

## Relative Hypoglycemia as a Cause of Neuropsychiatric Illness\*

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**R**ELATIVE hypoglycemia is a clinical syndrome in which patients develop symptoms referable to any system of the body as the result of a relative drop in blood sugar level in response to a high carbohydrate food intake and drinks containing caffeine. In the past the syndrome has been called functional hyperinsulinism, essential hypoglycemia, functional hypoglycemia, dysinsulinism, hypoglycemic fatigue, and neurogenic hypoglycemia. These older terms according to Buehler<sup>1</sup> are all inaccurate inasmuch as a patient may present this syndrome when there is only a relative drop in blood sugar levels without an absolute drop into low blood sugar or hypoglycemic levels. Also studies have never showed an excessive amount of insulin circulating in the blood.

The condition was first recognized by Seale Harris in 1924<sup>2</sup> and was subsequently elaborated upon by him in articles over the next 12 years. Since then articles have appeared by Moersch and Kernohan,<sup>3</sup> Portis and Zitman,<sup>4</sup> Abrahamson and Pezet,<sup>5</sup> Conn and Seltzer,<sup>6</sup> Gyland,<sup>7, 8</sup> and Phillips.<sup>9</sup> I reported my findings in 200 patients in 1959.<sup>10</sup> This report adds 100 cases to those previously reported.

Personal interest in this condition was aroused after reading a report by Gyland,<sup>8</sup> in which he stated that in his own three years of illness during which he was examined by 14 specialists and at three nationally known clinics, brain tumor, diabetes, and cerebral arteriosclerosis had been considered. Finally the correct diagnosis of relative hypoglycemia was made, and he recovered promptly by following a high protein, low sugar, caffeine free diet.

My curiosity was aroused as to how brain tumor, diabetes, and cerebral arteriosclerosis could have been misdiagnosed. In 1953 I made the diagnosis of relative hypoglycemia in one patient, in

1954 had recognized it sufficiently to make the diagnosis in eight cases, in 11 cases in 1955, and in 87 cases in 1956. Since then I have had several hundred patients with this syndrome.

This study deals with relative hypoglycemia of non-organic origin. It is well known that hypoglycemia may occur in a great variety of disorders, Conn and Seltzer<sup>6</sup> having listed more than 30 different causes of spontaneous hypoglycemia.

Relative hypoglycemia mimics any neuropsychiatric disorder, and in the past patients with relative hypoglycemia have been diagnosed as having psychoneurotic anxiety, psychoneurotic depression, depressive reactions, schizophrenia, manic-depressive psychosis, psychopathic personality, chronic alcoholism, convulsive disorders, migraine, idiopathic cephalalgia, second cervical root syndrome, neurodermatitis, and even hypertensive cardiovascular disease.

Major symptoms from a psychiatric standpoint are depression, insomnia, anxiety, irritability, lack of concentration, crying spells, phobias, forgetfulness, confusion, unsocial or antisocial behavior, and suicidal tendencies (Table 1).

The major neurological symptoms are headache, dizziness, inward and external tremulousness, numbness, blurred vision, staggering, fainting or blackouts, and muscular twitching (Table 1).

There are also extensive somatic symptoms as follows: exhaustion, fatigue, sweating, anorexia, tachycardia, cold hands and feet, obesity, chronic indigestion, bloating, abdominal spasm, muscle and joint pains, backache, muscle cramps, colitis, and convulsions (Table 1).

The criterion for making the diagnosis according to Gyland<sup>7</sup> was a drop of 20 mgm.% or more below the fasting blood sugar level during a six-hour glucose tolerance test. A potential relative hypoglycemia diagnosis was made if the drop was from 10 to 20 mgm.%. These criteria were used in this study. A patient need not have a blood

