

Spontaneous Hypoglycemia

(A Review and Report of a Case due to Hyperinsulinism associated with Carcinoma of the Pancreas.)

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THIS subject is one which has emerged in the past decade from a mere line in a text book of medicine to definite and important clinical entity. Its literature is growing by leaps and bounds and serves to impress one with the necessity for considering this disease as a possibility in all obscure cases, the more so when it is appreciated that its manifestations are protean. For example, in the case reported below the only symptom was loss of consciousness. When confronted with a case of coma a mental review of the possible causes conjures up the usual list with insulin shock standing foremost, yet hyperinsulinism, per se, is apt to be forgotten. The need for careful and routine laboratory studies is thus emphasized. In some cases a diagnosis can be made from the symptoms, but there are others where the diagnosis rests solely on blood sugar determinations. Some idea of the frequency of this disorder may be obtained from the following statement by Seale Harris: "Judging from the number of cases of hyperinsulinism now being reported by many clinicians and from blood sugar studies in 3,076 cases, in my series of 6,641 adult patients largely ambulatory with gastro-intestinal and nutritional disorders, it seems probable that hyperinsulinism is almost as frequent as the opposite secretory disorder of the insulin-forming cells of the pancreas, hypoinsulinism (diabetes mellitus)."

Symptoms: Signs and symptoms may affect almost every system of the body, yet there is never anything to indicate directly the change in the pancreas itself. All the manifestations of the disorder result from the action of excessive secretion of insulin in causing an abnormal decrease in the blood sugar level. Acquaintance with the variable features of the hypoglycemic syndrome is therefore essential. The occurrence of hypoglycemia in patients treated with insulin injections has made the symptoms associated with low blood sugar well known. The symptoms which occur spontaneously from overproduction of insulin by the pancreas are identical. Yet they may be far more difficult to identify since in the former case the relation of the symptoms to the injection and action of insulin may be readily apparent, and points to their origin. Harris divides these cases into (1) The mild type where the patient complains most frequently of excessive hunger, weakness, nervousness, anxiety or irritability, one or two hours before meals. All these subjective symptoms are relieved by eating, only to recur three or four hours after meals and often during the night. In addition there may be trembling, flushed face or pallor, profuse perspiration and tachycardia. These symptoms may be exaggerated by exercise, overwork, either mental or physical, worry and other emotional disturbances. Recurring headaches and inability to concentrate the

mind on work late in the afternoon have been observed. Fatigability and insomnia are frequent complaints. Vertigo, dyspnea, "smothering spells," cardiac palpitation and precordial pain have been noted and have been relieved by dieting, with frequent feedings between meals. In the mild cases the fasting blood sugar usually ranges between 0.075 and 0.060 per cent. (2) Moderately severe type where the symptoms outlined as occurring in the mild type may be present in an exaggerated form. Eating gives relief for only one or two hours when more food is demanded, in order that the victim can continue to perform his regular duties. The vicious circle of getting hungry and weak and eating keeps up until the patient becomes obese. In this type the fasting blood sugar level usually ranges from 0.060 to 0.050 per cent. (3) The severe type where attacks of unconsciousness predominate, either with or without convulsions. In some cases there is associated violent delirium. Sometimes the patients have appeared as if they were intoxicated from alcohol but would become normal after taking food. Some have complained of "crazy spells", and actual psychotic symptoms have been observed by several clinicians. Abdominal pain has been pronounced in several cases and has simulated appendicitis, gallbladder infection and duodenal ulcer, so that exploratory operations, with removal of the appendix and gallbladder, and gastro-enterostomies have been performed without relieving the abdominal pain. The blood sugar levels in the severe type are usually very low, below 0.050 per cent.

Rynearson and Moersch reviewed all cases of spontaneous hypoglycemia that had been reported up to 1934 to see how many patients presented neurological symptoms and it was found that they all had such symptoms of one type or another. To show their varied nature a few of the symptoms will be mentioned: Stupor, coma, muscular twitching, convulsions, loss of memory, general change in behavior, disturbance of speech, nervousness, restlessness, mania, epileptiform seizures, ocular symptoms such as diplopia, blurred vision and dilated pupils, vertigo, listlessness, headache, tremors, a positive Babinski sign, vague paresthesias, loss of sphincteric control, irrationality and emotional instability foaming at the mouth, etc. It does not surprise us therefore, that diagnoses of epilepsy, tumors of the brain and insanity should have been made where patients were suffering from hypoglycemia.

