with more normal GTT responses report less symptoms than would be predicted from baseline.

The final approach to analyzing the subsidiary hypotheses was to calculate bivariate correlations between the residual gain symptom scores and the predictor variable scores. These correlations were not computed for the residual heart rate scores as heart rate was not significant in any of the analyses. Table 20 shows the correlations, which are highest for INDEX, SPEED, and MAGNITUDE (range $\underline{r}$ = .371 to $\underline{r}$ =.682). Conversely, the correlations for DROPFASTING and LOWPOINT range in absolute value from $\underline{r}$ =.075 to $\underline{r}$ = .360.

Additional Analyses

Hotelling's tests were also conducted on five other grouping variables of peripheral interest: age, weight, gender, diagnosis, and family history of diabetes (DIABFAM). For the age grouping, subjects were divided into the 11 oldest (range 33 to 66 years; $\underline{M}$ = 39.6) and youngest (range 24 to 31 years; $\underline{M}$ = 27.6). Similarly, for the weight grouping, subjects were split into the 10 with weights the greatest percent above ideal body weight (range -1% to 22%; $\underline{M}$ = 5.3%), and the 12 with weights the least percent above ideal (range -2% to -16%; $\underline{M}$ = -7.4%). There were 9 men and 13 women; 13 subjects who had received diagnoses of hypoglycemia in the past and 9 subjects who had not; and 7 subjects who knew of a family history of diabetes and 15 subjects who did not. The Hotelling's tests for age ($\underline{F}$(4, 16) = 0.37, $\underline{p}$ = .8279), weight ($\underline{F}$(4, 16) = 2.55, $\underline{p}$ = .0792), gender ($\underline{F}$(4, 16)

Table 20

Correlations Between Residuals and Predictor Variables

Predictor Variable	Residual Gain Score		
	POMS-Total	SSS-Total	SST-Time
INDEX	.529 p=.006	.371 p=.045	.413 p=.028
SPEED	.499 p=.009	.464 p=.015	.551 p=.004
MAGNITUDE	.682 p=.000	.452 p=.017	.549 p=.004
DROPFASTING	.142 p=.264	.172 p=.222	.166 p=.230
LOWPOINT	--.360 p=.050	--.243 p=.138	--.075 p=.371

Note. Figures based on n=22. INDEX = hypoglycemic index score. SPEED = rate of decrease in blood sugar. MAGNITUDE = magnitude of decrease in blood sugar. DROPFASTING = size of decrease from fasting blood sugar level. LOWPOINT = glucose nadir.

= 0.28, p = .8884), diagnosis (F(4, 16) = 0.55, p = .7028), and DIABFAM (F(4, 16) = 0.37, p = .8282) were all insignificant. The mean residual gain scores are presented in Tables 21 and 22.

Final Summary

The results can be summarized as follows. The subjects reported more mood disturbance half an hour after glucose nadir than half an hour or an hour before nadir. Somatic symptoms were higher half an hour after nadir than half an hour before nadir. Thus, for both the POMS and the SSS, less symptomatology was reported before nadir than after nadir, with the peak symptomatology being reported half an hour after nadir.

The mood symptoms most affected by the GTT were tension and confusion. More tension was reported half an hour and an hour after nadir than an hour before nadir, and more tension was reported half an hour after nadir than half an hour before nadir. The somatic symptoms most affected during the GTT were trembling, pounding heart, weakness, and hunger. For all of these symptoms, subjects reported higher levels after nadir than before nadir. For hunger, subjects also reported less hunger an hour before nadir than at any other measurement point.

Performance on the SST was impaired at nadir. This is in contrast to the usual pattern seen with sequential SST testing, in which subjects' performance is worst at Time 1 and gradually improves with subsequent trials. Heart rate was higher an hour before nadir than half an hour or an hour after nadir, and higher at nadir than half an hour after nadir.

The above results are for the sample of subjects as a whole. Dividing the subjects into groups on the basis of their blood sugar responses revealed

Table 21

Residual Gain Means (Standard Deviations) for Age, Weight, and Gender

	Group			
Variable	Old Age (n=10)	Young Age (n=11)	High Weight (n=10)	Low Weight (n=11)
POMS-Total	0.85 (15.93)	--3.43 (24.71)	--9.90 (15.64)	6.35 (22.14)
SSS-Total	0.41 (19.34)	--0.85 (11.54)	--5.29 (11.36)	4.32 (17.49)
SST-Time	3.09 (19.32)	--5.05 (21.59)	1.36 (20.99)	--3.48 (20.69)
Heart rate	--1.64 (1.78)	--0.40 (4.04)	--0.95 (2.31)	--1.03 (3.90)

	Female Gender (n=12)	Male Gender (n=9)
POMS-Total	--2.39 (20.97)	--0.05 (21.27)
SSS-Total	--2.36 (11.96)	2.56 (19.39)
SST-Time	--3.41 (19.34)	1.81 (22.68)
Heart rate	--0.78 (3.44)	--1.28 (2.92)

Note. Figures based on n=21.

Table 22

Residual Gain Means (Standard Deviations) for Diagnosis and DIABFAM

Variable	Group			
	Yes Diagnosis (n=12)	No Diagnosis (n=9)	Yes DIABFAM (n=7)	No DIABFAM (n=14)
POMS-Total	--6.31 (17.89)	5.17 (23.15)	--9.34 (15.66)	2.58 (22.10)
SSS-Total	--2.85 (12.10)	3.21 (19.06)	--5.32 (9.24)	2.28 (17.37)
SST-Time	--1.70 (19.86)	--0.48 (22.43)	--7.49 (21.16)	1.99 (20.12)
Heart rate	--0.86 (2.88)	--1.17 (3.67)	--0.89 (2.80)	--1.05 (3.43)

Note. Figures based on n=21. Diagnosis = whether received diagnosis of hypoglycemia in the past. DIABFAM = whether know of a family history of diabetes.

that the effects described were strong, or present, for only a subsample of the subjects.

Subjects with high hypoglycemic index scores reported more mood disturbance and somatic symptoms after glucose nadir than before nadir, whereas there were no significant differences in mood or somatic symptoms for subjects with low index scores. On the SST, high INDEX subjects' performance was worse at nadir and half an hour after nadir than it was an hour or half an hour before nadir. No differences in performance were found for the low INDEX group. The interaction between group and measurement point was not significant for heart rate.

Subjects exhibiting a fast drop in blood sugar took longer to complete the SST at nadir and half an hour after nadir than an hour or half an hour before nadir. Performance was also worse at nadir than an hour after nadir. There were no differences in SST performance for subjects with a slow drop in blood sugar. The interaction effects for the POMS, SSS, and heart rate were not significant for speed of fall in blood sugar.

