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PANCREATIC ISLET ADENOMATOSIS WITH HYPOGLYCAEMIC EPISODES

BY

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The clinical manifestations of endogenous ("spontaneous") hypoglycaemia were probably first described by Porges (1910), of Vienna, in a patient with Addison's disease; in 1912 Harvey Cushing described several more examples in patients suffering from pituitary chromophobe adenoma. As a result of the discovery of insulin in 1921 the clinical picture of exogenous hypoglycaemia in the form of "insulin reactions" soon became familiar, and Seale Harris (1924) described five cases in which the patients had experienced similar attacks of hunger, anxiety, weakness, and sweating which were correlated with low blood-sugar levels; in this way he introduced the term "spontaneous" hypoglycaemia, suggesting that this may result from hyperinsulinism produced by overaction of the pancreatic islet cells.

The first example of a pancreatic islet adenoma recorded in the literature was described by Nicholls in 1902, but this was an incidental necropsy finding and the clinical details are not available. The first successful surgical removal of such a tumour was carried out by Roscoe Graham (Howland, Campbell, Maltby, and Robinson, 1929); by 1950 Howard, Moss, and Rhoads were able to analyse the findings in almost 400 cases of islet-cell tumour previously recorded in American medical writings. The rare condition in which there is widespread diffuse adenomatosis of the pancreatic islet cells was first discovered by Lang in 1925, and the relevant literature was reviewed in 1955 by Bickerstaff, Dodge, Gourevitch, and Hearn, who described the first example seen in Great Britain and the seventh in the world. In this the surgically resected body and tail of the pancreas showed very numerous adenomata varying in diameter from 0.2 to 7 mm., together with many hyperplastic islets, though there had been no corresponding visible or palpable abnormality at operation. The

following case report relates to the first example of islet-cell adenomatosis seen in the General Infirmary at Leeds, and appears to be the second example in Great Britain and the eighth in the world.

Case Report

A schoolmistress aged 49 suffered from "attacks" which started in 1949 and occurred about once a week but later became irregular, with free periods of several months, though sometimes there were as many as six in a fortnight. She was of above average intelligence and her previous medical and psychiatric history was non-contributory. It was, however, difficult to elicit an accurate account of her symptoms, but the attacks were apparently all similar in pattern, starting with sudden diplopia in all directions and often associated with tingling round the lips, followed by disturbance of consciousness which varied in severity from a lack of concentration to drowsiness or sleep, though she was probably never in a completely unrousable state and she never had a convulsion; they lasted from 15 minutes to about two hours, and often occurred before lunch or in the evening. During many attacks she continued to walk about but was unsteady and talked nonsense, so that she was often thought to be drunk, and she always had total amnesia for the whole episode except the aura. Soon after the onset a general physician made a diagnosis of hysteria. In 1952 I was consulted and considered (with reserve) that this was "idiopathic" psychomotor epilepsy; at this time the electroencephalogram (E.E.G.) was normal (Fig. 1). In 1953 she was sent to a neurosurgeon, who investigated her condition fully, including air-encephalography, with negative results.

During 1956 the attacks became more frequent, and consequently she was admitted to the neurological department of Pinderfields Hospital, Wakefield. Routine physical examination was repeatedly negative, and during several days of observation she had no attack. A glucose-tolerance test (by the Hagedorn-Jensen method using capillary blood) gave the following results: Fasting blood sugar, 65 mg./100 ml.; blood sugar $\frac{1}{2}$ hour after 50 g. glucose, 75 mg.; at 1 hour, 45 mg.; at $1\frac{1}{2}$ hours, 55 mg.; at 2 hours, 60 mg.; at 3 hours, 65 mg.; at 4 hours, 45 mg.; at 5 hours, 30 mg.; at 6 hours, 35 mg. Urine tests were not recorded.

After this test had been pursued for five hours, consciousness was seriously disturbed, so that she was only just able to swallow glucose, which produced a rapid return to her normal mental state.