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TABLE 1.—MAJOR SYMPTOMS IN 300 CASES OF RELATIVE HYPOGLYCEMIA

<i>Psychiatric</i>	
Depression .....	60%
Insomnia .....	50%
Anxiety .....	50%
Irritability .....	45%
Crying Spells .....	32%
Phobias .....	31%
Lack of Concentration .....	30%
Forgetfulness or Confusion .....	26%
Unsocial or Antisocial Behavior .....	22%
Restlessness .....	20%
Previous Psychosis .....	12%
Suicidal .....	10%
<i>Somatic</i>	
Exhaustion or Fatigue .....	67%
Sweating .....	41%
Tachycardia .....	37%
Anorexia .....	32%
Chronic Indigestion or Bloating .....	29%
Cold Hands or Feet .....	26%
Joint Pains .....	23%
Obesity .....	19%
Abdominal Spasm .....	16%
<i>Neurologic</i>	
Headache .....	45%
Dizziness .....	42%
Tremor (Inward or External) .....	38%
Muscle Pains and Backache .....	33%
Numbness .....	29%
Blurred Vision .....	24%
Muscular Twitching or Cramps .....	23%
Staggering .....	18%
Fainting or Blackouts .....	14%
Convulsions .....	4%

sugar drop into the hypoglycemic levels of 70 mgm.% or below; but the diagnosis of relative hypoglycemia can be made, for example, in a patient whose fasting blood sugar is 110 mgm.% and whose blood sugar drops to 85 mgm.% during the course of a six-hour glucose tolerance test, a drop of 25 mgm.% being involved (Table 2). Likewise, the fasting blood sugar need not be low.

This report is based on the records of 300 cases with relative hypoglycemia. Women predominated in the series, there being 185 women and 115 men. The majority of the cases were between 30 and 50 years of age, and approximately 50 per cent of the patients had symptoms of over five years' duration. These patients had usually been to other physicians, had been treated with sedatives and tranquilizers, and even electro-convulsive therapy, without showing improvement. Some had even been on corrective dietary treatment without showing improvement because the diet was not followed strictly enough.

In 1957, before my interest in treating patients with relative hypoglycemia became generally known, an attempt was made to determine the percentage of neuropsychiatric patients with relative hypoglycemia. Two hundred seventy-five consecutive new patients seen in private neuropsychiatric practice over a period of 15 months were tabulated, and 31 per cent of these patients were found to have relative hypoglycemia with an additional 8 per cent considered as having potential relative hypoglycemia.

TABLE 2.—MAXIMUM MILLIGRAM DROP FROM FASTING

Milligrams	No. of Patients	Percentage
10- 20	69	23.0
21- 30	83	27.7
31- 40	85	28.4
41- 50	31	10.3
51- 60	13	4.3
61- 70	5	1.7
71- 80	1	0.3
111-120	1	0.3
Flat Curve	6	2.0
Dysinsulinism without Drop	6	2.0

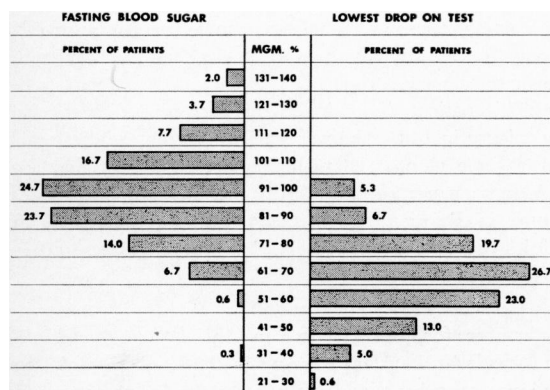


Fig. 1. Blood sugar levels.

A complete neuropsychiatric history was obtained from every patient, and a neurological examination was done. It was considered essential that a thorough dietary history be taken to encompass exactly what was eaten at breakfast, lunch, and supper, even to the number of slices of bread, beverages containing caffeine, and the type of snacks between meals and during the evening.

When a complete dietary history was obtained, it was evident that the patients with relative hypoglycemia were on a diet that contained excessive amounts of carbohydrate or drinks containing caffeine or both. Many patients reported that they were worse around Thanksgiving, Christmas and Easter times when their intake of sweets and other carbohydrates would increase.

Every patient had a four, five or six-hour oral Exton-Rose glucose tolerance test. This method may not be free of errors caused by faulty absorption and variations in the height of the initial fasting blood sugar level, but it is the simplest method of testing for hypoglycemia. If the patient can tolerate it, a six-hour test is the one preferred. To determine the normal boundaries of the six-hour test, controls have been run by Phillips<sup>9</sup> and Buehler.<sup>1</sup>

Several cases are summarized here because they illustrate some of the problems involved in the diagnosis and treatment of relative hypoglycemia.

