

Hypoglycemia: Implications and Suggestions for Research

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Abstract

This review paper attempts to summarize the available information on the relationship between hypoglycemia and a variety of social and emotional disorders. It is pointed out that much of the information relating hypoglycemia and emotional and social disorders comes from observations made by practitioners. These practitioners have observed that individuals with hypoglycemia have exhibited a variety of maladaptive behaviors including such behaviors as amnesia, chronic fatigue, schizophrenia, and aggression. These relationships exist only at the level of description and need to be verified. Additionally the review illustrates a need for a more accurate definition of the disorder currently labeled hypoglycemia. Finally, the review calls for new avenues of research into the etiology of what is now labeled hypoglycemia.

In 1973 the American Diabetes Association, the Endocrine Society and the American

Medical Association published a statement in the Annals of Internal Medicine concerning the diagnosis and treatment of hypoglycemia. This statement, which was to be released to the public during the same year, included a condensed definition, symptoms, diagnostic procedures, possible causes, and typical treatment of hypoglycemia. Also included was a statement that "there is no good evidence that hypoglycemia causes depression, chronic fatigue, allergies, nervous breakdowns, alcoholism, juvenile delinquency, childhood behavior problems, drug addiction or inadequate sexual performance" (1973). The impetus for this statement seems to have arisen from the fact that authors of popular books (Ab-rahamson and Pezel, 1951; Airola, 1977; Brennan, 1975; Cheraskin, Ringsdorf and Brecher, 1974) had made such a cause and effect relationship and the general public believed this causal relationship and attributed many of their symptoms to this disorder. Not infrequently, physicians have treated patients as hypoglycemic which has led to even further widespread belief of the ubiquitous nature of this disorder (Yager and Young, 1974).

Although the American Diabetes Association, the Endocrine Society and the American

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Medical Association would apparently like to discount any relationship between hypoglycemia and various emotional, social, and behavioral disorders, there does appear to be some relationship. Recently, Kelly (1979) has summarized the evidence relating hypoglycemia to crime and Moyer (1976) has summarized the relationship between hypoglycemia and aggression. Based on the evidence presented in these two reports there does seem to be a portion of maladaptive behavior that is attributable to hypoglycemia. However, the strength of this relationship is unknown. The vast majority of studies in this area are descriptive case studies. Only a few studies have attempted to systematically relate hypoglycemia to a specific disorder.

The purpose of the present article is to attempt to demonstrate the relevance of hypoglycemia for a variety of social and emotional behaviors. It is hoped that such an article will stimulate systematic research into this area in an attempt to isolate the disorders that are confounded by hypoglycemia as well as those disorders that have no relationship to hypoglycemia. As will be apparent from the remainder of this article, hypoglycemia has been implicated in a wide variety of disorders. It would be absurd to think that it could be the cause of all of them. However, it is equally inappropriate to suspect that all of the implicated relationships are false. To sift out the valid from the invalid relationships, one must conduct systematic, continuous, ongoing research. This has been almost totally absent in the area of hypoglycemia.

In presenting the literature on hypoglycemia several points need to be made at the outset. First, the literature presented will consist only of that considered to be relevant to the behavioral scientist. Consequently, literature of relevance only to the medical profession such as surgical procedures required for removal of a pancreatic tumor or hypoglycemia caused by cancer will not be presented. Second, the majority of the literature which has relevance for the behavioral scientist is quite old. It appears that a number of individuals in the 30's, 40's and 50's were working on the

relationship between hypoglycemia and emotional and social disorders. When these individuals either retired, passed away or changed areas of research their line of investigation was not continued. This seems to be particularly true for the decade of the 70's. Virtually all the research conducted during this period of time was related to organic causes of hypoglycemia. Third, the bulk of research conducted on hypoglycemia is of the descriptive case study variety or, what I believe is referred to as clinical investigation. Therefore, the evidence which exists suggesting the relationship between hypoglycemia and social and emotional behavior does, in agreement with the statement on hypoglycemia (1973) seem to be weak. However, the fault, at present, seems to lie with the research methodology which has been used in the past. The suggested relationships are still valid and need to be investigated in rigidly controlled experiments. Fourth, the focus of attention in this article will be on reactive hypoglycemia as opposed to fasting hypoglycemia. This delimiting condition exists because fasting hypoglycemia can be traced to a specific organic cause such as a pancreatic tumor. Therefore, it is totally a medical problem.

SYMPTOMATOLOGY

A detailed description of the symptomatology accompanying hypoglycemia was not provided until insulin was discovered and used in the treatment of diabetics. This was because insulin lowers blood sugar concentrations and, with the ability to provide an individual with an exogenous supply of insulin, one could deliberately decrease a person's blood sugar level to hypoglycemic levels and record the symptoms experienced. This is in fact what happened with numerous diabetics taking insulin. Although a complete description of symptomatology accompanying hypoglycemia did not occur until the discovery of insulin, earlier studies had been conducted which investigated the symptoms of hypoglycemia in animals. Mann (1921), for example, removed the liver in animals, a procedure that had previously been shown to diminish the blood sugar levels, and observed muscle weakness, loss of

reflexes, hyperactive reflexes, muscle twitching, unconsciousness and convulsions.

