HYPERINSULINISM AND FUNCTIONAL HYPOGLYCEMIA

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The purpose of this article is to present two typical cases of hyperinsulinism associated with islet cell adenoma of the pancreas, to present four unusual cases of functional hypoglycemia, and to emphasize the differential diagnosis of these two conditions.

In this article the term "hyperinsulinism" is restricted to hypoglycemia due to adenoma of the islands of Langerhans, and the term "functional hypoglycemia" to hypoglycemia without clinical evidence of organic disorders commonly associated with hypoglycemia. Cases of obvious adrenal, pituitary, or liver disease are excluded. It is beyond the scope of this communication to review the etiology of hypoglycemia or cases reported in the literature.[1, 2, 3, 4]

CASE REPORTS

Case 1—*Adenoma of pancreas cured by excision.* A man, aged 22, was seen on March 29, 1943 because of attacks characterized by trembling, weakness, sweating, and at times unconsciousness. The attacks began two and one-half years previously, occurred three or four times weekly, and were increasing in frequency and severity. They usually

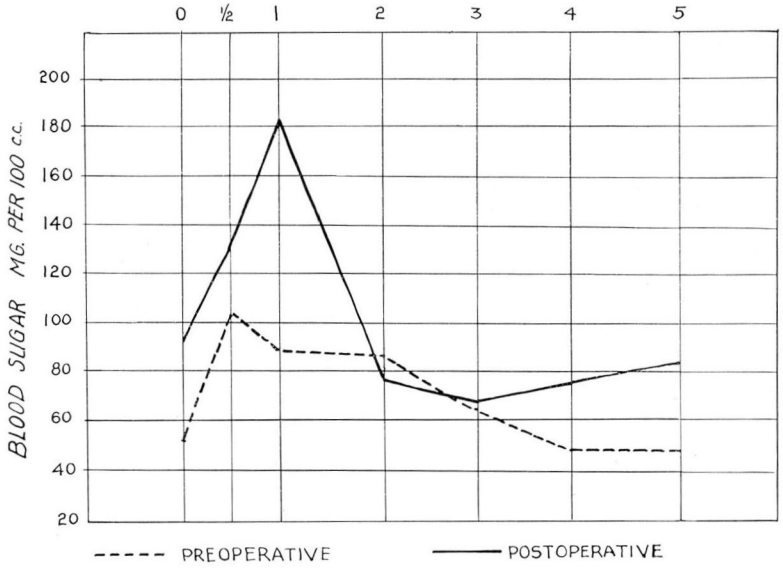

FIG. 1—Preoperative and postoperative glucose tolerance curves (case 1).

appeared at night but were often induced by exertion or fasting. The patient was repeatedly relieved by drinking orange juice. His illness was accompanied by a gain of 40 pounds.

Fasting blood sugar levels were 39 and 51 mg. per 100 cc. A single dose, hundred gram, oral glucose tolerance test on March 31 produced a curve as shown in figure 1. An insulin tolerance test on April 10 in which 5 units of standard insulin was given intravenously revealed the following:

Minutes	Fasting	20	30	40
Blood sugar—mg. per 100 cc.	52	33	33	40

Symptoms of stupor and drowsiness during the test were partly relieved by 7 minims of a 1:1000 solution of adrenalin.

The pancreas was explored on April 12 by Dr. T. E. Jones, and a benign adenoma 1 cm. in diameter was removed from the anterior surface of the body of the pancreas. The postoperative course was uneventful except for the development of a pancreatic fistula, which healed in two months.

The patient remained free from further attacks of hypoglycemia and lost 30 pounds. Glucose tolerance on June 30 became normal as shown in figure 1. The patient had been given a well balanced diet for one week prior to this test.

Case 2—*Adenoma of pancreas associated with menstrual disorder surgically cured.* A housewife, aged 30, first seen on January 24, 1944, complained of attacks of circumoral tingling, generalized nervousness, weakness, profuse drenching sweats, mental confusion,