CASE REPORTS

*Case No. 201.* The patient, a 52-year-old widow, seen for the first time on 2/1/60, had been well until Thanksgiving 1959, when she became unable to concentrate, had anorexia, lack of interest, panic about driving a car, forgetfulness, blurred vision, exhaustion, muscular jerking, and a feeling of generalized numbness particularly of the head. In the past a patient with these symptoms would have been diagnosed as having a psychoneurotic depression.

She was on a diet of fruit, toast, and two cups of coffee for breakfast; soup and two cups of coffee for lunch; and in the evening she would have meat, potatoes, a vegetable, two helpings of ice cream, and coffee. Neurological examination revealed a mild degree of peripheral neuritis.

A six-hour glucose tolerance test was obtained. The fasting blood sugar level was 82 mgm.%. At one hour the blood sugar level was 170 mgm.%, and at the fourth hour the blood sugar had dropped to 47 mgm.%, a total fall of 35 mgm.% below the fasting level (Fig. 2, Chart 1).

A high protein, low carbohydrate, caffeine free diet was started. Six weeks later she had a return of interest

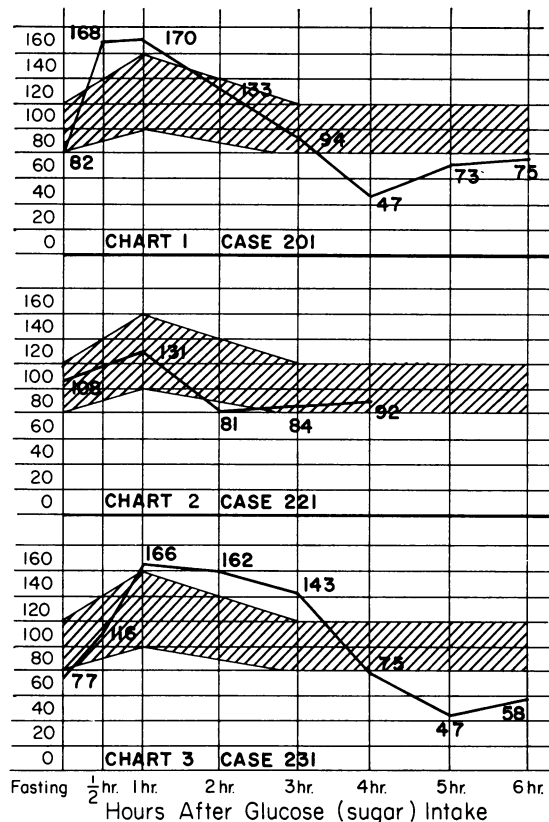


Fig. 2. Left margin shows the blood sugar in milligrams (mgm.) per 100 c.c. or 3 1/3 oz. (100 mg. of sugar per 100 c.c. is the same as 1 1/2 grains of sugar in 3 1/3 oz. of your circulating blood.)

Shaded area shows normal range differences.

Normally sugar will be lost through the kidneys at 160 to 200 mgm. At 1/2 hour the blood sugar level should not exceed the fasting level by more than 75 mgm.; the one hour level should not be over 160 mgm.

A drop of 10 points below your fasting level is considered suspicious of relative hypoglycemia and a drop of 20 or more points is definite. A flat response is also considered relative hypoglycemia.

and had improved so much physically that she had gone out to shovel snow. When seen on 5/20/60, she said, "I came to see how you were." She had no depressive symptoms.

This patient discontinued the corrective diet and had a relapse in 1963. She was started back on the diet again, and three months later she reported, "I can't find anything to worry about." When she was seen for the last time in February 1964, she was feeling fine and was following the high protein, low carbohydrate, caffeine free diet.

*Case No. 221.* The patient, a 39-year-old housewife, was seen for the first time in April 1965, complaining of headache, constant buzzing in the head, inward tremulousness, exhaustion, weakness of the lower extremities, palpitation, tension, abdominal bloating, irritability, diz-

ziness, night sweats, and twitching of the facial muscles. A patient with these symptoms usually would have been diagnosed as one of psychoneurotic anxiety.