With the advent of insulin, the objective and subjective symptoms of hypoglycemia in humans were elaborated. Most of the descriptions of these symptoms come from observations of diabetics made hypoglycemic by exogenous injections of insulin and/or from schizophrenics undergoing insulin shock therapy. Kepler and Moersch (1937) have described the symptoms of hypoglycemia as follows: "In attacks of any severity the attitude and general behavior of the patient are always disturbed. Any one of the following mental states, to mention only the more common ones, may dominate the clinical picture: apathy, irritability, restlessness, fatigue, anxiety, incorrigibility, negativism, automatic behavior, somnambulism, confusion, excitement, disorientation, 'drunken behavior', fugue states, unconscious attacks, delirium, mania, stupor, coma. The motor activity may be decreased or increased. Speech is distorted: there may be garrulity, dysarthria or even aphasia. Emotional instability ranges from all forms of anxiousness to querulousness and violence. The character of the thinking becomes confused and sluggish: the patient may be delirious. The trend of thought may remain within reasonable bounds, but obsessions, compulsions and even hallucinations or delusions frequently may be present. The mental group becomes distorted, the patient may become disoriented as to time, place and persons. There is loss of memory for events and the patient does not remember the attack. The mental symptoms may be associated with neurologic disorders of varying type, as motor retardation or convulsive attacks of tonic or clonic type" (p. 96-97). As can be seen from this description, the symptoms of hypoglycemia are numerous, difficult to classify, and readily misdiagnosed as some emotional or neurological disorder.

A number of individuals (Adlersburg and Dolger, 1938-1939; Wilder, 1943; Moersch and Kernahan, 1938) have attempted to classify the symptoms of hypoglycemia into various stages. These classifications have typically resulted from observations of individuals who were

made hypoglycemic by injection of insulin. Wilder (1943) gives as vivid an illustration of this progression of symptoms as does anyone. He describes three stages of symptoms: minor or small attack, medium attack and major attack. In the minor attack many somatic symptoms such as fatigue, hunger, perspiration and tremor can occur. This can be accompanied by an inability to concentrate and difficulty in making decisions. The individual may be depressed or anxious and occasionally demonstrate irritability and negativism. One of the outstanding features of this stage seems to be extreme fatigue and lack of energy. Wilder quotes one patient who stated that she didn't want to talk or move and that moving a pencil from a table was like climbing a mountain.

During the medium attack the symptoms may become even more varied. Here the individual may experience double-vision, vertigo, ataxia, and aphasia. Responses may be exaggerated as excessive gesticulation, the individual may cry easily and speech may change from being slow, stuttering and indistinct to explosive. In rare cases echolalia may occur. In the medium attack the individual may demonstrate even more negativism and aggressive behavior than occurred in the minor attack and may even hallucinate. In the severe attack an individual may experience paralysis, stupor or coma. It may also initiate seizures, catatonic states and hyperkineses. Wilder (1943) reports a case of an individual who knocked at his bedstead for hours and another kept pouring coffee over his head for hours. Others experience "A wild, maniacal impulse to talk, run or destroy" (Wilder, 1943, p. 432). Still others experience fugues where they have a desire to wander or run and later have amnesia for such events.

Descriptions of symptoms such as those just provided were obtained from exogenous injections of insulin. The relevant question is whether these symptoms are indicative of individuals with endogenously produced hypoglycemia. Marks and Rose (1965) consider such descriptions as more of historical interest than of practical use. However, it is such symptoms that are used to suggest that an individual may have hypogly-

cemia. Harris (1924) was the first individual to observe that similar symptoms occurring spontaneously may also be due to hypoglycemia. He presents and discusses several cases of individuals with symptoms similar to those of insulin produced hypoglycemia who were found to have blood sugar concentrations in the hypoglycemia range. Since that time and at the present time many of the symptoms produced by insulin induced hypoglycemia are used to suggest that an individual may have hypoglycemia. For example, Service (1976) lists the symptoms of hypoglycemia as including sweating, palpitations, weakness, confusion, bizarre behavior, amnesia, blurred vision, convulsions and coma. These symptoms are strikingly similar to those of insulin induced hypoglycemia.

The symptoms of hypoglycemia, as has been illustrated, are extremely varied, nonspecific, and emulate a variety of emotional disorders. Consequently, diagnosis is typically difficult and there would seem to be a dramatically enhanced probability of misdiagnosis. Marks and Rose (1965) have provided a rather impressive list of conditions simulated by the symptoms of hypoglycemia. These include psychiatric syndromes such as schizophrenia, intoxications, neurologic syndromes such as migraine, and vascular and endocrine disorders. Due to the non-specific nature of the symptoms and the many disorders it can emulate, it would seem desirable for behavioral scientists to maintain an appreciation of this disorder.

EMOTIONAL AND SOCIAL DISORDERS EMULATED BY HYPOGLYCEMIA

The symptoms of hypoglycemia or neuroglycopenia (Marks and Rose, 1965) cover the entire range of possible manifestations of emotional disorders. Due to the vague and diverse nature of the symptoms it would appear to be instructive to present examples of the documented cases of hypoglycemia presenting as a specific emotional or social disorder. A review of such cases would seem to suggest perhaps the major types of disorders emulated by hypoglycemia. If this is true it would give researchers and practitioners an indication as to

which disorders may be confounded by hypoglycemia.

Amnesia

In reviewing the literature on hypoglycemia it is quite common to encounter articles which illustrate cases of individuals experiencing amnesia not infrequently resembling a fugue state. Ziskind and Bayley (1937) report a case of a woman who had, at several times during the prior two years, experienced attacks of emotionally disturbed and uncontrollable behavior. During one of these times she beat her son unmercifully and at another time she threw articles of furniture about. During both of these periods she was restless, throwing her body back and forth and exhibited course jerking movements. However, she experienced amnesia for the events which transpired during these periods. Romano and Coon (1942) illustrate a case of an individual who was initially diagnosed as exhibiting a hysterical fugue state. This individual repeatedly experienced attacks of confused, bizarre behavior for which he had partial or complete amnesia. These episodes would last from a few minutes to several hours in length. One episode commenced following some 15 minutes of vigorous wood chopping. According to Romano and Coon, on one occasion "...he suddenly clutched his axe menacingly and with a dazed and glassy-eyed expression, wandered about the neighborhood terrifying people" (p.284). Similar accounts are reported by other investigators (Zivin, 1970; Bovill, 1973). The common denominator in all of these cases is that they are suffering from hypoglycemia. From a review of the literature it appears as though most of the cases of amnesia due to hypoglycemia can be attributed to fasting hypoglycemia or hypoglycemia due to a tumor on the pancreas. Baruk, Sherman, Koladny and Singh (1973) appropriately point out that individuals with insulinoma leading to fasting hypoglycemia typically exhibit bizarre behavior, poor judgment and episodes of amnesia or unconsciousness. These periods can be separated by intervals of well-being. For example, the case presented by Romano and Coon (1942) experienced

more than a year of good health between two of his attacks.

