HYPERINSULINISM DUE TO AN ISLET-CELL ADENOMA

A CURE, WITH METABOLIC STUDIES BEFORE AND AFTER OPERATION

BY

W. G. DUNCAN MURRAY, M.B., Ch.B.

(From the Aberdeen Royal Infirmary)

Hyperinsulinism due to an islet-cell adenoma of the pancreas is not a common condition. From 1931, when an operative cure was first recorded by Carr *et al.*, until 1945, only 56 cases of cure had been reported (Walker and Boger, 1945). Some cases have since been recorded, but the diagnosis is occasionally missed simply because the condition is not kept in mind. In many of the published cases the initial diagnosis was wrong and the condition was confused with narcolepsy (Walker and Boger, 1945), cerebral tumour (Womack, Gnagi, and Graham, 1931), and psychosis (Lups, 1944). Sendrail (1947) discussed the history of this condition and gave an exhaustive review of the older literature.

The following case is reported because the history was the key to the diagnosis, and the standardized insulin-tolerance test of Fraser and Smith (1941) was performed. These authors standardized this test for the diagnosis of endocrinological disorders of glucose metabolism. Many writers (Fraser, Maclay, and Mann, 1938; Fraser, Albright, and Smith, 1941; Burtneiss, Koehler, and Saint, 1941; Sendrail, 1947) have stressed the importance of the response to insulin injection in the diagnosis of hyperinsulinism, but a search of the literature has failed to reveal a case in which the standardized intravenous test has been carried out.

Case History

A 40-year-old housewife was admitted to Aberdeen Royal Infirmary on July 19, 1947, for investigation. The history was obtained from the patient and her husband, both of whom were good witnesses.

Nine months before admission she began to have occasional periods of drowsiness in the mornings and difficulty in waking. These attacks lasted for one to two hours and she was well for the remainder of the day. Her husband noticed a change in her behaviour during the attacks: she often wandered aimlessly about the house and wept for no apparent reason. Retrograde amnesia was occasionally associated with the drowsiness.

The attacks became more frequent, and on one occasion, three months before admission, she suffered from general weakness of the legs and was unable to move her right arm. She was given a whisked egg and milk and quickly recovered. Her physician prescribed amphetamine sulphate, one 5-mg. tablet to be taken at 6 a.m. and another at 8 a.m. She took these daily for eighteen days, and during that time and for two weeks after she was free from symptoms.

Ten days before admission she had a three-hour period of amnesia with automatism. During that time she wandered outside to the washing-house, lit the boiler fire, and did a considerable amount of washing. Her husband found her in a dazed condition, with a burn of her arm and parts of her clothing charred. He took her indoors and revived her by giving her food.

For one week before admission she had periods of drowsiness every morning, but now they were more severe and lasted up to eight hours. During an attack she had never been seen to shake or go stiff, to have incontinence, or to bite her tongue. In addition to the burn she had only once fallen and hurt herself. There had been no personality change apart from the abnormal behaviour during the attacks. At no time had she had the sensation of warmth or sweating associated with the drowsiness. Her appetite, though poor, showed no change, and her weight remained constant.

There was nothing of note in the family and personal histories. She had two healthy children aged 18 and 10 years.

Physical Examination.—The patient was fairly well nourished; height, 5 ft. 3½ in. (161 cm.); weight, 9 st. 7 lb. (60.5 kg.). She was intelligent, but often her actions were of a childish nature. No abnormality was found on physical examination. Her blood pressure was 126/66. There were no masses or tenderness in the abdomen. No signs of hypothyroidism or other endocrine disorder were present. Urinalysis was negative, and neither sugar nor urobilinogen was present.

Special Investigations.—X-ray examination showed no abnormality of the bones of the skull. No abnormal shadows appeared in the abdominal skiagram and no abnormality of the alimentary tract was demonstrated by barium meal. In particular the duodenum was normal. The visual fields were full and the fundi normal. Fasting blood-sugar estimations were carried out from July 21 (Chart 1). The cerebrospinal fluid showed

CHART 1.—Fasting blood-sugar levels before and after operation, with incidence of hypoglycaemic attacks.

no abnormality, but the sugar content was 42 mg. per 100 ml., the blood-sugar level at the same time being 100 mg. per 100 ml. The blood Wassermann reaction was negative. Blood examination showed: haemoglobin, 102%; red cells, 5,010,000; colour index, 1.02. The red cells were normal and no macrocytosis was present. Plasma chloride as NaCl was 525 mg. per 100 ml.; plasma cholesterol, 200 mg. per 100 ml. The basal metabolic rate was minus 16.

