SPONTANEOUS HYPERINSULINISM DUE TO BENIGN HYPERPLASIA OF ISLET CELLS

BY

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Since Cushing (1930) reported the first successful operation on a patient with an insulin-secreting adenoma, over 400 cases, found to have symptoms associated with tumours of the islet cells, have been reported in the world literature; but there have also been cases in which the diagnosis has been made clinically, but examination of the pancreas, either at operation or autopsy, has failed to reveal anything in the nature of a tumour. In some of these cases the pathologist has reported a generalized hyperplasia of the islets, the cells being increased both in size and number. The subject has been well reviewed by Howard, Moss and Rhoads (1950). These authors found reports in the literature of 81 patients diagnosed as suffering from hyperinsulinism, in whom no tumour was discovered at operation. In 10 of these no histological report was available. Of the remaining 71, 48 were reported as having normal pancreatic tissues, four showed 'chronic inflammation', one hypoplasia, and 18 hyperplasia of the islet cells. Two of the latter group were children. One (Callaway, 1946) was a boy of 8 years, who had a history of 'faints' and convulsions for a year; on one occasion his blood sugar was found to be 23 mg. %. Subtotal resection of the pancreas was performed, after which the symptoms did not recur during the following five years and subsequent blood sugar levels were within normal limits. The other case was a girl of 4½ months (Agustsson, Tudor and Chisholm, 1947), with a six-weeks' history of convulsions. On one occasion a blood sugar level of 18 mg. % was found. Subtotal resection of the pancreas was carried out with clinical and biochemical cure. She was followed up for eight months after operation. In reporting this case the authors emphasized the importance of early diagnosis and treatment if serious neurological sequelae were to be avoided. The criteria they accepted as indicating the need for surgery were those propounded by Whipple (1938). They are as follows:

- (1) There should be proof of a persistent or a frequent recurring hypoglycaemia by blood analysis.
- (2) It should be shown that the symptoms expected to be relieved by surgery can be relieved by dextrose administration.
- (3) It should be shown that the symptoms cannot be relieved by conservative measures of diet regulation.

Case Report

Baby W. F., the third child of healthy parents, was admitted to the Royal Hospital for Sick Children, Edinburgh, in July, 1951, because of recurrent fits. He had been born at full term and weighed 7¼ lb. When he was 6 weeks old his weight gain was considered unsatisfactory, so breast feeding was discontinued and he was put on to a modified cow's milk formula. This he evidently took satisfactorily. One morning, when 7 weeks old, he was found in his cot, unconscious and twitching. This turn lasted a few minutes only and then he appeared well, but he had further similar attacks seven and 10 weeks later, and thereafter each morning before being given his first feed of the day. He was given phenobarbitone, gr. ¼ t.d.s. with apparent benefit, for the fits became less frequent, only recurring about once a week. This state of affairs continued till he was 8 months old, when he commenced having fits about twice a day. It was then that he was admitted to hospital for fuller investigation. It was noted on admission that he was a well nourished infant, weighing 20 lb. 10 oz. He could not sit up unaided and appeared very lethargic. No other abnormality was discovered on physical examination. Many investigations were carried out but no abnormality was discovered. However, a lumbar puncture revealed a clear cerebrospinal fluid, normal cytologically and biochemically except that the sugar level was only 20 mg. %. A glucose tolerance test was therefore carried out. The result was as follows:

	(mg. %)
Fasting blood sugar	40
After ½ hour	52
After 1 hour	60
After 1½ hours	74
After 2 hours	56

Essentially similar results were obtained when the test was repeated on three occasions.

The blood sugar levels were estimated on a number of occasions that coincided with the onset of the convulsive episodes. These levels varied from 32 to 42 mg. %. An attempt was made to control the seizures by the administration of large quantities of sugar; this was partially successful but it was found necessary to give over 100 g. of sugar per day to be effective. This was clearly impracticable as a long term dietetic measure. An insulin sensitivity test produced no untoward reaction (1 unit of soluble insulin injected intravenously) and so on October 23, 1951, laparotomy was carried out by Mr. Mason Brown. An apparently normal pancreas was found and about two thirds of it were resected. The child made a satisfactory recovery from the operation, took normal feeds for his age, and the fits did not recur during the post-operative period. He also appeared more alert and vigorous. Seventeen days after operation a further glucose tolerance test was carried out. The result was as follows:

	(mg. %)
Fasting blood sugar ..	70
After $\frac{1}{2}$ hour ..	112
After 1 hour ..	123
After $1\frac{1}{2}$ hours ..	109
After 2 hours ..	80

Six months later the test was repeated and found to be essentially unchanged, the occasion being a further admission to hospital on account of an isolated convulsion. He was then aged 18 months, weighing 26 lb., and looking very fit. He was not walking or saying any words but no other abnormality could be discovered and he was discharged home. During the next year he had four further isolated fits and he was therefore given phenobarbitone, gr. 1 daily, and the fits did not recur. When seen at the age of $7\frac{1}{2}$ years, it was noted that he was mentally retarded. He was walking well and his mother claimed that he understood most of what was said to him, but his vocabulary consisted of only about three or four words. There was some slight stiffness of his right arm and hand and he tended to use his left hand more willingly. The reflexes of both the right arm and leg were rather more brisk than those of the left. It was considered that he had a right hemiplegia. In other ways his condition was satisfactory.

PATHOLOGICAL REPORT ON THE PANCREAS (Dr. Agnes Macgregor). The entire specimen, comprising about half the length of the pancreas and including the tail and the left part of the body, was divided into eight blocks and all of these were serially sectioned, producing nearly 4,000 sections. About 800 of these were stained and examined. No islet cell adenoma was present in the specimen. The islets of Langerhans showed certain abnormalities. (1) There was probably some increase in the average size of the islets as compared with normal controls from infants of the same age (Fig. 1). (2) The shape of many islets was irregular; often lateral projections or buds were present, suggesting active growth. (3) Many islets contained an unusual number of cells, the nuclei being packed close together, especially at the periphery of the islets. (4) Many other islets showed remarkable irregularity in the size of the cells (these islets were not, as a rule, those that had an increased number

of cells). The nuclei of the large cells were much increased in size and sometimes irregular in shape, being lobulated. Sections stained by Gomori's method indicated that there was no obvious alteration in the proportion of alpha and beta cells, and that the abnormally large cells were beta cells. The acinar tissue was healthy.

Discussion

Graham and Oakley (1950) have suggested that the clinical picture produced by a tumour of the islet tissue of the pancreas may also be produced by diffuse hyperplasia of the islet cells, but Skillern and Rynearson (1953) have thrown doubt on this hypothesis, and suggest that, in some of the cases reported as showing diffuse hyperplasia of islet cells, a more careful search might have revealed a small tumour. In the case reported here, Whipple's (1938) criteria for the diagnosis of functioning islet-cell tumours were fulfilled, yet no tumour was found after very careful examination of the portion of pancreas removed at operation. It may be that a minute adenoma, not noted during the operation, still exists in the portion of pancreas remaining *in situ*, but this seems unlikely, as, during the five years the patient has been followed up, there has been no further evidence of hypoglycaemia. The histological appearances of the pancreas strongly suggest that a diffuse hyperplasia of the islet tissue was, in fact, present.

While partial resection of the pancreas does seem to have controlled the hypoglycaemic state of this child, complete 'cure' cannot be claimed, for it is not possible to forecast what may happen to the remaining islet cells. The hyperplasia is presumably due to some stimulating factor, possibly a pituitary hormone, which may continue to act, producing

FIG. 1.—Photomicrograph of the pancreas showing an enlarged islet of Langerhans ($\times 120$).

further hyperplasia or even exhaustion and death of the islet cells. Thus further attacks of hypoglycaemia may eventually occur or a state of diabetes mellitus be produced.

Nevertheless it seems likely that the mental defect of this patient may be related to the recurrent attacks of hypoglycaemia and, in retrospect, one wishes that the operation had been carried out earlier.

Summary

A baby started having convulsions at the age of 7 weeks. These fits generally occurred before the first feed of the day. He was investigated in hospital at the age of 8 months and was found to have a blood sugar level ranging from 32 to 42 mg. % at the onset of a fit. A diagnosis of islet cell tumour was made and two-thirds of the pancreas were

removed. The blood sugar levels returned to normal and the fits were controlled. Histological examination of the resected portion of pancreas revealed a diffuse hyperplasia of islet cells, but no tumour was found.

No record of a similar case has been found in the British literature.

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