While the evidence does suggest that amnesia is more common in hypoglycemia caused by a tumor, it does occur in cases where a tumor does not exist. Bovill (1973) reports a case of a physician's wife, who by all available evidence, had been involved in an accident with a cyclist in which the cyclist was killed. However, she had total amnesia for the event and continued her daily routine in somewhat detached fashion. Subsequent examination revealed that she was hypoglycemic and the inference was made that the amnesia was due to this fact. The evidence did not suggest that there was a tumor on the pancreas.

Neurasthenia

The American Psychiatric Association's DSM II (1968) has characterized neurasthenic neurosis by complaints of weakness, fatigue, and exhaustion. DSM III (1980) has placed neurasthenia under the affective disorders. Specifically, neurasthenia is labeled as a Dysthymic disorder. While DSM II (1968) has attempted to limit the definition of this neurosis, Nemiah (1975) has appropriately pointed out that such symptoms characterize only the central symptoms of these individuals. He points out that individuals with the neurasthenic pattern also complain of other difficulties including such symptoms as depression, digestive disturbances, headaches, and inability to make decisions. Coleman (1976) presents the neurasthenic individual as a person who complains primarily of fatigue and difficulty in mental concentration. Such characterizations of neurasthenia show an uncanny isomorphism with many of the symptoms of hypoglycemia. It should be remembered that one of the dominant symptoms of hypoglycemia is fatigue. Wilder (1943) reports that individuals in the minor attack may experience difficulty in thinking and inability to make decisions extending to an absence of what Wilder called "will-power". He illustrates this absence of will-power by the reports of an individual who had hypoglycemia induced by injection of insulin. About an hour

following the injection of the insulin the subject reported that it "...required enormous will-power to merely shift her arm from one position into another" (Wilder, 1943). About two hours after induced hypoglycemia she reported that she didn't want to move or talk and that taking "...a pencil from a table requires as much will-power as climbing a mountain" (p. 430). Such symptoms seem to suggest extreme fatigue and weakness, two of the primary symptoms of neurasthenia. When such symptoms are coupled with other hypoglycemic symptoms such as the inability to make decisions and the headaches and depression, it seems highly likely that at least some cases of neurasthenia result from hypoglycemia. Portis (1944) reports that the fatigue characteristic of hypoglycemia presents some rather striking and uniform characteristics. "It (fatigue) was usually present on awakening, somewhat relieved by breakfast, usually reappeared in the mid-afternoon and disappeared after a large dinner. ...There was characteristically a pernicious inertia, even to the extent of continuous bed rest. ...Psychologic investigation revealed a lack of zest and enthusiasm" (Portis, 1944, p. 415). Such a description has some striking parallels to Coleman's (1976) description of neurasthenic neurosis. Coleman (1976) states that these people drag themselves out of bed but the fatigue gets "worse as the day wears on, although by evening he may feel somewhat better and may go to a movie or party..." The dragging out of bed reported by Coleman may be due to the fact that these individuals have not eaten for some time and their blood sugar is low. The observation that the neurasthenic's fatigue gets worse during the day may be due to the fact that some physical exertion has taken place which used up some of the available supply of glucose. Also, as the day wears on, particularly in the afternoon, the length of time since the last feeding increases. Both of these factors would contribute to a drop in blood sugar level with the accompanying feelings of fatigue. The improvement that may occur in the evening may be due to the fact that the evening meal is typically the largest. Ingestion of this meal could raise the blood sugar

resulting in an improved condition.

In an attempt to verify this relationship between chronic fatigue and hypoglycemia, several studies have investigated the carbohydrate metabolism of individuals with this primary complaint. Portis and Zitman (1943) administered an intravenous dextrose tolerance test to four patients with a primary complaint of fatigue and found all four to meet the diagnosis of hypoglycemia. Dietary intervention and small doses of atropine to paralyze the right vagus nerve eliminated or drastically reduced the fatigue. Additional studies by Portis (1950) and Portis and Zitman (1950) on larger samples provided confirmation to this earlier study. Portis and Zitman (1950), for example, found that 60 percent of a group of 50 business executives who consulted them as patients presented fatigue as their primary complaint and 43.3 percent of these had hypoglycemia.

Based on such evidence, it seems that hypoglycemia may indeed be a factor in neurasthenic neurosis. Such a suggestion would also seem compatible with the fact that current psychotherapeutic modalities are ineffective in treating this disorder (Nem-iah, 1975; Coleman, 1976). If hypoglycemia is indeed a primary component of this disorder then this would explain the lack of success of psychotherapy. Dietary intervention must be included to gain control of the chronic fatigue. Only when the fatigue is controlled by dietary intervention can psychotherapeutic techniques be effective in dealing with the psychological factors. Such a dual approach has in fact been suggested by Alexander and Portis (1944). These investigators found that dietary intervention greatly improved or completely eliminated the fatigue and exhaustion presented by the patients they studied. Once the fatigue disappeared it "brought the underlying emotional situation more sharply into consciousness and facilitated the psychotherapeutic approach to the basic problem" (p. 203). Based on their studies these authors conclude that dietary intervention is in some cases indispensable to the success of psychotherapy.