Dividing subjects by magnitude of fall in blood sugar, drop from fasting blood sugar level, or lowest blood sugar level reached, did not result in significant interaction effects.

Subjects with high index scores showed a greater increase in mood disturbance at nadir than subjects with low indices did. Similarly, the high INDEX subjects showed a greater increase in time to complete the SST at nadir than did low INDEX subjects. Comparisons of these residual gain scores were not significant for any of the other dependent measures or predictor variable groups. However, for the POMS, SSS, and SST, subjects with the more abnormal blood sugar response showed positive residual scores,

whereas the subjects with the more normal blood sugar response showed negative residual scores. Thus, subjects with high index scores, rapid speed of fall in blood sugar, large magnitude of drop in blood sugar, large drop below fasting blood sugar level, and low glucose nadirs, all showed more symptomatology at nadir than would be expected from baseline symptom level. Conversely, subjects with low index scores, slow speeds of fall, small magnitudes of drop, small drops below fasting, and high glucose nadirs, all exhibited less symptomatology at glucose nadir than would be predicted from baseline scores.

Index scores, speed of fall, and magnitude of drop were all moderately correlated with symptom gain at nadir. Drop below fasting and lowest blood sugar level reached showed much lower correlations with symptom gain.

Finally, no difference was found in symptomatology at nadir with respect to age, weight, gender, past diagnosis of hypoglycemia, or family history of diabetes.

Discussion

In general, the hypotheses were supported. However, the hypotheses, as stated, were too broad and are in need of refinement. Additional findings to be discussed include: (1) the lack of differences in symptoms between subjects divided on the basis of age, weight, gender, diagnosis, or family history of diabetes; (2) the unexpected variety of GTT curves found; (3) the lack of concordance between absolute values of blood sugar found with different glucose analysis instruments; and (4) the structure and sensitivity of the POMS and SSS. Weaknesses of the present study will be delineated, and methods to overcome these shortcomings will be suggested. Similarly, questions for future research arising from the results, and possible ways of testing these, will be described. Finally, recommendations for clinicians and hypoglycemic patients will be made.

Support for Hypotheses

Primary Hypothesis. The first hypothesis -- that lowered blood sugar levels are associated with impaired cognitive performance, adverse emotional changes, and somatic symptoms -- was supported. Subjects reported greater mood disturbance and more bodily symptoms half an hour after glucose nadir than an hour or half an hour before nadir. It is of interest to note that these symptoms were highest, not at nadir, but half an hour after nadir. This is congruent with the idea that symptoms may be caused by the release of epinephrine, a counterregulatory response to insulin (e.g., Berger, 1975; Hofeldt et al., 1972). When blood sugar is high, insulin is released to decrease the blood sugar level. When blood sugar becomes too low, epinephrine is released (along with glucagon, growth hormone, and cortisol) to suppress the insulin secretion, thus allowing blood sugar homeostasis to

be restored (Corenblum & Volpe, 1983). Within this model, it would be reasonable to expect a peak in symptoms half an hour after nadir, when blood sugar is slightly higher than at nadir. The counterregulatory epinephrine could be causing both an increase in symptoms and an increase in blood sugar level. (This possibility could be tested by giving subjects an epinephrine blocker.) The fact that some subjects report their highest symptoms at nadir could be accounted for by the half hour blood sampling intervals. Without continuous blood sampling, one does not know when a subject's true nadir occurs. It could be that subjects who report peak mood disturbance and somatic symptoms at nadir, experienced their lowest level of blood sugar sometime between their last blood sample and the sample of observed nadir.

Subjects' cognitive performance, as measured by the SST, was impaired at nadir. Whereas subjects normally show steady improvement with practice on this mental arithmetic task, lowered blood sugar levels were associated with longer times to complete the 14 subtractions. In contrast to the peak mood disturbance and somatic symptoms half an hour after nadir, this effect was greatest at nadir. This suggests that different mechanisms may be responsible for the different symptoms. Hale et al. (1982) suggested that impairments in SST performance reflect a neuroglycopenic symptom -- one caused by deficient glucose for nerve cell metabolism. Perhaps symptoms of neuroglycopenia would occur when blood sugar was lowest, rather than after glucose had begun to rise again. At present, however, any discussion of postulated causes of symptoms is speculative. The mean differences between any of the symptoms at nadir

and half an hour after nadir were small and require replication. Direct tests of these etiological hypotheses are needed.

The only result that failed to support the main hypothesis was the absence of elevated heart rate during lowered blood sugar levels. Heart rate was lower half an hour and an hour after nadir, than an hour before nadir, and was lower half an hour after nadir than at nadir. As can be seen in Table 8, heart rate fluctuated greatly, showing no apparent trend. And whereas the other dependent variables showed clearer effects when subjects were divided on the basis of blood sugar response parameters, heart rate did not reach significance in any of these predictor group comparisons.

It should not be concluded from this negative finding that lowered blood sugar levels are not associated with increased heart rate. The conditions of the experiment were inconsistent and may have prevented such an effect from being observed. The experiment was conducted in a room at the Diabetes Specialty Centre. At times during the GTT, this room was unoccupied, but at other times, nurses and patients were coming in and out. The noise level varied, as did the subjects' ability to relax while heart rate was being recorded. When no one but the experimenter was present, most subjects closed their eyes and attempted to relax. Conversely, when others were present, a lot of subjects became distracted or nervous, opened their eyes, and watched and listened to what was going on around them. Heart rate fluctuated under these different conditions. Therefore, heart rate should be tested in future under more standardized conditions.

Subsidiary Hypotheses. The subsidiary hypotheses were that cognitive impairment, adverse emotional changes, and somatic symptoms are

greater: (a) the greater the magnitude of the drop in blood sugar; (b) the more rapid the decrease in blood sugar; (c) the greater the drop in blood sugar from fasting level; (d) the lower the absolute level of blood sugar; and (e) the higher the hypoglycemic index score. While there was some support for each of these hypotheses, the strongest evidence was found for hypothesis (e). Heart rate did not support any of the hypotheses, and therefore, will be excluded from further discussion.

With respect to hypothesis (a), no significant differences were found between groups formed on the basis of magnitude of drop in blood sugar. As can be seen in Tables 15 and 19, however, the subjects with high magnitudes of drop in blood sugar showed greater increases in symptomatology than did the subjects with low magnitudes of drop. The correlations between magnitude of drop and symptom gain at nadir were all moderate, ranging from .452 to .682 (see Table 20). Thus, there is some support for hypothesis (a), suggesting that the magnitude of the drop in blood sugar does have some role in predicting symptom changes.

Hypothesis (b) received more support than hypothesis (a). Subjects with high speeds of drop in blood sugar were more impaired on the SST at nadir and half an hour after nadir, than an hour or half an hour before nadir. Also, subjects took longer to complete the SST at nadir than an hour after nadir, providing evidence against a simple order effect. Conversely, subjects with low speeds of drop in blood sugar showed no significant differences in SST times.