Diagnosis: This rests on the blood sugar determination, which before the ingestion of food is usually between 80 and 110 mg. for each 100 cc. If the blood sugar falls below 70, hypoglycemic symptoms are likely to appear; if it drops below 50 they are usually serious. Allan points out, however, that the occurrence of symptoms is not related directly to the blood sugar level alone, for sometimes it may fall below 40 without any apparent effect. The report must be interpreted carefully, for a healthy individual may have a blood sugar below the range usually considered normal and in children particularly it may even drop below 60. The greatest difficulty arises from the fact that the blood sugar may be reported normal in a case of hyperinsulinism unless the specimen of blood is taken exactly

at the time that symptoms are present. The same investigator adds that to elicit the hypoglycemia and show the origin of symptoms one may observe (1) Influence of fasting which causes the symptoms to manifest themselves. Sugar should be given to the patient for a therapeutic test and if the symptoms are due to hypoglycemia, they will be relieved within a few minutes. (2). Influence of exercise. Where the symptoms are not apparent at the time of examination, an exercise test may cause them to appear. It must be remembered that hypoglycemia may be found in a normal individual after exertion, particularly if it is strenuous and prolonged. Therefore it is only when a change in blood sugar after ordinary activities causes definite symptoms that it may be considered pathological. (3). Response to sugar tolerance tests. The curves obtained in these cases have been variable but as a rule they all show a low level of the blood sugar at the end.

Etiology: Most of the recent work favors the view that true hyperinsulinism is a result of a tumor, either adenoma or carcinoma, of the island cells of the pancreas. Thus in a case of Wilder's at the Mayo Clinic in which surgical exploration, subsequent necropsy and histological examination revealed carcinoma of the islands of Langerhans, extracts of metastases of the tumor in the liver provided material which acted like insulin on injection into rabbits. Extractions from the non-cancerous part of the liver were without activity. This is apparently the only case of paroxysmal hypoglycemia in which the evidence of secretion of insulin by a tumor is conclusive. There remain, however, many cases of hypoglycemia wherein not only exploration by the surgeon but also examination after death have shown nothing abnormal in the pancreas.

Harris stresses the view that a previous, usually unrecognized, pancreatitis is a factor in the causation of hyperinsulinism and diabetes. And the most important predisposing cause of the pancreatitis is a diet deficient in vitamins. Focal and general infection may involve the pancreas as a complication and the pancreatitis may be unrecognized. An hereditary tendency has been mentioned, as well as worry, other emotional disturbances and overwork as playing a part in producing excessive and uncontrolled insulogenesis.

Wilder, however, is of the opinion that where nothing abnormal exists in the pancreas, the case is not one of abnormal secretion of insulin. His discussion of paroxysmal hypoglycemia from causes other than hyperinsulinism is now summarized:

1. Experimental studies bearing on the relation of the anterior lobe of the pituitary body to the metabolism of carbohydrate seems to indicate that the anterior lobe elaborates a hormone which is antagonistic to the action of insulin. Lucke claims to have proved that it accomplishes this effect by nervous stimulation of the medulla of the suprarenal glands while others consider its action to be on the cortex of the suprarenal glands or directly on the liver. Whatever the mechanism, the removal of the influence leads to hypoglycemia, this being observable even in the absence of the pancreas, as was shown by the experiments of Houssay.

2. The role of the suprarenal and thyroid is still a matter of some controversy and therefore will merely be mentioned in passing. It should be noted that the function of adrenalin and thyroid hormone in provoking glycogenolysis, in the liver and muscle, is well established.

3. Paroxysmal hypoglycemia of hepatic origin. The presence of the liver is necessary for the maintenance of an adequate level of sugar in the blood. This is a positive fact about which there is perfect agreement. Destruction of the liver must be extensive before it is reflected by any disturbance of the regulation of the sugar of the blood. Eighty per cent of the total substance may be removed without producing hypoglycemia. Thus while hypoglycemia from destruction of the liver has been a clinical observation after poisoning with cinchophen, phosphorus, carbon tetrachloride and other drugs, it occurs usually only as a terminal event. Acute yellow atrophy and yellow fever likewise provoke abnormal depression of the sugar of the blood but only as a terminal event. Carcinoma, if massive, has been found associated with hypoglycemia. Cirrhosis of the liver and fatty liver may have this effect.