Schizophrenia

In discussing the symptomatology related to hypoglycemia, Marks and Rose (1965) point out that these symptoms can simulate the psychotic manifestations indicative of schizophrenia. Knowledge of such a fact is accepted among those familiar with the literature on hypoglycemia since it is not uncommon to encounter instances where individuals have been diagnosed as schizophrenic prior to the identification of their hypoglycemia. Baruk et al. (1973), for example, reports a case of a woman with hypoglycemia who at one time had been admitted to a psychiatric institution and diagnosed as schizophrenic. Forestner (1971) reports a case of a patient who was admitted to a psychiatric hospital and treated for involuntal psychosis until it was diagnosed that she had hypoglycemia due to pancreatic tumor. Tintera (1967) provides several examples of schizophrenics who were demonstrated to be hypoglycemic when given an oral glucose tolerance test. One individual was diagnosed by a psychiatrist as being schizophrenic with paranoid tendencies. As long ago as 1935 Greenwood recognized the potential of hypoglycemia for imitating various emotional disorders. He examined the records of patients admitted to the psychopathic ward of the hospital at which he was working. This hospital had, during the prior 10 years, checked blood glucose concentrations of incoming patients as a standard procedure. Greenwood (1935) identified 132 patients who had low blood sugar concentrations. Of this group 20 percent were classified as schizophrenic. One case was a classic example of a catatonic. Blood glucose determinations revealed very low fasting blood glucose concentrations indicative of fasting hypoglycemia. Dietary intervention of a high caloric, high fat diet with orange juice between meals and before going to bed were reported to have controlled her symptoms.

Evidence such as that just presented would seem to strongly suggest that at least a portion of schizophrenics are suffering from hypoglycemia. The problem seems to be one of identifying those schizophrenics that may have hypoglycemia. Due to the vague

and chameleon-like nature of the symptoms of hypoglycemia this could prove to be difficult. Frericks and Creutzfeldt (1976) have revealed that individuals with diagnosed cases of hypoglycemia due to insulinoma have experienced symptoms for up to 20 years before the correct diagnosis was made. This does not mean that such a situation has to continue to exist. It would seem logical that a psychometric instrument could be developed, based on the symptomatology reported, that could screen for hypoglycemia. Tata (1972), for example, identified 21 individuals attending the Diamond Head Mental Health Center who complained of many of the typical symptoms of hypoglycemia and who also ate very poorly or ingested large quantities of carbohydrates or coffee. Included in this group were a number of individuals diagnosed as schizophrenic. Of these 21 individuals over 50 percent were diagnosed as hypoglycemic. Tata reports that "very good results were obtained" on those individuals who were cooperative in following their diet. While this study does not have the degree of control that is desirable in research investigations, it does suggest that the symptoms of hypoglycemia can be used to construct a valid and reliable psychometric screening device.

Aggression

In discussing the causes of aggression one must consider both the environmental and biological substrates. Some authors (Coleman, 1976) emphasize the environmental determinants such as frustration and learning whereas others (Moyer, 1976; Corning and Corning, 1975) focus more attention on the biological aspects of aggression. The biological determinants which are emphasized include such things as brain tumors and hormone secretions. Seldom is any attention or even mention given to hypoglycemia. The exception to this is Moyer (1976). This neglect appears to exist in spite of the fact that there is a small body of clinical evidence supporting the link between hypoglycemia and aggression. Wilder (1943) reports that during a medium attack of hypoglycemia the individual may become negative, and oppose virtually anything. This is similar to the second state of hypoglycemia

identified by Moersch and Kernahan (1938). During this stage the patient may become increasingly excited and agitated. Ad-lersburg and Dolger (1938-1939) report a case of a mother, who, during an attack of hypoglycemia "...stuck a pin into her infant son's eye several times, mishandled and strangled him..." (p. 1806). Kepler and Moersch (1937) report a case of a severe diabetic who, while hypoglycemic as a result of insulin injection, shot at his brother until he had emptied all chambers of the gun. Ziskind and Bayley (1937) report a case of a woman with hypoglycemia due to pancreatic tumor who had, on several different occasions during the prior two years, exhibited "nervous hysterical spells". During one of these spells she beat her son.

Most of the reports linking hypoglycemia to aggressive behavior are quite old. If there was a total absence of such evidence in more recent literature one may conclude that the suggested link was subsequently shown to be invalid and found to be a function of some other variable. However, this is not the case with the suggested link between hypoglycemia and aggressive behavior. More recent reports also suggest that hypoglycemia is a causative factor in aggressive behavior. Hansen (1966) reports a case of a 16-year-old female who had been given a variety of diagnoses including social maladjustment. Extensive testing revealed that she had hypoglycemia resulting from a milk intolerance. Carney, Weinbren, Jackson and Purnell (1971) report a case of a 27-year-old man who was referred as a psychiatric emergency because of the periodic aggressive and destructive behavior he exhibited. During these attacks he was disoriented, behaved inappropriately, sweated and displayed a violent tremor. Prolonged fasting resulted in a hypoglycemic blood sugar concentration and laparotomy revealed several pancreatic tumors. Removal of these tumors was followed by an elimination of the violent attacks. Consequently, the tumors were apparently stimulating insulin production resulting in hypoglycemia.

The cases that have been reported suggesting a link between hypoglycemia and

aggression are reported cases of individuals seen by physicians. A number of these individuals had hypoglycemia produced by pancreatic tumor. This may suggest that most cases of hypoglycemic aggression are a function of such a cause. Bolton (1973), however, conducted a study which would seem to dispel any such notion. He noted that other anthropologists had consistently observed that the Aymara-speaking Qolla Indians are very aggressive and hostile. Pelto (1967, p. 151) had described them "...as perhaps the meanest and most unlikable people on earth." Bolton postulated that one possible cause of the extreme degree of violence exhibited by these individuals was due to hypoglycemia. In an attempt to verify this hypothesized relationship Bolton obtained ratings of aggressiveness (defined as someone who fights a lot, gets into a lot of trouble, is nasty and ill-tempered) on a sample of the male residents of the villages. These aggression ratings were positively related to the number of times the subjects were accused of homicidal acts and the frequency with which they were engaged in litigation. Bolton then related these results of the glucose tolerance test to the ratings of aggression. He found a statistically significant relationship with high aggressors having a disproportionately large number of cases of moderate to severe hypoglycemia. Additionally, his study estimates that 55.5 percent of the Qolla Indians are hypoglycemic. It is recognized that this study is a field study with the lack of control that accompanies such a study and that it is of a correlational variety. However, when the results of this study are combined with the medical reports of aggressive individuals who have hypoglycemia, one must at least entertain the possibility that this is a potential cause of aggressive behavior in a segment of the population.