No other differences were found between groups divided on the basis of speed of drop in blood sugar. As with the magnitude of drop, however, greater symptoms were seen in subjects with high speeds than in subjects

with low speeds in all comparisons (see Tables 14 and 19). Correlations were also moderate between speed of drop and symptom gain at nadir (range .464 to .551; see Table 20). Thus, some support was obtained for the hypothesis that with more rapid decreases in blood sugar, symptom changes will be greater.

Budd (1981) conjectured that the speed of decrease in blood sugar might cause symptoms to occur, but provided no data. Johnson et al. (1980) presented data suggesting that lower speeds of decrease were associated with symptom onset. They did not report how symptom presence was determined, however, nor did they use statistical analyses. Another problem is that blood sugar was sampled hourly. In the present study, subjects who showed a high speed of drop had a mean rate of descent of 48.7 mg/h; low speed of drop subjects had a mean of 30.3 mg/h. Johnson et al. (1980) reported means of 67.9 mg/h (asymptomatic subjects with nadirs less than 50 mg/dl), 50.8 mg/h (symptomatic subjects with nadirs less than 50 mg/dl), 35 mg/h (asymptomatic subjects with nadirs greater than 50 mg/dl), and 31 mg/h (symptomatic subjects with nadirs greater than 50 mg/dl). Research needs to be done to resolve these disparate findings.

Very little support was found for hypothesis (c). No significant differences were found between groups divided on the basis of size of decrease of blood sugar from fasting level. The effects were all in the predicted direction; subjects with large drops below fasting levels exhibited greater symptom changes than did subjects with small drops (see Tables 16 and 19). The correlations between decrease from fasting blood sugar level and symptom gain at nadir were very small (range .142 to .172; see Table 20). Thus, there is only very slight support for hypothesis (c), indicating

that magnitude of the drop from fasting blood sugar level is not a very strong predictor of symptom changes.

Bolton (1976) labeled subjects hypoglycemic on the basis of a decrease from fasting blood sugar level of 10-25 mg/dl. Similarly, Salzer (1966) diagnosed patients with a decrease of 20 mg/dl below fasting. The present study not only indicates that using drop from fasting blood sugar level to predict symptoms may be invalid, but that the decreases employed were insufficient in size. The subjects with a high drop from fasting in the present study had a mean decrease of 35 mg/dl; the subjects with a low drop from fasting had a mean decrease of 22 mg/dl.

Very little support was found for hypothesis (d). There were no significant differences between groups divided on the basis of absolute value of glucose nadir. Again, the effects, although small, were in the predicted direction (see Tables 17 and 19). Subjects with low nadirs showed greater symptom increases than subjects with high nadirs. The correlations between lowest level of glucose and symptom gain at nadir were small, ranging from -.075 to -.360 (see Table 20). These results indicate that, like drop from fasting blood sugar level, glucose nadir is not a very strong predictor of symptom changes

This negative finding is of potential significance because cut-off values of glucose nadir are the most frequently used diagnostic criterion for reactive hypoglycemia. For instance, some authors have suggested that hypoglycemia be diagnosed if blood sugar falls below 40 mg/dl (e.g., Hofeldt et al., 1972; Young & Karam, 1983). Others have suggested a criterion of less than 70 mg/dl (Budd, 1981). Similarly, empirical studies have used a cut-off of 60 mg/dl to predict which subjects should experience symptoms

of lowered blood sugar (Hale et al., 1982; Holmes et al., 1983). The present findings indicate that defining lowered blood sugar levels solely on the basis of nadir values is not advisable. Other aspects of the blood sugar response appear to be better predictors of subjects reporting symptoms at times of lowered blood sugar.

In the present study, subjects in the high nadir group had a mean nadir of 65 mg/dl; those in the low nadir group had a mean nadir of 53 mg/dl. The lowest nadir reached by any subject was 48 mg/dl. Within the range of nadirs observed (48 to 75 mg/dl), symptoms were not found to be very dependent upon level of nadir. It remains possible that below a certain level of blood sugar (one lower than that reached by the low nadir subjects in the present study), all subjects would experience symptoms. This hypothesis awaits study. However, even if it is found to be true, one will still need to use a different predictor variable for those subjects with higher nadirs. It cannot be concluded that because subjects' or patients' blood sugar does not fall below a predetermined cut-off value, that they will not become symptomatic at glucose nadir.

Hypothesis (e) received more support than any of the other four hypotheses. Subjects with high hypoglycemic index scores reported more mood disturbance after glucose nadir than before nadir. Similarly, these subjects reported more somatic symptoms at and after nadir than before nadir, and showed a deterioration in SST performance at nadir and half an hour after nadir relative to performance before nadir. Conversely, subjects with low hypoglycemic index scores exhibited none of these effects. Dividing subjects on the basis of their hypoglycemic index scores reveals striking differences in symptom patterns (see Table 13). Of particular

interest are the different results for SST-Time. Subjects with low hypoglycemic index scores showed the usual pattern of improving performance across trials. This is in sharp contrast to the pattern exhibited by subjects with high hypoglycemic indices.

Examining the data in a different way revealed that subjects with high hypoglycemic index scores showed symptom gain at nadir, whereas subjects with low hypoglycemic index scores showed symptom loss at nadir (see Table 18). That is, high index score subjects experienced more symptoms (or more intense symptoms) at nadir than would be predicted from symptoms an hour before nadir. Subjects with low indices reported less symptoms (or less intense symptoms) at nadir than would be predicted on the basis of symptoms an hour before. These results were significant for mood disturbance and cognitive performance. This conservative test yielded significant results for the hypoglycemic index variable only.

Finally, there were moderate correlations between hypoglycemic index score and symptom gain at nadir (range .371 to .529; see Table 20). All of these results suggest that hypothesis (e) is very well supported, indicating that symptoms will be greater, the higher the hypoglycemic index score. The hypoglycemic index score appears to be the best predictor of which subjects will experience symptoms at times of lowered blood sugar.

The hypoglycemic index score is defined as the fall in blood glucose during the 90-minute period before glucose nadir, divided by glucose nadir (Hadji-Georgopoulos et al., 1980). It takes into account the level of nadir, the amount of decrease in blood sugar, and the speed of the drop in blood sugar. The success of taking these variables into account is corroborated by the correlations betweeen the hypoglycemic index score and the other

four predictor variables (see Table 12). The hypoglycemic index is particulary highly correlated with the rate of decrease in blood sugar (r = .768), the second most useful predictor variable found in the present study. Hadji-Georgopoulos et al. (1980) seem to have developed an index which optimally combines several aspects of the blood sugar response, resulting in better prediction than that which could be obtained using any of the blood sugar responses in isolation.