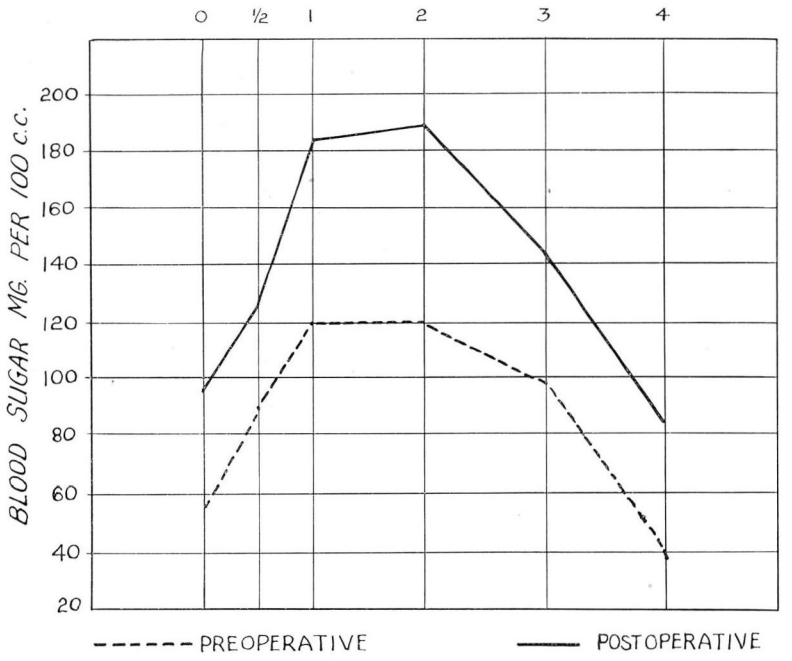

FIG. 2—Preoperative and postoperative glucose tolerance curves (case 2).

ptyalism, and unconsciousness. The attacks began four years previously and had increased in frequency and severity. They were precipitated by fasting and/or exercise and were relieved promptly by food. A weight gain of 30 pounds occurred. The menstrual cycle varied from twenty-eight to forty-two days. The flow was very dark on the first day and lasted from five to six days. Libido was absent.

At the time of symptoms blood sugar levels ranged repeatedly from 29 to 50 mg. per 100 cc. Random fasting blood sugar levels ranged from 37 to 46 mg. per 100 cc. but were not always accompanied by symptoms. A single dose, hundred gram, oral glucose tolerance test produced a curve as shown in figure 2. Adrenalin tolerance test after administration of 8 minims of 1:1000 adrenalin solution subcutaneously was as follows:

Minutes	Fasting	15	30	45	60	75
Blood sugar—mg. per 100 cc.	37	20	35	35	35	46

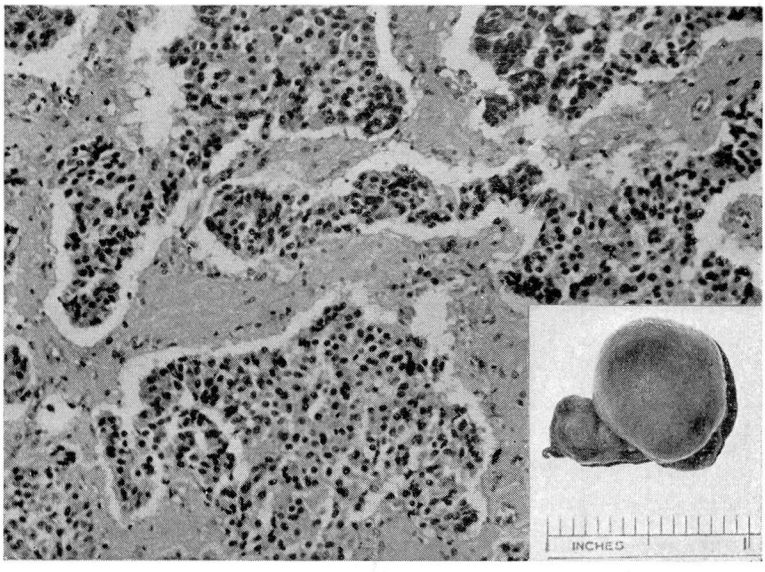

Fig. 3

On February 21 an exploratory laparotomy was performed by Dr. T. E. Jones. No adenoma was found. Since the patient's symptoms progressed during the next few months and were regarded as pathognomonic of islet cell hyperplasia, a second laparotomy was performed on June 4. An adenoma measuring 1.5 by 1.2 by 1 cm. was removed from the substance of the pancreas beneath the anterior surface of the first part of the tail (fig. 3). Microscopically this proved to be a benign adenoma of the islands of Langerhans.

The patient remained symptom free and by limiting food intake lost 11 pounds in three months without development of symptoms. On occasions she fasted fifteen hours without symptoms. The irregular menses previously described promptly became normal.