A four-hour glucose tolerance test had been done slightly over a year previously. The fasting blood sugar level was 108 mgm.%. At one hour the blood sugar level was 131 mgm.%, and at the second hour the blood sugar level was 81 mgm.%. It was believed unnecessary to repeat the test because the blood sugar level had dropped 27 mgm.% (Fig. 2, Chart 2).

The patient had been put on the corrective diet in 1964 and felt better, but she discontinued the diet early in 1965. The importance of the high protein, low carbohydrate, caffeine free diet was discussed with the patient and she agreed to resume it.

Two weeks later she was free of headache and no longer had fatigue or palpitation. The dizziness, buzzing in the head, and abdominal symptoms had improved.

When she was seen again five weeks later on 6/21/65, she was virtually symptom free and stated, "My disposition has improved a lot; they can't get over it. I laugh about so many more things. I used to be a fanatic about keeping the house clean, and now I let the work go if I feel like it."

*Case No. 231.* The patient, a 50-year-old male accountant, was seen for the first time in February 1964. His case had been diagnosed as neurodermatitis, and he had had dermatologic symptoms since he was 20 years of age. He had received treatment at a nationally known clinic in Boston and at a major medical center there, as well as having been treated in a medical center in Virginia. In the past he had been advised to follow various types of diets for allergy; he had received numerous injections including ACTH: and he had taken cortisone and different antihistamines orally. In addition to the dermatologic complaint, he had drowsy spells relieved by taking crackers or a candy bar.

He was referred by a dermatologist for psychotherapy because all types of dermatologic treatment had failed to effect relief. At the time of his first visit in February 1964, the skin looked like crinkled red leather.

A six-hour glucose tolerance test had been done in 1960, the fasting blood sugar level having been 77 mgm.%; the one-hour blood sugar level was 166 mgm.%; and at the fifth hour the blood sugar had dropped to 47 mgm.%, a total drop of 30 mgm.% being involved (Fig. 2).

In spite of the fact that the patient was told the blood sugar level was low, he had never gone on a high protein, low carbohydrate, caffeine free diet. This therapy was instituted at the time of his first visit.

When the patient was seen six weeks later, he was generally better and the skin was not as red or as tender; and he had been able to reduce the amount of antihistamine. He had also discontinued non-specific desensitization treatment, and said he was about 50 per cent improved.

When the patient was seen for the last time on 3/18/65, the skin was approximately normal, and he

said: "I have had the best year I have ever had in 30 years. If you see the dermatologist, tell him you gave me psychotherapy because he will not believe the diet brought about my recovery."

#### TREATMENT

All patients were instructed to follow Gyland's<sup>8</sup> modification of the Seale Harris diet. This diet is high in protein and fat and low in carbohydrate. Nutriment between meals and every two hours throughout the evening was considered essential as well as abstinence from any medication or beverage containing caffeine. Caffeine is prohibited because it stimulates the adrenal gland; then liberated adrenalin causes glycogenolysis in the liver, and an elevation of the blood sugar level occurs, only to be followed by a drop just as in the case of eating carbohydrates.

Many articles have indicated that fructose or levulose is utilized much more efficiently than dextrose.<sup>15</sup> Fructose does not require insulin in order to be metabolized and therefore can provide immediate energy. Fructose is present in high concentration in embryonic blood and in amniotic fluid, and it is the only carbohydrate present in human semen.<sup>15</sup> Certainly this corrective diet calling for fruit and fruit juices at and between meals is high in fructose. Incidentally, I never permit a dehydrated or a post-operative relative hypoglycemia patient to have an intravenous injection of glucose, but insist on intravenous levulose which is readily available.

In addition to treatment with diet, nearly 70 per cent of the patients were treated with a series of injections of calcium-glycerophosphate. The reason for the use of calcium is that, according to Meltzer and Kitchell,<sup>11</sup> calcium levels control the activity of an enzyme which when present elevates blood sugar levels. The reason for using the phosphorus radical is that "all energy utilized by the organism is obtained by the hydrolysis of high energy phosphate bonds . . . the inherent energy is utilized in such diverse reactions as the phosphorylation of glucose."<sup>12</sup> In every step involving carbohydrate metabolism, either in its synthesis to stored glycogen or in its breakdown for utilization by muscle, phosphorylation has to take place.

Usually the patient received a series of 6 to 12 injections of calcium-glycerophosphate in a dosage of 10 cc. intragluteally. This can be given all at one site and is virtually painless because the

preparation has a neutral pH. Many patients return to ask for an injection because previous injections have made them feel greatly improved. In fact, some patients want an injection just before they go on vacation because they realize the injections have made them more energetic.

Buehler<sup>1</sup> treated many of his 350 patients with nicotinic acid, 100 mgm. before meals and at bedtime, and felt it was highly beneficial. He could not explain the rationale of this treatment, and I have had no experience with it.

By following the corrective diet and receiving injections of calcium-glycerophosphate, approximately 85 per cent of the 300 patients reported here were either recovered or greatly improved.\*

#### COMMENT

It is my belief that the condition of relative hypoglycemia is one of the most common causes of neuropsychiatric illness, and I should like to propose that it has been caused by changes in human dietary habits. Every animal is anatomically adapted for a particular type of diet. For example, an anteater has curved claws on the front legs, a long snout, and a long sticky tongue—physical features which make it adapted to a diet of ants. A squirrel, which is a member of the rodent species, has sharp teeth, front paws to hold a nut while it is being chewed open; so that it is physically adapted for its diet. A robin, with a bill, is adapted for pulling up worms; whereas a hummingbird, which is lighter in weight, has a longer bill and wings that beat faster, is anatomically adapted for sucking nectar from a flower. The entire animal kingdom shows physical adaptation of this sort, and these observations lead to the conclusion that there is phylogenetic adaptation to diet.

If the human animal will follow a diet that resembles that of primitive man, who ate the meat of small animals, fish, and fowl, who robbed nests of eggs, ate root and leaf vegetables, nuts, fruits, and berries, the body will function at maximum physiologic efficiency; whereas a high carbohydrate diet with drinks containing caffeine invariably elevates the blood sugar level, and in a person who is not diabetic, some type of insulin overreaction occurs<sup>13</sup> with hypoglycemia as the end result. Ideas as to the change in human diet over

the past ten thousand years have been excellently discussed by Yudkin.<sup>14</sup>

The diagnosis of relative hypoglycemia may be missed if we think a patient must have an attack of weakness, trembling, tachycardia, sweating, and a feeling he is going to faint instead of recognizing that symptoms of relative hypoglycemia will be those of depression, insomnia, anxiety, irritability, poor concentration, crying spells, and phobias. Seale Harris<sup>16</sup> said, "The neurologic manifestations of . . . hypoglycemia are varied and fantastic." It is, therefore, essential that every patient coming for psychiatric or neurologic evaluation have a six-hour glucose tolerance test as a routine procedure and that we get over the idea a fasting blood sugar will be of diagnostic help. A two or three-hour test is inadequate because in the first few hours the glucose levels may be high; whereas a major drop may occur after this point, and the diagnosis will be missed. It is extremely important that a complete dietary history be obtained.

#### SUMMARY

1. Relative hypoglycemia is considered as an important cause of neuropsychiatric illness.
2. Every patient with neuropsychiatric illness should have a six-hour glucose tolerance test, particularly those whom we have been prone to diagnose as having psychoneurotic anxiety states or depressive reactions.
3. The six-hour glucose tolerance test should be interpreted as positive if there is a blood sugar drop of 20 mgm.% or more below the fasting blood sugar level; or if the drop is from 10 to 20 mgm.% below the fasting blood sugar level, potential relative hypoglycemia should be considered.
4. A corrective diet high in protein, low in carbohydrate, and free of caffeine will effect recovery in approximately 85 per cent of the patients.
5. By making the diagnosis of relative hypoglycemia and teaching patients what they should eat, they will be spared years of suffering, electroshock therapy, and the hazards inherent in taking sedatives, stimulants, and tranquilizers.

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\* Calcium glycerophosphate is available as CALPHOSAN®, the Carlton Corp., 45 E. 17th St., New York, N. Y.

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