Headaches

Headaches can arise from a wide variety of conditions. Of the many potential causes of headaches, most investigators include, and, therefore, recognize the existence of hypoglycemia (Friedman, 1975; Dalton, 1973; Sherrill, 1974; Kudrow, 1974). While hypo-

glycemia is recognized as a potential cause of headaches, it is generally deemphasized and given only cursory treatment. Friedman (1975, p. 1715) states that "as a cause of headache, it (hypoglycemia) has been overemphasized, and the headache of these patients is emotional in origin in most instances." Such a stance seems to be quite premature since less than half-a-dozen studies could be identified which actually investigated the relationship between hypoglycemia and headaches. Of those studies which have been conducted, positive evidence has been identified supporting the link between hypoglycemia and headaches. These studies also support the contention that hypoglycemia headaches are of the migrainoid variety. This is in direct opposition to Friedman (1975) who placed hypoglycemia under the heading of nonmigrainous Vascular Headache. However, when comparing the symptomatology preceding a common migraine with that of hypoglycemia one finds a striking similarity. Friedman (1974) reports that the symptoms preceding a common migraine include edema, irritability, pallor, dizziness, and sweating which are also symptoms accompanying a drop in blood sugar. While such an analogy in symptomatology does not substantiate a relationship between hypoglycemia and migraine, it is suggestive of a relationship.

Research, what little there is, is also suggestive of the fact that hypoglycemia precipitates some migraine headaches. A number of the early studies (Wilder, 1943; Friedman, 1975; Rynearson and Moersch, 1934; Jordan, 1933) which were concerned with describing the symptomatology of hypoglycemia have reported that headache is not an uncommon symptom of hypoglycemia. At about the same time it was reported (Barbarka, 1930; Gainsborough, 1934; Bassoe, 1933) that a dietary intervention (ketogenic—high fat and low carbohydrate) was successful in treating 78 to 80 percent of patients with migraine. Wilkinson (1949) also reported on the results of two studies that obtained benefit in the treatment of migraine with a low carbohydrate and high protein diet (the standard dietary treatment of hypoglycemia).

The first detailed study of the relationship between hypoglycemia and migraine, seems to have been conducted by Gray and Burtness (1935). These investigators identified 20 patients with migraine headaches associated with a drop in blood sugar levels. Dietary intervention (frequent feedings of carbohydrate-containing foods) was successful in eliminating the migraine in all cases. Additionally, Cray and Burtness revealed that subjects who were given an oral glucose tolerance test during an attack of a migraine headache experienced relief at the end of the first hour when the blood sugar concentration was at its peak. However, when the blood sugar concentration fell, as it does over time, the migraine returned. Such evidence lends additional support to the fact that low blood sugar levels can induce headache in some individuals.

About a decade and a half following the publication of the Cray and Burtness (1935) study, Wilkinson (1949) also observed the connection between hypoglycemia and headaches. Having made this observation, he administered five-hour oral glucose tolerance tests to all patients with headaches which indicated to him even the slightest possibility of hypoglycemia. Over a seventeen month period he found that 12 percent of individuals complaining of headaches of a migrainoid nature seemed to be associated with hypoglycemia. Improvement or complete relief of the migraine was reported by all but one individual.

Although the evidence reported up to the late 1940's was strongly suggestive of a link between hypoglycemia and migraine, this relationship appeared to lie dormant for the next 15 years as evidenced by the inability to identify studies conducted during this time. In the mid 1960's a number of investigators again focused a minute amount of attention on the hypoglycemia-migraine connection. Blau and Cummings (1966) observed that 50 percent of the patients they reported on had an attack of migraine while fasting. Blau and Pike (1970) reported on six patients who developed a migraine following a missed meal. Byer and Dexter (1975) administered a five-hour oral

glucose tolerance test to patients who were referred to the authors because of intractable headache. Thirteen were found to also have hypoglycemia and administration of a high protein-low carbohydrate diet resulted in 75 percent improvement in the headache in 80 percent of these patients.

The evidence, sparse as it is, suggested that hypoglycemia triggers migraine headaches in a small but significant percentage of individuals. Based on this evidence and given the frequency of occurrence of migraine in the population it is surprising that it has received so little attention. Even more surprising is the fact that individuals (Friedman, 1975) who recognize the relationship of hypoglycemia to migraine headaches state that it is an overemphasized relationship. This seems to be particularly true since very few studies have been conducted on this relationship.

Additional Disorders Associated With Hypoglycemia

The above has briefly discussed the disorders that have been given most attention within the hypoglycemic literature. There are, however, a number of additional disorders which have been associated with hypoglycemia and need to be mentioned. Harris, in 1933, first brought attention to the fact that both epilepsy and narcolepsy could be triggered by hypoglycemia. He reported three cases of epilepsy associated with hypoglycemia. In each of these cases dietary intervention dramatically reduced both the frequency and severity of seizures. Since this time little attention has been placed on the hypoglycemic factor in epilepsy. Braidahl, Priestly and Rynearson (1956) reported that, of 55 cases of "proven" hypoglycemia due to pancreatic tumor which they investigated, 25.5 percent were referred with the diagnosis of epilepsy. Such figures suggest that a sufficiently large percentage of hypoglycemics resulting from pancreatic tumors may be inappropriately diagnosed as epileptic. To avoid the inference that epilepsy is manifested only in this type of hypoglycemia, it should be noted that Buckley (1963) observed an epileptic seizure in a case of hypoglycemia where a tumor was not indicated.