The success of the hypoglycemic index at predicting symptoms is in direct contrast with the lack of success of the absolute value of nadir. It seems the change in blood sugar level, and the speed of this change, are more important determinants of symptom change than the absolute value of blood sugar reached. As mentioned previously, it may be that level of nadir becomes a better predictor of symptoms at blood sugar levels lower than those reached by the low nadir group in the present study. Indeed, Hadji-Georgopoulos et al. (1980) suggest that the hypoglycemic index score is of greatest value in patients with nadirs between 50 and 65 mg/dl. Still, the point must be reiterated that nadir cannot be relied upon in all cases to predict which subjects will become symptomatic in response to glucose ingestion.

Hadji-Georgopoulos et al. (1980) recommended using a hypoglycemic index score of 0.8 or greater to predict which subjects will become symptomatic. Their data were based upon 28 subjects, 12 of whom were labeled symptomatic on the basis of physician observation or patient self-report of symptoms at nadir. In the present study, high hypoglycemic index score subjects had a mean index score of 1.44 (range 1.14 to 2.10); low index score subjects had a mean score of 0.84 (range 0.61 to 1.06).

For the purpose of comparison, in the present study, "symptomatic" was defined as having positive residual symptom gain scores for both POMS-Total and SSS-Total ($\underline{n}$ = 7 of the 22 subjects used for the main analyses); "asymptomatic" was defined as having negative residual scores for the POMS and SSS ($\underline{n}$ = 11 of the 22 subjects used for the main analyses). However, it should be noted (as will be discussed in the section on the POMS and SSS) that symptoms do not occur on such an all-or-none basis. That is, symptoms occur on a continuum and should be measured accordingly (i.e., quantitatively).

Using the recommended 0.8 index score in the present sample to predict which subjects became symptomatic would result in 14% (1/7) false negatives and 64% (7/11) false positives. Hadji-Georgopoulos et al. (1980) found that this value resulted in perfect prediction. This discrepancy could be due to the different methods of measuring symptoms used in the two studies. Also, the findings of Hadji-Georgopoulos et al. (1980) were based on a small number of subjects. A further problem, to be discussed in the section on glucose analysis instruments, is that cut-off values obtained in different laboratories may not be comparable.

The high number of false positives suggests that a higher cut-off index value would be required in the present study. However, in subjects defined as symptomatic, index scores ranged from 0.71 to 2.1. In asymptomatic subjects, index scores ranged from 0.61 to 1.84. Using a cut-off of 1.14 would result in 14% (1/7) false negatives (index score 0.71), and 18% (2/11) false positives (index scores 1.84 and 1.20). Clearly, while cut-off values are informative, especially at the extremes, they cannot be solely relied upon to predict symptom changes. At certain values, some

subjects experience symptoms and others do not. There is not a perfect correlation between any predictor variable and amount of symptom change (see Table 20). As will be discussed, the systematic and quantitative measurement of symptoms is essential for the prediction of blood sugar-symptom relationships.

It should be noted that the "asymptomatic" subject with the index score of 1.84 did show clear symptoms of lowered blood sugar levels, but only at half an hour after nadir. As the symptom gain scores were calculated on the basis of symptoms at nadir, this subject had negative residual symptom gain scores. This points out the importance of the finding that, for many subjects, symptoms peak half an hour after nadir -- not at nadir as would be expected from the literature. Perhaps some of the negative findings in the literature are due to researchers looking for symptoms only at nadir.

Finally, it is of interest to examine the index values of the subjects not used for the main analyses. Of the subjects with unexpected GTT patterns, 3 had positive residual symptom gain scores and 5 had negative residual symptom gain scores. For the symptomatic subjects, index scores ranged from 0.24 to 0.96; for the asymptomatic subjects, index scores ranged from 0.19 to 0.66. Similar results were apparent for subjects excluded from the main analyses due to nadir occurring at 4.5 or 5 hours. The 2 of these subjects who were symptomatic had indices of 0.45 and 0.67; the 2 who were asymptomatic had indices of 0.05 and 0.13. The values of these index scores are much lower than those of the main sample. As will be discussed, it may not be valid to calculate index scores for some of the GTT curves observed (in particular, the M-shaped curve).

In summary, the hypoglycemic index score received strong support as a predictor of symptom changes. However, a dependence on cut-off index scores is inadvisable for the following reasons. Absolute cut-off values obtained in one laboratory with certain glucose analysis instruments, may not generalize to other laboratories with different instruments. Certain index values, especially in the mid-range, will be associated with symptoms in some subjects but not others. Finally, it may not be valid to calculate index scores with atypical GTT curves.

It is apparent from this discussion that the subsidiary hypotheses were supported in general, but are in need of refinement. In particular, the various blood sugar response parameters vary in ability to predict symptom change. The hypoglycemic index score received the most support as a predictor of symptom change, followed by the rate of decrease in blood sugar. The magnitude of the drop in blood sugar received some slight support as a predictor of symptomatology. Both the size of the decrease in blood sugar from fasting level, and the absolute value of nadir, received very little support as symptom predictors.

General Conclusions. The results suggest that lowered blood sugar levels -- especially when defined as the decrease in blood sugar during the 90 minutes preceding glucose nadir, divided by glucose nadir -- are associated with impaired cognitive performance, adverse emotional changes, and somatic symptoms. This finding addresses the debate in the literature between those who claim hypoglycemia causes many psychological changes (e.g., Brennan & Mulligan, 1975; Budd, 1981), and those who claim "pseudohypoglycemia" is merely an excuse for psychologically caused

problems (e.g., Mundy, 1976; Yager & Young, 1974). The present study suggests that the claims of both these groups may be exaggerated.

The popular literature on hypoglycemia contains claims that lowered blood sugar levels can cause numerous symptoms and disorders. Some of the symptoms which have been attributed to low blood sugar include fatigue, irritability, anxiety, and forgetfulness (Budd, 1981). The results of the present study indicate that such symptoms may, at times, be caused by lowered blood sugar levels. However, other symptoms claimed to be attributable to hypoglycemia in some cases -- such as emotional outbursts, family violence, murder, and schizophrenia (Brennan & Mulligan, 1975) -- seem unlikely to be caused by low blood sugar in light of the present findings. While some subjects reported feeling anxious or confused, no bizarre behavior, thoughts, or feelings were observed or reported. Similarly, the proportion of the normal population claimed to experience symptoms from lowered blood sugar levels (10 to 50%; Budd, 1981) seems to be exaggerated. In the present study, approximately half of a group of subjects believing or suspecting that they have hypoglycemia actually experienced an increase in symptoms at or after nadir.