4. There are still some cases with mild attacks of paroxysmal hypoglycemia and some with very severe attacks for which no anatomic explanation is apparent. This is termed idiopathic hypoglycemia and it appears to be associated with the type of person who has some instability of the autonomic nervous system.

5. Infants of diabetic mothers may suffer from one type of hypoglycemia which is correctly attributed to overfunction of the anatomically normal pancreas. These infants are kept alive by frequent small feedings starting immediately after birth, supplemented if necessary, by the injection of 10 cc. of 10 per cent glucose subcutaneously.

6. Hypoglycemia may occur in the infants of normal mothers where the labor has been protracted and the obstetrician has followed the usual practice of not providing food for many hours after the delivery.

Treatment: Just as in insulin shock, glucose solution intravenously is a specific remedy for an acute attack of paroxysmal hypoglycemia. 10 grams are usually sufficient. Adrenalin or pituitary extract may be used as an emergency measure but glucose is more effective and practical. For the prevention of mild attacks a diet high in fat and low in carbohydrate is recommended. In this way it is hoped to reduce the insulin stimulating elements to a minimum. Frequent small feedings are necessary, of course, and the diet must fulfill the caloric, protein and vitamin requirements. In the severe cases early operation is demanded because of the prospect of securing relief. Furthermore, the danger of malignancy developing beyond control is a real one. The details of the operation depend on the individual case. Tumors are removed. In one case where no tumor was found, subtotal resection of the gland was carried out with excellent results. This was a suggestion of Wilder's and in this connection he says: "While I dislike the idea of curing one disease by producing another, in

this case it probably is justifiable. We are able effectively to control diabetes but are unable to manage severe cases of paroxysmal hypoglycemia."

Case Report:

(I am indebted to Dr. J. W. MacKenzie of the Polyclinic for permission to report this case.)

Mr. F. a 51 year old, married farmer was admitted to the care of Dr. J. W. MacKenzie at the Prince Edward Island Hospital on June 20th, 1936, with a history of coma. Wife and three children all living and well.

History of illness: Patient states he was unconscious for 4 days in April, 1936. Onset during sleep. He had been in good health up to that time except for "gas in stomach" and a pounding heart. Vision became poor but has been improving gradually. Members of his family noted profuse sweating and occasional quivering of the whole body while he was unconscious. Infrequent spells of dizziness. Since April he hasn't been feeling as well as usual and has been doing a reduced amount of work. Doesn't think he has lost any weight. Week before admission patient complained of soreness in the occipital region and on the following day he again lapsed into coma for a period of 12 hours. No aura and no recollection of events during that time. He awoke with no residua. Patient believes that his memory isn't as clear as it was formerly. Patient was seen by two physicians who were unable to arrive at a diagnosis and hospitalization was advised. Details of treatment, if any, are unknown.

Family history: Father died at the age of 75 with cancer of the rectum.

Personal history: Scarlet fever at 10 years and pneumonia at 36 years. Uncomplicated recovery in both.

Physical examination: Patient is an adult male who appears to be of stated age, well developed though somewhat underweight. Face weatherbeaten. Head and neck normal. Oral hygiene poor. A few carious teeth in lower jaw. Upper teeth replaced by artificial denture. Chest shows some scoliosis to the left. Prominent ribs. Slight limitation of movement on both sides. Percussion note not impaired. Bronchovesicular breathing at the left apex posteriorly. VR and WP increased slightly in same area. A few crepitant rales at right base posteriorly. Cardiovascular system normal. Abdomen: flat and soft. No tenderness or masses. Liver, kidneys or spleen not palpable. Hernial orifices and genitalia normal. Skin: normal tissue turgor. No glandular enlargements. Extremities normal. Rectal examination negative. Nervous system: Intelligence below average. Patient seems dull and occasionally laughs without provocation. Does not appreciate the seriousness of his illness. Motor and sensory functions normal. Cranial nerves: 3: Pupils equal and regular. React to light and accommodation. Fields of vision normal. Ophthalmoscopic examination reveals normal fundi. Other nerves apparently normal. Superficial and deep reflexes active. No clonus or Babinski. No asynergy. Romberg's sign negative. Pass pointing test negative.

Temp. normal, pulse 80, respirations 20, blood pressure 152/84.