Although the evidence, scant as it is, suggests that epilepsy may be a presenting mode of hypoglycemia, Marks and Rose (1965) consider this an inappropriate diagnosis due to the lapse of rigid criteria for diagnosing epilepsy. To support their case they cite Mulder and Rushton (1959). These investigators demonstrated that use of rigid criteria for diagnosing epilepsy resulted in a 58 percent reduction in misclassifying hypoglycemics due to pancreatic tumor as epileptic. However, 42 percent were still mis-classified. Marks and Rose (1965) state that epilepsy hypoglycemia is quite rare and accounts for less than 0.1 percent of all cases. Based on this they advise against testing epileptics for hypoglycemia.

Harris (1933) also reported a case of narcolepsy associated with hypoglycemia. Since this time virtually no additional evidence has been presented to substantiate or refute this observation. Dement, Carskadon, Guilleminault and Zarcone (1976) state that this disorder is commonly misdiagnosed as hypoglycemia because the complaints of these individuals are similar to those of the hypoglycemic individual. However, these investigators do not cite any evidence to support such a contention. Given Harris's (1933) observation and the similarity in symptomatology between the hypoglycemic and narcoleptic patient it would seem natural and important to further investigate the relationship which may exist between these two disorders.

Studies investigating the relationship between carbohydrate metabolism and peptic ulcers have repeatedly found that ulcer patients have an inability to tolerate glucose. Harris (1935) revealed that hypoglycemic patients frequently experience nausea, vomiting and upper abdominal pain associated with extreme weakness, hunger, and drowsiness. He also pointed out that many of these hypoglycemic patients were originally admitted to the hospital with an unconfirmed diagnosis of peptic ulcer. Later, Brown (1944) reported eight or ten cases of hypoglycemia where the prominent symptom was epigastric pain. Such evidence supports the contention that hypoglycemics often experience pain similar to that of the

ulcer patient and may in fact be thought to have ulcers. It does not, however, establish that confirmed ulcer patients have hypoglycemia.

Abrahamson (1945) investigated the glucose tolerance of patients with peptic ulcer and found that 66 percent of them demonstrated hypoglycemia. While Abrahamson did demonstrate hypoglycemia in a large percentage of ulcer patients, most investigators (Evenson, 1942) have found a hyperglycemic rather than a hypoglycemic reaction on the part of ulcer patients to glucose. The absence of finding a hypoglycemic effect may be due to the fact that most of these investigators did not use a five or six-hour glucose tolerance test. However, when Platt, Dotti, and Beekman (1949) compared the six-hour oral glucose tolerance curves of controls and ulcer patients, they found a definite and significant difference on the hyperglycemic end of the curve but not on the hypoglycemic end. Therefore, the evidence is somewhat conflicting on where the glucose impairment lies. However, the evidence consistently reveals that ulcer patients have impaired carbohydrate metabolism. To the extent that they do, dietary intervention would seem to be a reasonable intervention since it has been demonstrated (Carney, 1936) that the high protein - low carbohydrate diet eliminates not only the hypoglycemic dip in the glucose tolerance curve but also the hyperglycemic rise in the curve.

In 1941 Abrahamson made the observation that prior literature (Black, 1933; Wilmer, Miller, and Beardwood, 1936; Waldbott, Ascher, and Rosenzweig, 1939) had repeatedly demonstrated that asthmatics tend to also have hypoglycemia. He then reasoned that if hypoglycemia was a significant factor in the production of asthma, individuals with diabetes mellitus should be free of this disorder since they have a metabolic problem just the opposite of that of the hypoglycemics. The evidence does in fact support just such a contention. Swern (1931) identified only six diabetics among a population of more than 4,000 allergic patients and Wilmer et al. (1936) found only two among about 5,000 allergic patients.

Such evidence strongly suggests that asthmatic patients do have hypoglycemia and that they can benefit from dietary intervention. In fact, Peskin and Fineman (1930) recommended a low carbohydrate, ketogenic diet for relief and prevention of asthmatic attacks in children.

Research up to the 1940's had not, however, firmly established the connection between hypoglycemia and asthma because prior studies investigating glucose tolerance had used only a two or three hour oral glucose tolerance test and a five or six hour test is needed to investigate hypoglycemia. Abrahamson (1941) administered a six hour oral glucose tolerance test to 12 asthmatics and found all 12 to demonstrate hypoglycemia. These patients were then placed on a high protein - low carbohydrate diet which resulted in complete elimination of asthma in some of the patients and dramatic improvement in others. About one-fourth of the patients discontinued the dietary program following the end of the hay fever season. During the next year their asthmatic attacks returned once the hay fever season returned. Those patients who remained on their diet continued to experience complete freedom or dramatic relief from asthma.

If it is true that hypoglycemia triggers asthma, then all diabetics should be free from this disorder. However, the evidence (Severn, 1931) has demonstrated that a small percentage of diabetics also experience allergies. Abrahamson (1941) recognized this potential problem but also recognized that the condition called dysinsulinism existed. In this condition a diabetic curve occurs during the first several hours of the oral glucose tolerance test. However, hypoglycemia is evident if the test is prolonged to five or six hours. Abrahamson (1941) postulated that diabetics who also suffered from asthma experience dysinsulinism and that the asthma occurs during the hypoglycemic phase. To verify this contention he administered a six-hour oral glucose tolerance test to five cases of asthma with diabetes. In all five cases he found the dysinsulinism and found that the asthma disappeared when the patients were placed on a high protein -low carbohydrate diet. Given these positive

results he extended his study to include six cases of patients with seasonal hay fever but without asthma. All six of these patients also demonstrated hypoglycemia by the fifth or sixth hour of the oral glucose tolerance test and the symptoms of hay fever were negligible after being on the hypoglycemic diet for a few days.

Given the positive results on the relationship between hypoglycemia and asthma, Abrahamson (1952) observed that few diabetics have rheumatoid arthritis. This led him to hypothesize that hypoglycemia may also be a factor in arthritis. To test this assumption he administered the oral glucose tolerance test to five patients with this disorder. In all five patients the blood glucose concentrations fell to hypoglycemic levels confirming the fact that they were hypoglycemic in addition to being arthritic. All patients were placed on the high protein - low carbohydrate diet. However, only one patient had been on the diet long enough, at the time this article was written, to observe its effects. This patient had, at the end of six weeks on the diet, experienced an almost total relief of pain, and "knots" could no longer be felt in her muscles. Unfortunately, no additional studies could be found which continued this line of investigation.

The other disorders that have been related to hypoglycemia include multiple sclerosis (Roberts, 1966) premenstrual tension (Billig and Spaulding, 1947) hearing loss (Parking and Tice, 1970) and leg cramps and "restless legs" (Roberts, 1973). Roberts (1966), for example, found reactive hypoglycemia to be demonstrated in a group of 12 patients with multiple sclerosis and 60 multiple sclerosis prone patients. While such evidence is not supported by the investigations of others (e.g. Aprahamson, 1954), Roberts suggests that this is because these previous investigators did not consider the patients' Orcadian cycle. He demonstrates that patients should be given the oral glucose tolerance test when their symptoms are most prominent and this frequently occurs in the afternoon. For such patients this is the point in time at which hypoglycemia should be tested. The literature relating hypoglycemia to multiple sclerosis is, therefore, contradictory

but as yet very sparse. To settle the question much more research needs to be conducted.

Roberts (1973) has also demonstrated that patients with spontaneous leg cramps and "restless legs" are frequently accompanied by hypoglycemia. In fact, Roberts reports that hypoglycemia is the most consistent explanation for these two conditions in more than 350 patients. Parking and Tice (1970) have provided evidence of a patient with fluctuating hearing loss where the hearing loss experience correlated with blood glucose concentrations during the oral glucose tolerance test. Hearing improved during the first part of the test when blood glucose concentrations rise. However, when it began falling a progressive hearing loss also occurred. Billig and Spaulding (1947) related hypoglycemia to premenstrual tension. These authors conducted a glucose tolerance test on women who exhibited a triad of symptoms several days prior to menses consisting of a burst of energy, easy bruising and general irritability. Glucose tolerance tests revealed that the fasting blood sugar levels of these women decreased rapidly just prior to menses and that the glucose tolerance curve of these women tends to be somewhat flat and lower as menses approaches. These authors believe that such individuals are hypoglycemic and that this condition is exaggerated just prior to menses.

IMPLICATIONS FOR RESEARCH

The review of the literature just presented should adequately indicate that the literature relating hypoglycemia to a variety of social and emotional disorders is extremely sparse and is almost totally based upon the clinical observations of practitioners. As a result, it is impossible to draw hard and fast conclusions from these studies since the methodology does not control for the influence of numerous potential rival hypotheses. This does not, however, negate the significance of the clinical observations. Rather it means that the relationships that have been identified need to be verified in rigidly controlled experiments. It is interesting to note that the studies that have been conducted, with the exception of the literature

on the hypoglycemia-multiple sclerosis relationship, have quite consistently suggested that hypoglycemia is a causal agent in a number of social and emotional disorders. This may be due to the fact that such a miniscule amount of research has been conducted and it has attracted the attention of only a handful of researchers. As more researchers begin to delve more deeply into the implications of hypoglycemia for emotional and social disorders it is expected that this relationship will be demonstrated to be complex and influenced by numerous other factors. At the present time such evidence does not exist, which also indicates the desperate need for intensive investigation into this area.

In addition to investigating the relationship of hypoglycemia to emotional and social disorders there are several other aspects of hypoglycemia that need to be investigated. Each of these will be presented briefly.

Definition

Hypoglycemia literally means low blood sugar. Therefore hypoglycemia represents a biochemical definition of a given level of concentration of blood glucose. As such it is not a disease but a certain biochemical state of the organism. This biochemical state seems to have been elevated to the status of a disorder when it was observed that a hypoglycemic state can be accompanied by a variety of undesirable symptoms. Equating hypoglycemia with a disorder has, however, been shown to be somewhat tenuous on several fronts. First, it has been found that a relatively large percentage of biochemically and emotionally "normal" individuals experience blood sugar levels in the hypoglycemic range. Upon continuous monitoring of blood glucose levels Burns, Bregant, Van Peenan, and Hood (1965) found that 43 percent of normal individuals had blood-glucose levels that dipped into the hypoglycemic range. Cahill and Soeldner (1974) reported similar findings on 23 percent of the population. Such evidence suggests that using a biochemical definition of a disorder is subject to potentially large error in diagnosis. This deficiency in the biochemical def-

inition is even more suspect when it is recognized that many individuals who, according to the biochemical definition, would be classified as hypoglycemic, do not experience any of the symptoms of hypoglycemia during the period of time in which they are experiencing the low blood sugar. Hofeldt, Dippe and Forsham (1972) found that no symptoms were reported by 48 percent of the biochemically normal individuals whose blood-glucose levels fell into the hypoglycemic range. Cahill and Soeldner (1974) have reported asymptomatic individuals with blood glucose values as low as 35 mg/100 ml and Marks and Rose (1965) have observed an absence of symptoms in individuals with a blood glucose level as low as 20 mg/100 ml. The other side of the coin is that individuals may be symptomatic even when they have relatively high blood glucose levels. Bondy and Cardillo (1956) revealed that symptoms of hypoglycemia could occur when blood glucose levels were quite high, ranging from 80 to 146 mg/100 ml. While these symptoms were observed during continuous intravenous infusion of glucagon, other investigators have observed such results in the absence of such procedures.

Evidence such as this would seem to strongly suggest that a given concentration of glucose in the blood is not the primary factor causing the abnormal symptomatology. This lack of correspondence between blood glucose concentrations and symptomatology led Mark and Rose (1965) to advance the concept of neuroglycopenia. These investigators defined neuroglycopenia as "the signs and symptoms which develop when the supply of metabolizable carbohydrate to the neuron is inadequate for normal function" (p. 66). This concept was used since most of the symptoms equated with hypoglycemia seem to result from cerebral dysfunction occurring from a lack of glucose in the cortex. Since glucose is the primary source of energy within the cortex any deficiency could produce abnormal symptoms. Use of the concept of neuroglycopenia instead of hypoglycemia as a definition would seem to have the beneficial effect of focusing researchers' attention on factors which regulate cerebral glucose levels in addition to arterial and venous blood glucose

concentrations. Use of the term hypoglycemia as a definition of the disorder seems to have focused and maintained researchers' attention on the factors (e.g., adrenal cortex) which maintain blood glucose homeostasis within the venous and arterial circulatory system. Research has demonstrated that cerebral blood glucose concentrations are not necessarily the same as the non-cerebral blood glucose concentrations.

Etiology

In considering the etiology of hypoglycemia one must dichotomize hypoglycemia into its two main types—fasting and reactive hypoglycemia. Fasting hypoglycemia can be traced to some specific organic defect. Included among the known causative agents are insulinoma, non-pancreatic tumors, liver disease, endocrine diseases, and liver glycogen diseases. Fasting hypoglycemia does, however, seem to account for less than 30 percent of the cases (Conn, 1955). Most cases of hypoglycemia are of the reactive variety. This type of hypoglycemia is so named because it occurs as a reaction to the ingestion of food. While there are several known causes of reactive hypoglycemia (e.g., alimentary hypoglycemia and reactive hypoglycemia secondary to early diabetes) most fall under the classification of reactive functional hypoglycemia. This type of hypoglycemia has not been associated with a specific physical cause and has generally been assumed to originate from a psychogenic basis.

Dietary treatment of reactive functional hypoglycemia is the typical approach. However, psychotherapy is also a recommended treatment modality as emotional stress is not infrequently considered to be the underlying cause of the reactive functional hypoglycemia (Steinke, 1971). In fact, some individuals (Marks and Rose, 1965) consider psychotherapy to be the more important treatment modality. This assumption is based upon very minimal evidence typically of the case-study variety. For example, Smelo (1966) observed that patients frequently exhibit symptomatic functional hypoglycemia

during periods of stress. However, when no stress existed the patient was free of symptoms and exhibited a normal oral glucose tolerance curve. Rennie and Howard (1942) report a number of case studies in which psychotherapy resulted in a remission of the hypoglycemic symptoms. Anthony, Dippe, Hofeldt, Davis, and Forsham (1973) administered the MMPI to reactive hypoglycemic patients and found that they scored two standard deviations above the normal on the hypochondriasis and hysteria scales. Ford, Bray, and Swerdloff (1976) provide support for the Anthony et al. study in that over 50 percent of the patients referred to them with hypoglycemia had abnormal scores on the MMPI.

While such research does indeed suggest that emotional stress may well be a factor in hypoglycemia, the evidence is sparse and needs to be investigated more completely. Specifically, it is not known whether stress causes the hypoglycemic symptoms or the hypoglycemia enhances the possibility of emotional stress occurring. It may be that the two situations initiate a vicious cycle where each abnormality augments the other. If this is the case it may be that such a dual approach should be taken with regard to treatment. Both a dietary and psychotherapeutic approach would attain maximum benefit. Hoffman and Abrahamson (1949) have in fact reported on the significant advantages of such an approach in the context of a psychiatric practice "...the patients improved sufficiently during restoration of chemical and metabolic integrity to become much more receptive and responsive to psychiatric persuasion" (p. 246).

SUMMARY

The disorder defined as hypoglycemia has been known and discussed for over half a century. During this time the medical profession has described its symptoms and has revealed the numerous chameleon-like natures of these symptoms and the fact that these symptoms frequently manifest themselves as emotion and/or social disorders. In spite of the existence of such knowledge few researchers attempted to investigate the possibility of various social and

emotional disorders being produced by hypoglycemia. The few investigators who did follow this lead were rewarded with positive results. However, the information seems to have been buried with time. Given the potential significance of this disorder in terms of remediateing the emotional suffering of individuals it seems not only necessary but mandatory that more attention be given to this disorder. This attention should be focused on several fronts. First, attention should be focused on an alternative definition. The biochemical definition is inadequate since many asymptomatic individuals have low blood sugar concentrations. Perhaps Marks' and Rose's (1965) definition of neuroglyco-penia would be adequate. Additionally, research needs to be conducted that suggests the causes of hypoglycemia. In regard to this issue, it seems important to remember that hyperinsulinism is not the primary factor (Marks and Rose, 1965). Although it can produce hypoglycemia, the increased insulin production occurs from some factor such as insulinoma. For the most frequently occurring reactive functional variety, hyperinsulinism is not a factor. Therefore, other factors such as stress need to be investigated. It may be that conditioning (Woods and Kulkosky, 1976) in some manner generates hypoglycemia in some individuals, New and novel approaches also need to be investigated. For example, dietary intervention is the typical mode of treatment of functional hypoglycemia. This should suggest that diet may also cause this disorder. However, no study could be identified which even suggested that diet may be the culprit. Related to such a point is the fact that Hofeldt (1975) found beneficial effects from administering 15 mg per day of the vitamin folic acid. It may be that some hypoglycemics have a deficiency in certain vitamins or minerals.

Hypoglycemia seems to be one of those disorders that has been recognized but severely neglected over the years. Given the potential implications of this disorder, a call for a concerted effort toward investigating its implications seems to be in order.

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