The authors who espouse the view that people attribute their symptoms to low blood sugar levels, when the symptoms are actually psychologically caused, also appear to have exaggerated their claims. Some subjects in the present study showed a clear relationship between lowered blood sugar levels and impaired cognitive performance, adverse emotional changes, and somatic symptoms. However, many subjects, who believed that they were hypoglycemic, showed no increase in symptoms at or after nadir. As will be discussed in the section on questions for future research, the

reason some people erroneously conclude that they have hypoglycemia needs to be investigated. The finding that past diagnosis of hypoglycemia did not predict which subjects became symptomatic suggests that misdiagnoses may be one reason that people falsely conclude they are hypoglycemic.

It has been suggested that the symptoms of lowered blood sugar levels are caused by a delayed secretion of insulin (e.g., Hofeldt et al., 1974). The hypoglycemic index score is correlated with late hyperinsulinism (Hadji-Georgopoulos et al., 1980). That subjects with high hypoglycemic index scores in the present study became symptomatic, supports the hypothesis that symptoms may be caused by delayed insulin secretion.

There have been some empirical studies conducted on the relationship between blood sugar levels and cognitive performance, affective state, and somatic symptoms. Uhde et al. (1984) found that 9 patients with panic disorder experienced either an increase in anxiety, or 2 or more somatic symptoms (i.e., hunger, lightheadedness, diaphoresis, or palpitations), 3 to 5 hours after glucose ingestion. These four somatic symptoms, plus trembling, pounding heart, and sleepiness, were found by Pennebaker et al. (1981) to be associated with lowered blood sugar levels in diabetic patients. These findings are congruent with those of the present study. Hale et al. (1982) found that subjects with low nadirs experienced greater regressions in SST performance at nadir than did subjects with high nadirs. Similarly, lowered blood sugar levels have been associated with slower performance on tasks such as reasoning problems, motor coordination, visual reaction time, and simple addition (Holmes et al., 1983; Russell & Rix-Trott, 1975). Again, these findings corroborate those of the present study. That such diverse methods (GTTs, daily symptom-glucose correlations, insulin challenge, and

artificial insulin/glucose infusion) yield similar results further supports the hypothesis that lowered blood sugar levels are associated with impaired cognitive performance, adverse emotional changes, and somatic symptoms.

Additional Findings

Individual Difference Variables. Five grouping variables -- age, weight, gender, past diagnosis, and family history of diabetes -- were examined for their ability to predict which subjects became symptomatic at nadir. No support was obtained for any of these variables (see Tables 21 and 22).

Jung et al. (1971) found that younger women (20 to 45 years old) exhibited lower blood sugar levels during GTTs than older women did. They did not, however, report whether symptoms differed between the two groups. Research on the effects of carbohydrate meals on objective performance has found that older subjects' (greater than 40 years old) concentration on a dichotic listening task decreased after ingesting carbohydrates (Spring, Maller, Wurtman, Digman, & Cozolino, 1983). In the present study, no differences were found in symptoms between old and young subjects. According to the age criteria used in the above studies, however, most of the present subjects were young (i.e., the mean age in the old age group was only 39.6 years). Further research is needed to determine if age influences the response to lowered blood sugar levels.

Jung et al. (1971) also found that heavy women (greater than 145 pounds) had lower blood sugar levels than light women. They did not report whether these women weighed more than their ideal body weight, but did label them obese. Again, whether symptoms were experienced was not reported. The present study found no evidence of different symptoms

responses to lowered blood sugar when subjects were divided according to percent above or below ideal body weight. However, only 3 subjects were actually obese (weight more than 20% above ideal); therefore, whether obese people experience more symptoms in response to glucose ingestion remains untested.

It has also been suggested that women are more affected by low blood sugar than men. Spring et al. (1983) reported that women became sleepy after eating a carbohydrate meal, whereas men became calm. Merimee (1977) observed that women had lower fasting blood sugar levels than men. In the present study, no such evidence was obtained; however, more women ($\underline{n}$ = 26) than men ($\underline{n}$ = 10) responded to the recruitment notices, and participated in the study. Thus, the possibility remains that women show a greater association between blood sugar levels and symptoms than men do.

As there is such disagreement regarding diagnostic criteria for hypoglycemia, it was of interest to investigate whether there were differences in symptoms between subjects having received a diagnosis of hypoglycemia, and subjects not having received such a diagnosis. There were no differences between these two groups.

Finally, many authors have reported that some cases of hypoglycemia may be early manifestations of maturity-onset diabetes (e.g., Anthony et al., 1973; Berger, 1975; Hofeldt et al., 1972). As an indirect look at this question, subjects in the present study were asked if anyone in their family was diabetic. Dividing subjects on this basis yielded no differences in symptom changes at glucose nadir. Prospective studies are needed to provide a test of this question.

Variety of GTT Curves. As described in the Results section, 9 of the 35 subjects exhibited atypical responses to the GTT. In particular, flat curves, M-shaped curves (two peaks and drops), and late peaks in blood sugar level were observed. Flat curves have been reported to occur (e.g., Budd, 1981), and Burns et al. (1965) found that -- with continuous blood sugar sampling -- two to four peaks and falls in blood sugar level may be observed. No one has reported more than one peak and drop with intermittent sampling, however, nor has anyone reported subjects exhibiting peak glucose values at 2.5 hours. On the basis of this literature, the number of atypical curves observed was completely unexpected.

In the present study, subjects exhibiting atypical curves were excluded from the main analyses as there was no information available as to whether, or when, such subjects would experience symptoms. For instance, in a subject with an M-shaped curve, should symptoms occur after the first fall or the second (regardless of which fall resulted in nadir)? Or would the rapid fluctuations in blood sugar level alone cause symptoms? Similarly, do subjects with flat curves or late peaks experience symptoms? These questions are in need of empirical research. The physiological basis of these curves needs to be determined.

These atypical curves present problems of quantification; for example, how can one calculate hypoglycemic index scores, speed of descent, and glucose nadir? For example, suppose a subject with an M-shaped curve has blood sugar levels of 80, 140, 110, 90, 75, 59, 80, 100, and 57 mg/dl (at half hour intervals). Defining nadir as the lowest level of blood sugar reached demands that 57 mg/dl be called nadir. It is unclear, however, whether symptoms would be expected to occur at 59 or 57 mg/dl. In

calculating the speed of descent -- defined as the decrease between peak and nadir, divided by the time between peak and nadir -- it is unclear whether to use 2 hours or 3.5 hours as the time between peak and nadir (i.e., 140 to 59 mg/dl, or 140 to 57 mg/dl). Another alternative is that the time between peak and nadir is half an hour (i.e., 100 to 57 mg/dl). Finally, calculating the index score -- the drop in glucose during the 90 minutes preceding nadir, divided by glucose nadir -- is also difficult. In this hypothetical example, the decrease between 90 minutes before nadir and nadir would be 2 mg/dl, a figure unrepresentative of the blood sugar response. Similar problems of calculation arise with respect to the other atypical curves.