The patient was then transferred to the General Infirmary at Leeds, where a second glucose-tolerance test (by a modification of the Folin-Wu method using venous blood) was carried out after 24 hours' starvation; during the fifth hour of the test there was a similar disturbance of consciousness though the blood concentrations were higher (Table I).

A simultaneous E.E.G. by Dr. M. J. Parsonage (during which the patient was very drowsy, with evidence of a cold, clammy sweat) showed a comparatively small amount of alpha rhythm in the parieto-occipital and posterior temporal regions which was frequently interrupted by irregular, diffuse, slow activity of mixed theta and delta frequencies. The record was indicative of a diffuse disturbance of cortical activity compatible with a hypoglycaemic state; there were no precise localizing signs, but at times the slow activity appeared to be maximal in the right temporal region (Fig. 2).

Laparotomy was performed by Mr. A. J. Latchmore on

TABLE I

	Blood Sugar (mg./100 ml.)	Urine
Fasting	60 mg.	No sugar
50 g. glucose orally:		
$\frac{1}{2}$ hour	80 "	
1 hour	60 "	" "
$1\frac{1}{2}$ hours	60 "	
2 "	50 "	" "
3 "	50 "	
4 "	50 "	
5 "	50 "	

July 18, 1956; the pancreas appeared normal both to the naked eye and on palpation, but a hemipancreatectomy was performed. Pre-operatively blood-sugar concentrations of 40 and 60 mg. per 100 ml. were recorded and the immediate post-operative value was 230 mg. A further glucose-tolerance test was carried out eight days later and showed (Table II):

TABLE II

	Blood Sugar (mg./100 ml.)	Urine
Fasting	110	No sugar
50 g. glucose orally:		
1 hour	100	
1 1/2 hours	150	" "
2 hours	150	" "
3 "	110	
4 "	130	
5 "	120	
6 "	110	

At the time of writing the patient has had no attack since operation, and repeated blood-sugar estimations, carried out at different times of the day, have never been below 100 mg. per 100 ml.

Although there was no gross abnormality of the resected portion of the pancreas, multiple small adenomata were

present in stained serial sections cut at approximately 0.5-cm. intervals; they varied in size from 4 mm. in diameter down to about three times the normal diameter of an islet, and the largest ones were visible to the naked eye. Some of these adenomata displayed a papillary pattern, but they were all well circumscribed and there was no attempt at infiltration of the surrounding tissue. No malignant changes were seen (Figs. 3 and 4, for which I am indebted to Dr. F. O'M. Shiell).

The pathological process involved all the pancreatic tissue resected—that is, the tail and about half the body—and there was no evidence of reversion towards normal even in the sections nearest the head. This is an interesting feature, because, in the normal pancreas, islet tissue is found in greater concentration in the body and tail than in the head; thus it would seem likely that similar lesions are present in the remainder of the pancreas left *in situ*, and the prognosis must therefore be guarded.

Comment

In retrospect it is clear that the general physician, the neurosurgeon, and I were misled by the history. Had the patient's emphatic denial of any attack lasting more than a few minutes been rejected and the statement of her friend that the attacks lasted for about an hour been accepted, the diagnosis might well have been established earlier, and, indeed, when the latter account was adopted a diagnosis of endogenous hypoglycaemia was made with some confidence before laboratory investigations were instituted.

It will be noted that a glucose-tolerance test carried out by different methods in two hospitals showed fasting blood-sugar levels

FIG. 1.—E.E.G. Normal appearances. Blood sugar, 90 mg. per 100 ml. at commencement of recording.

FIG. 2.—E.E.G. Abnormal. Generalized slow activity of maximal amplitude in the right anterior temporal region. Blood sugar, 50 mg. per 100 ml. at commencement of recording.

FIG. 3.—A group of islets; the two upper left are approximately normal in diameter, the larger islet in the central field being typical of many seen in the sections ($\times 75$).