A glucose tolerance test two weeks postoperatively was normal (fig. 2). The diet preceding this test was regular and well balanced. An insulin tolerance test on June 19 failed to show any residual insulin sensitivity, and the response to 8 minims of adrenalin was altered slightly as follows:

Minutes	15	30	45	60
Blood sugar—mg. per 100 cc.	65	79	79	79

Case 3—*Functional hypoglycemia associated with sterility.* A woman, aged 32, complained of headaches, childlessness, and indigestion. She had been married for five years and had attempted pregnancy for three years. Menstrual periods were regular and normal. The headaches, which were frequent and lasted one to one and one-half hour, were experienced for five years, were usually unilateral, and often occurred during sleep or upon rising. Gaining weight or maintaining normal weight was difficult. Symptoms of indigestion were vague and consisted mainly of gas and belching.

Physical examination was essentially normal. An intradermal histamine test did not reproduce a typical headache. A single dose, hundred gram, oral glucose tolerance test revealed a curve in detail as follows:

Minutes	Fasting	30	60	120	180	240
Blood sugar—mg. per 100 cc.	82	107	75	45	60	79

A typical headache appeared at the second hour of the test.

The patient was placed upon a low carbohydrate, high protein, high fat diet. Both the headaches and the digestive distress were completely relieved. In the next three months she gained 16 pounds. The patient became pregnant approximately one month after she began the diet. Pregnancy and labor were normal.

One year later she was still symptom free but noted a recurrence of headaches with temporary dietary indiscretions. Two and one-half hours after eating the blood sugar level was 108 mg. per 100 cc.

Case 4—*Functional hypoglycemia associated with menstrual disorder.* A woman, aged 29, complained of irregular menses and nervousness. Menarche was at the age of 15. The periods were irregular from the start, occurring at intervals of twenty-three to thirty-three days, and lasted for five to seven days. She married at the age of 18 and promptly became pregnant. After delivery menstrual periods varied from twenty-one to thirty-eight or forty days. At times the flow lasted for ten days; spotting was common. Drainage of bilateral ovarian cysts elsewhere did not modify the menses. Intervals between periods became longer, and spotting continued. An endometrial biopsy on the twenty-sixth day of the menstrual cycle revealed an endometrial development consistent with that of the seventh or eighth day of a normal menstrual cycle.

The patient also complained of headaches, temporary confusion, weakness, excessive sweating, and severe hunger; these symptoms were frequently relieved by eating. She ate a great amount of rich food. Because of these symptoms suggesting hypoglycemia a single dose, hundred gram, oral glucose tolerance test was done and revealed the following:

Minutes	Fasting	30	60	120	180	240
Blood sugar—mg. per 100 cc.	91	96	92	35	95	37

Typical symptoms were experienced at the second and fourth hours of the test.

A low carbohydrate, high protein, high fat diet was prescribed. When the patient was seen about seven months later, the hypoglycemic symptoms were controlled. The last three menstrual periods occurred at twenty-eight to thirty-one day intervals. The flow was still prolonged but was more nearly normal in amount with less tendency to spotting between menses. Another endometrial biopsy on the twenty-sixth day of the menstrual cycle showed an endometrial development comparable with that of the twentieth to the twenty-second day of a normal cycle with evidence of secretory changes.

Case 5—*Functional hypoglycemia associated with unusual nail changes.* A housewife, aged 29, complained of redness, pain, and swelling of the nail beds with eventual deformity and loss of the nails. Other symptoms were anorexia, nausea and vomiting, excessive falling of scalp hair, cessation of menses, nervousness, and weakness. The fingernails of all but the fifth finger of the right hand and the fourth finger of the left hand were ridged. Along the edges the nails were rough and friable. At the base of the involved nails, except that of the second finger of the right hand, were paronychial changes with redness and swelling. Smears and cultures for fungus infection were negative. During diagnostic studies a glucose tolerance test was done and revealed the following:

Minutes	Fasting	30	60	120	180	240
Blood sugar—mg. per 100 cc.	81	107	88	53	63	63

The patient was placed on a low carbohydrate, high protein, high fat diet. Within two months all symptoms were alleviated. The fingernails were growing normally, although several remained deformed. She gained 10 pounds. After seven and one-half months her appetite was normal, and she had no attacks of weakness or nausea. Hair loss continued as did amenorrhea. Her fingernails were almost completely normal, being the best in four or five years.

Case 6—*Functional hypoglycemia associated with unusual nail changes.* A housewife, aged 39, complained of nervousness, palpitation, and tension in the neck muscles. General physical examination revealed no remarkable findings. A basal metabolic rate determination was normal. Vaginal smear tests indicated normal ovarian function. Because symptoms were not adequately explained and since hypoglycemia was suggested, a glucose tolerance test was performed.

Minutes	Fasting	30	60	120	180	240
Blood Sugar—mg. per 100 cc.	108	150	94	74	93	34

Symptoms appeared at the fourth hour of the test.

All symptoms were relieved for seven months by dietary manipulation. She then disclosed that her fingernails had been affected by the illness. A separation of the nail beds of all fingers occurred repeatedly in the previous three years, four or five nails being simultaneously affected. The changes began as a small red spot usually in one corner or in the center of the nail. This area would spread to the periphery of the nail, and after a time the reddened area would turn white and separate from the nail bed (fig. 4). Several toenails were similarly involved. Fungus infection had been previously excluded. During the next eight months all of the nails became completely normal and remained normal as long as the patient observed the diet; nail changes recurred with dietary indiscretion.

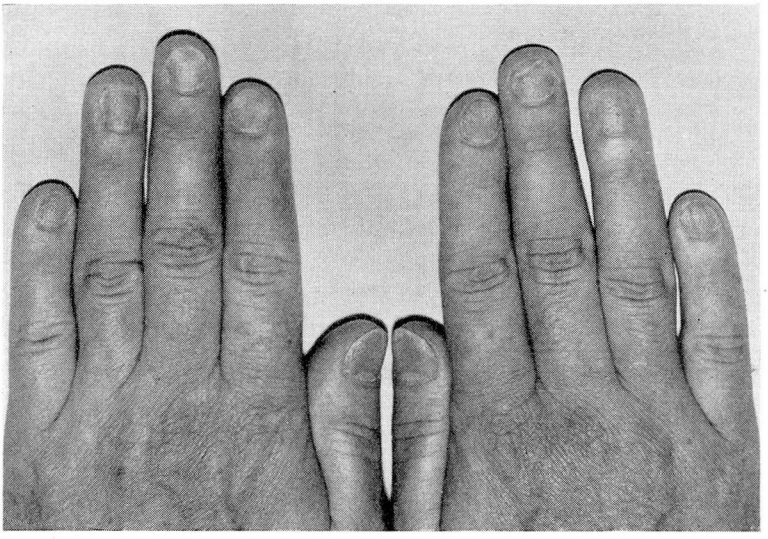

FIG. 4

COMMENT

Certain important features serve to differentiate functional hypoglycemia and hyperinsulinism. In hyperinsulinism the hypoglycemic episodes are usually more profound and tend to increase in frequency and severity. Attacks are often induced by fasting and/or vigorous muscular activity. The patient frequently discovers that food promptly relieves the symptoms, and consequently the total daily caloric intake is usually increased. Weight gain is thus a common accompaniment, unless the pancreatic lesion is malignant. Dietary manipulation usually fails to alleviate symptoms. Of these features the most important is intolerance to fasting and exercise. The diagnosis is strengthened by a fasting blood sugar level consistently below 60 mg. per 100 cc. More often the fasting blood sugar level is 50 mg. per 100 cc. or lower. Such a patient may be found unconscious during the night or before breakfast.

In contradistinction functional hypoglycemia is more bizarre in its clinical manifestations and thus more difficult to recognize. The symptoms are usually less severe and do not tend to progress. The patient is less apt to discover that symptoms are relieved by food, since hunger is not an outstanding symptom. Thus weight gain is not common; in contrast malnutrition is frequently observed. Dietary manipulation almost invariably controls and often corrects hypoglycemic trends and usually completely rehabilitates the patient. Fasting and exercise may

accentuate symptoms but less consistently than in hyperinsulinism. The fasting blood sugar may be low but is usually well within normal range. Hypoglycemia is most often apparent two to four hours after eating, especially with excessive carbohydrate intake after several hours of fasting.

These contrasting features are demonstrated by the cases reported. The functional cases are chosen mainly because of unusual features that have been corrected by treatment in such a way as to suggest strongly that they were intimately related to the hypoglycemia.

In case 3 we believed that the headaches were of hypoglycemic origin. Whether or not the apparent infertility was directly related to hypoglycemia, to malnutrition, or to totally unrelated causes is speculative. However, it is interesting that pregnancy occurred promptly after the diet was begun and before malnutrition was corrected or further studies of sterility were obtained. A further correlation is suggested between ovarian function and hypoglycemia in cases 2 and 4, because irregular and scant menses approached normal after the adenoma was removed.

In cases 5 and 6 unusual nail changes accompanied the hypoglycemia. In one instance the nails became completely normal, and in the other they remained healed as long as the patient adhered to the diet.

SUMMARY

Certain criteria are important in the differential diagnosis of hyperinsulinism with adenoma of the pancreas and functional hypoglycemia. Two typical cases of hyperinsulinism due to islet cell adenoma of the pancreas were encountered, both of which remained well after excision of the tumor. In four cases of functional hypoglycemia sterility occurred in one, a menstrual disorder in one, and nail changes in two.

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