Nine subjects had to be excluded from the analyses of the present study. It was impossible to calculate scores for these subjects' blood sugar response parameters, and it was not known whether to expect symptoms on the basis of their curves. How to calculate the blood sugar response parameters with atypical curves needs to be clearly explicated. Similarly, information on the symptoms associated with the variety of atypical curves is required.

Glucose Analysis Instruments. Another finding of interest was that, while the YSI Glucose Analyzer's blood sugar values correlated highly with those of the hospital's laboratory instrument, the absolute values obtained with the two methods differed greatly. This indicates that the blood sugar values observed in the present study cannot be compared, in absolute value, with those found in other studies. Nurses at the hospital commented that it was common for blood sugar values obtained with different instruments to vary. If this finding does generalize to other instruments besides the YSI,

one should not directly compare blood sugar levels found in different studies. Perhaps this finding explains some of the different blood sugar norms reported in the literature. For instance, Park et al. (1972) found that 23% of normal subjects had blood sugar levels below 50 mg/dl, whereas Hofeldt (1975) reported that 48% of normal subjects had such low values. In the present study, 2 out of 35 subjects had blood sugar levels less than 50 mg/dl.

This finding provides an additional caution against depending on glucose nadir cut-off points for the diagnosis of hypoglycemia. Values obtained in one laboratory may not correspond to those in other laboratories. Research is needed on the reliability of glucose analysis instruments. It may be that more robust methods of glucose analysis are needed.

POMS and SSS. The POMS and SSS were found to have good structure, and to be sensitive to the blood sugar manipulation. The symptoms assessed by these two measures have frequently been reported in the literature to occur at times of low blood sugar; however, they had never been systematically and quantitatively measured. Most researchers relied on patient self-report or clinical observation to document symptoms. However, as Pennebaker et al. (1981) discuss, people are poor at perceiving their own physiological changes. In the present study, the subjects' spontaneous self-report of symptoms was not always indicative of when blood sugar had decreased, nor were external observations of the subjects sufficient to determine when blood sugar was lowered. The symptoms associated with low blood sugar levels are not simply present or absent.

They must be measured quantitatively at regular intervals to determine if symptom change occurs.

The 6 POMS scales were highly intercorrelated, with one factor accounting for 62% of the variance (see Tables 3 and 4). This supports the original finding that the sum of the 6 scales may be used as a measure of overall mood disturbance (McNair et al., 1971). Looking at the individual scales showed that only tension and confusion were significantly affected by lowered blood sugar levels (see Table 10). Reports that depression (e.g., Brennan & Mulligan, 1975), aggression (e.g., Virkkunen, 1982), and fatigue (e.g., Portis et al., 1950) are associated with lowered blood sugar were less well-supported. These results require cross-validation, however, and it may be that different symptoms occur for different subjects.

The 11 SSS items were derived from the literature on the symptoms of hypoglycemia. They were found to be highly intercorrelated, with one factor accounting for 59% of the variance (see Tables 5 and 6). An examination of the 11 individual items revealed that trembling, pounding heart, hunger, and weakness were significantly higher after nadir than before (see Table 11). Similar effects were apparent for flushed face and sweating, but did not reach significance due to the stringent Bonferroni-corrected probability level (.0045). As with the POMS, these results should be cross-validated. Some symptoms which did not reach significance may, nonetheless, be reported by a minority of subjects. Pennebaker et al. (1981) point out that the physiological effects of changes in blood sugar level may differ from patient to patient.

It is recommended that the SSS be used in future research. It is highly sensitive to the effects of low blood sugar levels. It is advised,

however, that hunger be deleted from the scale. Hunger showed lower item intercorrelations than the other 10 items of the SSS (see Table 5). It was observed that hunger scores were higher than scores for the other items. Also, hunger tended to increase steadily across trials, whereas other symptoms increased after nadir and then decreased again. Thus, including hunger in the total score could obscure the effects of lowered blood sugar levels on somatic symptoms.

Weaknesses and Suggestions for Remediation

The main weakness in the present study is the lack of a control group to rule out order or practice effects as an alternative explanation of the results. It is possible that the effects observed were due to the passage of time, rather than to changes in blood sugar level as hypothesized. However, some arguments make this alternative explanation less plausible. For one, subjects' nadirs occurred at different times; therefore, nadir was not completely confounded with time of testing. The dependent measures were analyzed with reference to blood sugar response; that is, an hour before nadir, half an hour before nadir, nadir, half an hour after nadir, and an hour after nadir. This renders order effects a less plausible explanation than if the dependent measures had been analyzed by time of testing (i.e., first trial, second trial, and so on).

Another argument against the order effect explanation is the pattern of results obtained. If there had been a steady increasing or decreasing trend in symptoms, order effects could provide a reasonable explanation. However, the peak mood disturbance and bodily symptoms observed at half an hour after nadir is less easily explained as an effect of order or

practice. Blood sugar changes provide a more parsimonious explanation of this pattern than the passage of time.

An even more compelling argument against the practice effect explanation is the pattern of results observed for the SST. Subjects took longest to complete the subtractions when blood sugar was lowest (see Table 8). This is in direct contrast to the effect observed in the pilot study and the first five trials of the present study (i.e., before any subject had reached nadir; see Table 9). The pattern for these latter groups was one of decreasing time to complete the SST across trials.

A final argument against order effects accounting for the effects is the different patterns of results observed for the groups of subjects divided on the basis of blood sugar response parameters. For example, subjects with high hypoglycemic index scores responded very differently than subjects with low hypoglycemic index scores (see Table 13). Whereas the subjects with high index scores report peak mood disturbance and bodily symptoms half an hour after nadir, subjects with low index scores report much less change in symptoms, and a pattern of slightly increasing symptoms across trials. Similarly, high index subjects show peak SST-Time at nadir, whereas low index subjects' times gradually decrease across trials. The groups of subjects with more normal blood sugar responses can serve as post hoc control groups to get an indication of what the effect on symptoms would be without an abnormal response to glucose ingestion.

Another weakness in the present study is the possibility of experimenter or subject expectancy effects. While both the experimenter and the subjects were blind to blood sugar levels, they were not blind to the hypotheses of the study nor to the fact that a GTT was being

conducted. However, it would have been difficult for subjects or the experimenter to predict when symptoms should occur. Similarly, subjects and the experimenter were blind to the blood sugar response parameter groupings. It is difficult to explain how expectancy effects could influence the symptoms reported by subjects with high hypoglycemic index scores, but not the symptoms experienced by subjects with low hypoglycemic index scores.

The small sample size is another weakness of the present study. All of the results need to be cross-validated, preferably with a larger sample. Also, the conditions of the experiment were inconsistent, and should be more rigorously controlled in future.