FIG. 4.—An example of one of the larger islets, which is visible to the naked eye ($\times 65$).

of 65 and 60 mg. per 100 ml., despite the fact that the latter test was done after 24 hours' starvation. Not only are there many who would regard these figures as within the normal range, and therefore not conforming with Whipple's triad for the diagnosis of organic hyperinsulinism, but there is a further departure from the Whipple dictum in that this patient never seems to have had an attack in the fasting state. According to Whipple (1944), the diagnostic criteria for establishing hyperinsulinism are: (1) a neuropsychiatric disturbance occurring in the fasting state, (2) blood-sugar levels below 50 mg. per 100 ml., and (3) rapid relief of symptoms following the administration of glucose. It will be noted that in spite of prolonged fasting no blood-sugar level below 50 mg. per 100 ml. was recorded in the General Infirmary at Leeds, and though this level was maintained from the second hour to the end of a prolonged glucose-tolerance test it was not until the fifth hour that symptoms developed.

Despite these anomalies I felt confident that the clinical picture was that of organic hyperinsulinism, and it was agreed with the surgeon in advance that in the event of the pancreas appearing normal at laparotomy a hemipancrcreatectomy would be carried out. It would seem that failure to remove part of the pancreas in patients who have appropriate symptoms but in whom no pancreatic abnormality is found may well be the explanation for the apparent rarity of islet-cell adenomatosis.

Attention has already been drawn to the probability that this patient still has adenomatosis of the remaining half of the pancreas, and in the event of a return of symptoms consideration would have to be given to further surgical intervention, though this will not be undertaken without a careful trial of the only valuable medical treatment available for organic hyperinsulinism—namely, a high-carbohydrate diet.

It is interesting that both the neurosurgeon and I took the view that this patient was suffering from temporal lobe seizures, and there would seem to be little doubt that her attacks did result from disturbance of function in one or both temporal lobes, though the duration of the episodes was much longer than that usually seen in temporal lobe epilepsy. It is therefore interesting that the E.E.G. showed an abnormality in the right temporal region, and attention has already been drawn by Moorhouse (1956) to the importance of disturbed temporal lobe function in hypoglycaemic states. Though most references in the literature describe symmetrical E.E.G. patterns in hypoglycaemic states, a similar asymmetry was recorded by Bickerstaff *et al.* (1955).

Summary

A case of pancreatic islet adenomatosis is described, being probably the second in Great Britain and the eighth in the world.

The history, which extended over seven years, consisted of recurrent episodes of disturbed consciousness with amnesia and automatism, reminiscent of the symptoms of temporal lobe dysfunction.

Attacks did not occur in the fasting state, and the fasting blood-sugar levels were never below 60 mg. per 100 ml.

When a diagnosis of organic hyperinsulinism is established a hemipancrcreatectomy should be carried out if the pancreas appears to be normal at operation.

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HUMAN LIVER METABOLISM

BY

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In the last 20 years much has been learnt about the enzyme patterns and synthetic processes taking place in living tissues. More recently, accurate localization of these processes to certain parts of the cell has been achieved. In carbohydrate metabolism, the enzymes concerned with glycolysis—that is, breakdown of glucose to pyruvic acid—are soluble and are present in the cytoplasm, whereas the enzymes concerned with completing

the oxidation of pyruvic acid to carbon dioxide and water (tricarboxylic acid cycle) are insoluble and are localized on the mitochondria. This latter enzyme system is also the pathway for the oxidation of fatty acids and amino-acids (see Diagram). These oxidations are responsible for energy production (the process of oxidative phosphorylation), the majority of this energy being produced by the mitochondria. Claude has called the mitochondria "the energy dynamos of the cell." The mitochondria are also the site of a number of syntheses, such as the synthesis of fats and nucleic acids.

Much of this information has been obtained from investigations carried out on the liver of experimental animals, notably the rat. In this species a great deal is known about the levels of activity of these enzymic processes, and changes resulting from experimental liver damage. In man, however, there are many gaps in our knowledge of these matters, mainly because samples of liver as required for enzyme studies have to be removed either during life or immediately after death. Waterlow