Laboratory data: Urinalysis and Mosenthal test normal. R. B. C. 4,190,000. Hb 84%. W.B.C. 4,400. Neutrophiles 75%, lymphocytes 16%, monocytes 7%, eosinophiles 1%. Blood urea 13 mg. per 100 c.c. Blood calcium 9mg per 100 c.c. Negative Kahn test. Spinal fluid: 2 W.B.C. per cu. mm. Globulin nil. Sugar 0.02%. Colloidal gold curve normal.

Blood sugars: in coma 0.02%. Various fasting blood sugar values ranged from .03% to 0.05%. Values obtained on July 3rd: noon 0.06%, 1 p.m. 0.10%, 2p.m. 0.08%, 3 p.m. 0.07%. Glucose tolerance test:

Hours:	Blood Sugar in per cent:
0	0.02
1/2	0.25
1	0.20
1 1/2	0.16
2	0.11
2 1/2	0.09
3	0.06
3 1/2	0.04

X-ray of skull showed no abnormalities.

Diagnosis: Hyperinsulinism due to tumor of the pancreas.

Treatment: On July 1st, patient was placed on a high fat and carbohydrate diet, i.e. P 76, F 164, C 200 gms. Calories 2580. The feedings were divided up as follows: Day: 8, 10 and 12 a.m., 3 and 5 p.m. Night: 8, 10 and 12 p.m., 2 and 4 a.m. However, he still continued to go into coma, especially if the food was delayed several moments. 20% glucose-saline intravenously would soon bring him around. Its effect was remarkable. Patient would be drenching wet, frothing at the mouth and quite rigid. When approximately 100 c.c. had run into the vein, he would open his eyes, smile and when asked how he felt, would reply, "First rate". Later though, when coming out of these attacks, he was disorientated, with hallucinations, frequent shouting and struggling. On July 17th the diet was increased in fat. However, patient still continued to go into coma every third or fourth night. On July 23rd a high carbohydrate diet was decided upon with the idea of "soaking up" the excess insulin: P 98, F 40, C 318. Calories 2,112. This was found to be more effective and he went one week without taking one of his spells. However, his stomach rebelled against so much sweet stuff and he asked to be put back on the previous diet. This was done and he immediately began to go into coma again. Adrenalin was frequently injected while getting the glucose solution ready, and while its effect was transitory, it afforded a rough estimate of liver function. The adrenalin mobilized the glycogen reserve of the liver.

It was obvious that conservative medical treatment was unsatisfactory and therefore more radical measures were considered. The arguments for operative interference were as follows:

1. Even if frequent feedings proved to be effectual, they were not compatible with a normal life.
2. Dieting did not reduce the frequency of the attacks.
3. Diet offered no hope of a cure.
4. Other clinics have reported cures by removing adenomas from the pancreas.

Patient was operated on by Dr. Seaman, who entered the abdominal cavity via a left para median incision from the costal margin to the umbilicus. The pancreas was exposed through the gastrohepatic omentum. Findings: Nodular mass about the size of a goose egg in the tail of the pancreas. Adhesions to the lateral abdominal wall, kidney and spleen. Several smaller nodules around head of pancreas. Regional lymph glands were enlarged and hard. The distal third of the pancreas with the tumor was removed. Post-operative notes: While the patient stood the operation well, he developed a high temperature and rapid pulse a few hours later. 10 per cent glucose-saline solution was administered. After a stormy course the patient died on August 16th, three days after the operation.

Pathologist's report: Scirrhus carcinoma of the pancreas.

SUMMARY

1. Paroxysmal hypoglycemia is not an uncommon disorder.
2. Symptoms are referable chiefly to the nervous system, although any system may be affected.
3. The diagnosis is made by careful blood sugar studies.
4. Hypoglycemia, due to hyperinsulinism, is a result of tumor of the island cells of the pancreas.
5. Paroxysmal hypoglycemia may be a result of disease of the pituitary, thyroid and adrenal, liver or an unstable autonomic system, and has been observed in infants of diabetic mothers and in infants of normal mothers after prolonged labor.
6. The treatment of the acute attack is the administration of sugar. Mild attacks may be prevented by frequent feedings of a diet high in fat and low in carbohydrate. Early surgical exploration is warranted in severe cases.
7. A case report is presented where the outstanding symptom was periodic attacks of loss of consciousness, due to hyperinsulinism as a result of carcinoma of the pancreas.

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