Finally, the results of the present study are of limited generality. The sample consisted of people who believed or suspected that they have hypoglycemia, and were willing to undergo a 5-hour GTT. They were volunteer research subjects, not patients spontaneously requesting that their glucose response be evaluated. It remains to be seen whether the same results would be found in subjects not suspecting they were hypoglycemic. Also, severe hypoglycemics may not have been willing to go through a GTT, knowing how it would affect them. Indeed, some of the subjects responding to the recruitment notice declined to participate in the study for this very reason. The sample was also biased towards young, unmarried, highly educated women. There was also a disproportionate number of nurses participating. In addition, the results only generalize to subjects exhibiting the typical response to the GTT, as subjects with atypical GTT curves were excluded from the main analyses.

The weaknesses in the present study can be overcome in future research. To rule out alternative explanations of the present results, a randomized double-blind experiment with glucose and placebo tolerance tests must be conducted. One method would be to compare glucose and saline. The saline group subjects would provide information about order and practice effects of taking tests repeatedly. An even stronger test would be to give all subjects both glucose and saline tests, in counterbalanced order. Having subjects and experimenters blind to the test condition would eliminate expectancy effects. Ideally, subjects and experimenters would also be blind to the hypotheses of the study. Finally, including normal subjects and more severe hypoglycemics in the sample would increase the generalizability of the findings.

The weaknesses in the present study do not preclude alternative explanations for the results. It is not known how subjects' mood and somatic symptoms would change over 6 hours in the Centre, without the ingestion of glucose. However, it is argued that while these alternative explanations remain possible, they do not appear to be plausible.

Questions and Recommendations for Future Research

Better information is needed on the prediction of which subjects will experience symptoms at times of lowered blood sugar levels. The present study indicated that the speed and magnitude of the drop in blood sugar (as measured by the hypoglycemic index) are more important determinants of symptoms than the absolute lowest value of blood sugar reached. Indirect support for this idea comes from reports that diabetics may experience symptoms with blood sugar levels of 100 mg/dl, whereas patients with insulin-producing tumors may be asymptomatic with blood sugar levels of 20

mg/dl (Cahill & Soeldner, 1975). But it may be that below a certain nadir all subjects experience symptoms, while above a certain nadir no subjects experience symptoms. Similarly, subjects with hypoglycemic indexes above a certain high score may all experience symptoms, while subjects with indexes below a certain low score may never experience symptoms. Empirical research is needed to determine if any such cut-off values are reliable predictors of symptomatology.

At present, cut-off values of nadir or of index scores cannot be relied upon to predict symptoms in individual subjects. However, the hypoglycemic index score was successful in discriminating a group of subjects experiencing symptoms from a group of subjects not experiencing symptoms. It is recommended that the index be used in future research. Nadir values did not differentiate symptomatic from asymptomatic subjects in the present study, and should not be used as the determinant of hypoglycemic states in future research of this type.

Many subjects in the present study believed they were hypoglycemic but did not exhibit symptoms in response to glucose ingestion. This raises the question of why some people erroneously believe they are hypoglycemic. It also leaves their symptoms unexplained. Some authors have suggested that these asymptomatic patients may have personality disorders (e.g., Johnson et al., 1980; Yager & Young, 1974), but there is no evidence that this is the cause of their symptoms.

Also in question is the generalizability of the results to other manipulations and settings. It is of interest to investigate whether the same findings would obtain if subjects were given substances other than 75 grams of liquid glucose. In particular, would symptoms occur in response to

foods people normally eat? In subjects complaining of symptoms of hypoglycemia, one could test the response to a meal reported by the subject to be associated with symptoms.

Also of interest is whether blood sugar manipulations other than the GTT produce symptoms at times of lowered blood sugar levels. For instance, insulin tolerance tests and insulin/glucose infusion techniques should be further investigated. Such techniques could provide information as to which aspect of the blood sugar change is important in causing symptoms. For example, insulin challenge causes fluctuating blood sugar levels (Russell & Rix-Trott, 1975), and insulin/glucose infusion holds blood sugar at a specified target level (Holmes et al., 1983). And, of course, research is needed to determine if blood sugar changes in the natural environment cause symptoms. Not only may it be that effects found with the GTT do not occur in the natural environment, but perhaps more people experience symptoms of lowered blood sugar levels in their natural environment than would in response to the GTT. This is very important to determine as it could account for the large number of people who believe they have hypoglycemia, but do not exhibit symptoms during formal testing.

Related to this is the question of whether the symptoms of lowered blood sugar could be interpreted as psychological disorders in the natural environment. In particular, it is conceivable that a person experiencing symptoms of low blood sugar (e.g., trembling, palpitations, sweating), and not knowing what was causing them, could develop an anxiety disorder such as panic disorder (see DSM-III; APA, 1980). Two subjects in the present study spontaneously remarked that they had been diagnosed with panic disorder because of their hypoglycemic symptoms. And the most significant mood

change in subjects with low blood sugar -- in a safe hospital setting where subjects knew their blood sugar was being manipulated -- was tension-anxiety. It is possible that in a less controlled environment, such anxiety would be heightened and perhaps conditioned to become associated with certain stimuli, resulting in the development of a phobia (e.g., Wolpe, 1982).

It would be interesting to observe subjects in situations more anxiety-provoking than the hospital setting, at times of low and normal blood sugar levels. Stimuli the subject had some fear of could be used; for example, a mildly claustrophobic subject could be exposed to a small dark closet. It would also be of interest to study the responses of panic disorder patients to lowered blood sugar levels. Uhde et al. (1984) found that panic patients reported increased symptoms when blood sugar was low. Perhaps in settings other than the hospital, these symptoms develop into a panic attack.

Finally, the question remains of how to treat hypoglycemia. Research must be conducted to determine which dietary measures, if any, will prevent the symptoms of hypoglycemia. Research is also needed on how to reverse the symptoms once they have been precipitated. Related to this is the need to document how long the symptoms of low blood sugar normally last. Such information would be valuable to patients even if they could not curtail the symptoms once started.

Clinical Recommendations

Hypoglycemia refers to a syndrome of somatic and psychological symptoms occurring in response to lowered blood sugar levels. Thus, most authors agree that symptoms should be documented at nadir if a diagnosis

of hypoglycemia is to be made (e.g., Hale et al., 1982; Permutt, 1976). But, cut-off hypoglycemic index scores or nadirs cannot be used to predict which individual subjects will experience symptoms. Factors against the use of cut-off scores include the lack of reliability between glucose analysis instruments, the variety of atypical GTT curves observed, and the need for cross-validation of findings.