Description of the Attacks

Spontaneous.—These varied in detail from day to day, but followed the same general pattern. The patient appeared to wake normally, but soon fell into a drowsy condition and appeared to be asleep. She resisted attempts to wake her and would turn away, pull the bedclothes over her head, and curl up in bed. She showed some perseveration and repeated such phrases as "I'm all right," "I'm not asleep," and "Leave me alone." Occasionally when left alone she chattered to herself. Her speech at all times was clear. She would not carry out orders to move arms or legs or to sit up, and at times tended to be negativistic, gripping her eyes tightly when attempts were made to open them. There was no significant change in pulse or blood pressure; skin colour and temperature remained the same and at no time during an attack was sweating a feature. During the more severe attacks twitching of the facial muscles and tremors of the fingers and eyelids were seen. The pupils were dilated and reacted briskly to light. The muscles appeared hypotonic; the muscle reflexes were exaggerated, but muscle clonus could not be elicited, and the plantar responses were flexor. The attacks were quickly terminated by administration of carbohydrate, either by mouth or intravenously, without the patient's knowledge. Retrograde amnesia was present.

Induced.—Only during the insulin-tolerance test were the spontaneous attacks fully reproduced, but in addition sweating and the sensation of warmth were present. There was no retrograde amnesia after the hypoglycaemic attacks that occurred during the glucose-tolerance and insulin-tolerance tests and it was possible to elicit the following symptoms. The most constant of these were increasing frontal headache and blurring of vision. Less severe were the weakness, lassitude, and increasing hunger; the latter was present only in the glucose-tolerance tests, and may have been due to the length of the total fasting

period (eighteen hours with only 50 g. of glucose) or to the fact that meantime other patients were being fed.

Specific Investigations

Glucose-tolerance Tests.—Glucose, 50 g., was given after a twelve-hour fasting period, and blood-sugar estimations were carried out every half-hour for six hours. The blood-sugar curve during the first two hours was normal, the fasting level being reached in about that time, but all the readings were low, especially at the fourth and fifth hours. During one of these tests 0.03 mg. of adrenaline was injected subcutaneously and

CHART 2.—Glucose-tolerance test before operation.

though the symptoms were aggravated, there was no change in the blood-sugar level (Chart 2).

Insulin-tolerance Test.—This was carried out as recommended by Fraser and Smith (1941). The patient was given extra carbohydrate for four days before the test was carried out. Insulin in the dose of 3.7 units per square metre of body surface was given intravenously and the blood-sugar levels were estimated at intervals (Chart 3). Normally the maximum fall to about 50%

CHART 3.—Insulin-tolerance test before operation. Dotted line shows composite normal from six cases.

higher is the index. **Report:**—120th minute sample, 81% of fasting sample (normal=90–110%). Index of hypoglycaemia responsiveness, 449 (normal=470–620). **Interpretation:**—The curve shows hypoglycaemia unresponsiveness. In the absence of evidence of hypopituitarism, adrenocortical insufficiency, liver disease, or marked emaciation from anorexia nervosa this finding is suggestive of hyperinsulinism.

From the history and investigations a clinical diagnosis of organic hyperinsulinism was made and surgical treatment advised.

Operation

On Aug. 20 an operation was performed by Mr. G. Gordon Bruce. Glucose, 50 g., was given at four hours and one hour before operation. The anaesthetic used was nitrous oxide, oxygen, and ether, the latter because it tends to raise the blood-sugar level. The abdomen was opened by a right paramedian incision and the gastro-colic omentum was divided. The stomach was then hooked up by two malleable retractors and the transverse colon displaced downwards, exposing the entire anterior surface of the pancreas. At this point a bluish tumour mass about 2 cm. in diameter immediately became visible, lying slightly to the left of the midline on the lower border of the pancreas near the junction of the tail with the body of the pancreas. This lower border was freed so that the tumour could be held between the finger and thumb, a series of chain

sutures of fine linen was inserted into the pancreas, and the mass was excised by cutting freely into the surrounding tissue. The gap in the pancreas was then sutured and the gastro-colic omentum closed. A soft rubber drain was left *in situ*.

Pathological Report.—“The tumour is 7 mm. in diameter and is embedded in normal pancreatic tissue. There is no true capsule to the tumour, but the surrounding pancreatic tissue is flattened and compressed. The tumour is vascular, and the cells show acinar formation. There is no evidence of malignant change. Special staining methods fail to demonstrate that the tumour cells are of the β cell type. **Diagnosis:**—benign islet-cell adenoma.”

Post-operative Progress

There have been no more drowsy attacks, and the patient is well (sixteen months after operation). Immediately after the operation blood-sugar estimations were carried out at approximately four-hourly intervals, and after an initial rise to 187 mg. per 100 ml. and a fall to 162 mg. the blood-sugar level rose steadily to a maximum of 197 mg. at the twenty-fourth hour, though nothing but sips of water were being given. The hyperglycaemic period lasted four days and was accompanied by slight glycosuria for two days. After four days the fasting blood-sugar level fell to normal (average 86 mg. per 100 ml.). Convalescence was uneventful, apart from a small pancreatic fistula which discharged for five weeks.

Forty days after operation the following tests were carried out:

Glucose-tolerance Test.—This showed a normal response, although at the third hour the blood sugar fell to a low level (Chart 4).

Insulin-tolerance Test (Chart 5).—**Report:**—120th minute sample, 92% of fasting sample. Index of hypoglycaemia responsiveness, 488. **Interpretation:**—Curve shows: insulin resistance (maximum fall in blood sugar delayed beyond thirty minutes after intravenous insulin), and normal hypoglycaemia responsiveness.

CHART 4.—Glucose-tolerance test after operation.

CHART 5.—Insulin-tolerance test after operation. Dotted line shows composite normal from six cases.

Discussion

The present case illustrates the steps by which a diagnosis of organic hyperinsulinism can be arrived at, first by the demonstration that the patient's symptoms are due to spontaneous hypoglycaemia, and then by the elucidation of the special features that distinguish organic hyperinsulinism from other causes of spontaneous hypoglycaemia.

Of the three main causes of spontaneous hypoglycaemia mentioned by Conn (1940)—hepatogenic hypoglycaemia, functional hyperinsulinism or cryptogenic hypoglycaemia (found in persons of unstable personality and almost always associated with psychoneurotic symptoms), and organic hyperinsulinism from an adenoma or carcinoma of islet tissue—the first two could be excluded. There was no clinical evidence of hepatic insufficiency and the glucose-tolerance test did not show the high plateau curve characteristic of liver disease. The intolerance to fasting, with hypoglycaemic blood-sugar levels, the lack of correlation of the attacks with previous ingestion of a carbohydrate meal, and the patient's stable personality before the onset of the

present attacks excluded the condition of cryptogenic hypoglycaemia.

The occurrence of hypoglycaemia unresponsiveness in the insulin-tolerance test, with restoration of a normal response after removal of the islet-cell adenoma, indicates a causal relationship and affords confirmation of the suggestion of Fraser, Albright, and Smith (1941) that organic hyperinsulinism would be expected to produce hypoglycaemia unresponsiveness in the insulin-tolerance test.

This case is typical of the cases of islet-cell adenomata already reported and illustrates many points. It shows the successful results of surgery in hyperinsulinism due to islet-cell adenomata. Medical treatment is indicated in cryptogenic hypoglycaemia but is dangerous in organic hyperinsulinism. A high-carbohydrate diet tends to fatten the patient and so makes for a poor operative risk later. Repeated prolonged hypoglycaemic attacks can cause permanent damage to the central nervous system. These tumours show a tendency to become malignant and there should be no delay in attempting operation.

From this case it would appear that the coma, muscular twitches, and altered behaviour—equivalent to Himwich's (1944) cortical and subcortical phases of hypoglycaemia—were due to the low blood-sugar level. The symptoms such as lassitude, headache, and visual disturbances would seem to be due to adrenaline secretion reflexly induced by a sudden fall in the blood-sugar level. The small dose of adrenaline given during the glucose-tolerance test seemed to aggravate the symptoms of hypoglycaemia without altering the blood-sugar level. This case also showed that amphetamine sulphate could temporarily relieve the hypoglycaemic attacks, presumably by raising the blood-sugar level.

A short post-operative period of hyperglycaemia has been found in cases in which blood sugars have been estimated. This would appear to be due to the partial depression of the activity of the normal islets, while the requirements of the body were covered by the adenoma. The insulin resistance after operation may be due to persistence of a high level of the insulin antagonists, such as the glycotropic factor of the anterior pituitary.

Finally, the case illustrates the great importance of accurate differential diagnosis in cases of spontaneous hypoglycaemia, the difficulty of attempting to diagnose hyperinsulinism by the glucose-tolerance test alone unless this is prolonged for several hours, and the value of the insulin-tolerance test in diagnosing organic hyperinsulinism.

Summary

A case of organic hyperinsulinism is reported. The condition was cured by the removal of an islet-cell adenoma. Glucose-tolerance and insulin-tolerance tests were carried out before and after operation. The usefulness of the latter in the differentiation of hyperinsulinism from other causes of hypoglycaemia is emphasized.

I wish to thank Professor John Craig for permission to publish this case, and Professor J. Young and Dr. W. M. Davidson for the pathological report. I am indebted to Dr. Ian A. Anderson for carrying out the insulin-tolerance tests and for his help and guidance so freely given.

REFERENCES

- Burtress, H. I., Koehler, A. E., and Saint, J. H. (1941). *Ann. intern. Med.*, **14**, 1915.
 Carr, A. D., Parker, R., Grove, E., Fisher, A. O., and Larimore, J. W. (1931). *J. Amer. med. Ass.*, **96**, 1363.
 Conn, J. W. (1940). *Ibid.*, **115**, 1669.
 Fraser, R. W., Albright, F., and Smith, P. H. (1941). *J. clin. Endocrinol.*, **1**, 297.
 ———, Maclay, W. S., and Mann, S. A. (1938). *Quart. J. Med.*, n.s., **7**, 115.
 ——— and Smith, P. H. (1941). *Ibid.*, n.s., **10**, 297.
 Himwich, H. E. (1944). *Amer. J. digest. Dis.*, **11**, 1.
 Lups, S. (1944). *Acta med. scand.*, **117**, 261.
 Sendraill, M. (1947). *L'Hyperinsulinie*. Masson, Paris.
 Walker, H., and Boger, W. P. (1945). *Arch. intern. Med.*, **75**, 109.
 Womack, N. A., Gnagi, W. B., and Graham, E. A. (1931). *J. Amer. med. Ass.*, **97**, 831.

RINGWORM OF THE SCALP

TREATMENT BY X-RAY EPILATION WITHOUT SUBSEQUENT LOCAL APPLICATION

BY

F. L. LYDON, M.B., M.R.C.P.

Dermatologist, Ringworm Clinic

T. STEPHANIDES, M.D., D.M.R.D.

Assistant Radiologist

AND

T. M. ROBB, M.R.C.S., L.R.C.P., D.M.R.T.

*Director, X-ray Department
Lambeth Hospital, London*

The many ingenious attempts made by various schools to increase the efficiency of local treatment in cases of tinea capitis have so far been unsuccessful, and the latest report by Brain *et al.* (1948) on the effect of fungicides in penetrating bases, although suggestive, must be evaluated in the light of further experience before we can hope to dispense with epilation by x rays as the method of choice in these cases.

Sequeira, Ingram, and Brain (1947) state that "it must be realized that they [x rays] have no parasitocidal action, but are simply used to remove the hair, after which continuous treatment must be applied to the bald scalp in order to eradicate the fungus before the hair grows." Again, Becker and Obermayer (1947) say: "It is the long period between epilation and regrowth that gives roentgen irradiation a superior advantage over all other methods of epilation, for during this time the surface of the scalp can be rendered antiseptic. . . . After epilation is complete local treatment . . . is carried out vigorously until no evidence of the disease can be found."

It can be seen from the preceding quotations that x-ray epilation is regarded only as ancillary, and that it is the local application of fungicides that really brings about cure. The late Mr. G. Stebbing, Director, X-Ray Department, Lambeth Hospital, however, believed that local treatment was unnecessary, and it has been the policy at the Lambeth Clinic to treat all cases of tinea capitis by the following method.

Method

X-ray epilation is carried out by the four-field technique (four main fields and one subsidiary field), the following factors having been worked out by Dr. L. H. Clark.

Victor KX10 Apparatus.—K.V.P. 100. Half-value layer 1.6 mm. Al. Tube current 7mA. Primary volt reading 75v. (selector switch—high). F.S.D. 19.5 cm. Open field 16.6 in. (42 cm.) diameter.

Dose.—Four main fields: 500 r skin dose (backscatter factor, 1.24). Subsidiary field: 124 to 160 r according to the size of the patient's head, the average being 142 r. In very small children this, of course, is omitted.

Instructions to Patients.—The patients are simply instructed to wash the scalp with soap and warm water from the fifteenth day after treatment until epilation is complete. A cotton cap is provided by the department, and the patients are advised to make another like it. The patient wears one of these caps while the other is sterilized by boiling on alternate days.

After-care.—Inspection is carried out by the clinic about three weeks later, and thereafter as is considered necessary. Local application of ung. adipis lanae is prescribed to soften