Therefore, symptoms should be measured quantitatively and at regular intervals during the GTT, in order to diagnose hypoglycemia. All patients should be assessed individually to determine whether their symptom pattern corresponds with their blood sugar response. It should be kept in mind that symptoms may occur after nadir rather than directly at nadir. Any of the three dependent measures shown to be sensitive to blood sugar changes in the present study could be used by the clinican (i.e., POMS, SSS, SST). However, for practical reasons, it is recommended that the SSS (with hunger deleted as discussed above) be used. It takes less time to complete than the POMS, and yields more useful information than the SST. While diagnosing patients in this way, clinicians could also be developing norms for their particular clinic as to what hypoglycemic index scores and nadir values are reliably associated with symptoms. The relationship between the findings of laboratory testing and hypoglycemic symptoms in the natural world, also needs to be investigated.

As there is little evidence available on the treatment of hypoglycemia, clinicians could assist their patients in self-management of their disorder. People experiencing symptoms from lowered blood sugar levels could use glucometers (individually-operated portable glucose analysis instruments) to observe their symptom responses to changes in blood sugar

level. They could learn which foods cause symptoms to arise, the time interval between eating and symptom onset, and which symptoms can be attributed to low blood sugar levels. Patients could then develop self-control of their symptoms by systematically observing the effects of diet, if any, on their symptoms. Similarly, patients could empirically determine which foods are capable of stopping their symptoms once started.

If patients became more aware of their symptom-glucose correlations, they might be less likely to misinterpret symptoms as anxiety. Or they could avoid stressful situations at times of low blood sugar. Gross et al. (1985) trained diabetics to estimate their blood sugar levels. These patients were then better able to prevent episodes of hypoglycemia. It is strongly recommended that patients with hypoglycemia be assisted in developing individually-tailored self-management programs, in keeping with the practice of modern behavioral medicine.

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Appendix A

Appendix B

Appendix C

NAME _____

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle the number under the answer to the right which best describes HOW YOU ARE FEELING RIGHT NOW.

The numbers refer to these phrases.

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

	0 NOT AT ALL	1 A LITTLE	2 MODERATELY	3 QUITE A BIT	4 EXTREMELY
1. Friendly	0	1	2	3	4
2. Tense	0	1	2	3	4
3. Angry	0	1	2	3	4
4. Worn out	0	1	2	3	4
5. Unhappy	0	1	2	3	4
6. Clear-headed	0	1	2	3	4
7. Lively	0	1	2	3	4
8. Confused	0	1	2	3	4
9. Sorry for things done	0	1	2	3	4
10. Shaky	0	1	2	3	4
11. Listless	0	1	2	3	4
12. Peeved	0	1	2	3	4
13. Considerate	0	1	2	3	4
14. Sad	0	1	2	3	4
15. Active	0	1	2	3	4
16. On edge	0	1	2	3	4
17. Grouchy	0	1	2	3	4
18. Blue	0	1	2	3	4
19. Energetic	0	1	2	3	4
20. Panicky	0	1	2	3	4
21. Hopeless	0	1	2	3	4
22. Relaxed	0	1	2	3	4
23. Unworthy	0	1	2	3	4
24. Spiteful	0	1	2	3	4
25. Sympathetic	0	1	2	3	4
26. Uneasy	0	1	2	3	4
27. Restless	0	1	2	3	4
28. Unable to concentrate	0	1	2	3	4
29. Fatigued	0	1	2	3	4
30. Helpful	0	1	2	3	4
31. Annoyed	0	1	2	3	4
32. Discouraged	0	1	2	3	4
33. Resentful	0	1	2	3	4
34. Nervous	0	1	2	3	4
35. Lonely	0	1	2	3	4
36. Miserable	0	1	2	3	4
37. Muddled	0	1	2	3	4
38. Cheerful	0	1	2	3	4
39. Bitter	0	1	2	3	4
40. Exhausted	0	1	2	3	4
41. Anxious	0	1	2	3	4
42. Ready to fight	0	1	2	3	4
43. Good natured	0	1	2	3	4
44. Gloomy	0	1	2	3	4
45. Desperate	0	1	2	3	4
46. Sluggish	0	1	2	3	4
47. Rebellious	0	1	2	3	4
48. Helpless	0	1	2	3	4
49. Weary	0	1	2	3	4
50. Bewildered	0	1	2	3	4
51. Alert	0	1	2	3	4
52. Deceived	0	1	2	3	4
53. Furious	0	1	2	3	4
54. Efficient	0	1	2	3	4
55. Trusting	0	1	2	3	4
56. Full of pep	0	1	2	3	4
57. Bad-tempered	0	1	2	3	4
58. Worthless	0	1	2	3	4
59. Forgetful	0	1	2	3	4
60. Carefree	0	1	2	3	4
61. Terrified	0	1	2	3	4
62. Guilty	0	1	2	3	4
63. Vigorous	0	1	2	3	4
64. Uncertain about things	0	1	2	3	4
65. Bushed	0	1	2	3	4

MAKE SURE YOU HAVE ANSWERED EVERY ITEM

Appendix D

SST

589	493	296	543	382	211
582	486	289	536	375	204
575	479	282	529	368	197
568	472	275	522	361	190
561	465	268	515	354	183
554	458	261	508	347	176
547	451	254	501	340	169
540	444	247	494	333	162
533	437	240	487	326	155
526	430	233	480	319	148
519	423	226	473	312	141
512	416	219	466	305	134
505	409	212	459	298	127
498	401	205	452	291	120
491	395	198	445	284	113

329	258	376	436	459
322	251	369	429	452
315	244	362	422	445
308	237	355	415	438
301	230	348	408	431
294	223	341	401	424
287	216	334	394	417
280	209	327	387	410
273	202	320	380	403
266	195	313	373	396
259	188	306	366	389
252	181	299	359	382
245	174	292	352	375
238	167	285	345	368
231	160	278	338	361

Appendix E

Please read each descriptor. Then place a mark on the dashed line to indicate how you are feeling right now.

Trembling
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ a great deal

Pounding heart
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ a great deal

Flushed face
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Lightheaded
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Sweating
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ a great deal

Hungry
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Weak
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Headache
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ a great deal

Blurred vision
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ a great deal

Dizzy
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Nauseous
not at all ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ extremely

Appendix F

HEART RATE

Blood sugar sample	10-second period						
	1	2	3	4	5	6	Average
1							
2							
3							
4							
5							
6							
7							
8							
9							

Appendix G

Data Sheet

Name: _____ Date: _____
Sex: _____ Age: _____ Years of education: _____
Height: _____ Weight: _____
Address for results: _____

_____

Blood sugar sample

	1	2	3	4	5	6	7	8	9
Time									
Blood sugar									
SSS 1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
total									
SST time									
errors									
POMS T									
D									
A									
V									
F									
C									
total									
Heart rate									

Magnitude of drop in blood sugar:
Speed of fall in blood sugar:
Drop from fasting blood sugar:
Glucose nadir:
Hypoglycemic index score: