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SPONTANEOUS HYPERINSULINISM DUE TO ISLET-CELL ADENOMA

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Spontaneous hyperinsulinism resulting from a tumour of the islets of Langerhans is not a common condition, and the diagnosis is easily overlooked. Failure in diagnosis usually results in the early death of the patient, while diagnosis followed by operative removal of the tumour cures the majority of patients.

Nicholls (1902) first described an adenoma of the islet cells of the pancreas, but this was an incidental finding at necropsy and no clinical details of the case were recorded. Following the discovery of insulin, Harris (1924) suggested that symptoms might be caused by excess secretion of the hormone, and the first demonstration of an insulin-secreting tumour was by Wilder *et al.* (1927); they explored the pancreas of a doctor, aged 40, who had suffered from attacks of spontaneous hypoglycaemia for eighteen months, and found a carcinoma in the tail of the pancreas with metastases in the liver. The cells of the carcinoma bore a striking resemblance to islet cells, and insulin was extracted from one of the liver metastases.

The first successful operative removal of an insulin-secreting tumour was by Roscoe Graham in 1929 (Howland *et al.*, 1929), who found a small tumour in the body of the pancreas of a woman of 52 who had a seven-years history of attacks of spontaneous hypoglycaemia. The tumour was composed of islet cells, and as it lacked a capsule it was thought possibly to be a carcinoma, but no metastases were found. This lack of a capsule has been a feature of a number of islet-cell tumours subsequently studied, and is not now regarded as an indication of malignancy. Another successful operation was performed at about the same time, for Harvey Cushing (1930), in his Lister Lectures on neurohypophysial mechanisms, mentioned that a small islet-cell adenoma which had caused recurrent attacks of hypoglycaemia had recently been removed in his clinic. Since then the condition has attracted much attention in the United States, no fewer than 38 cases being reported from the Mayo Clinic in twenty years (Lopez-Kruger and Dockerty, 1947), while reviews have been published on both medical (Crain and Thorn, 1949) and surgical aspects of the problem (Howard *et al.*, 1950).

In Great Britain the number of reported cases is comparatively small. Apart from Nicholls's early pathological observation, the first report is that of Barnard (1932), who found an islet-cell adenoma at the

post-mortem examination of a patient in whom the diagnosis had been suspected clinically but who had declined further investigation or operation; post-mortem reports have also been published by Cairns and Tanner (1933), Lawrence *et al.* (1942), Webster and Blades (1952), and Cunningham *et al.* (1952). The first successful operative removal of an adenoma in Great Britain seems to be that reported by Fraser *et al.* (1938), and nine other reports of single cases successfully treated by operation have subsequently been published (Rudd and Walton, 1941-2; Rayner and Rogerson, 1943; Haines, 1946; Dickie, 1946; Holmes *et al.*, 1946; Bishton and Malins, 1947; Murray, 1949; Wood, 1951; Smith and Cochran, 1952); and Cohen (1950) has recorded two cases. There has also been a single report of an islet-cell carcinoma with liver metastases (Brearley and Laws, 1950), and one case in which attacks of spontaneous hypoglycaemia were thought to be caused by diffuse hyperplasia of the islet cells without tumour formation (Graham and Oakley, 1950). Richardson and Russell (1952) have reported five cases from the London Hospital; operation was carried out in three of these; in two an islet-cell adenoma was removed with complete relief of symptoms, while in the third patient the tumour was a carcinoma with a metastasis in the liver.

We have had under our care in St. Bartholomew's Hospital in the course of four years three patients with attacks of spontaneous hyperinsulinism, in each of which an islet-cell adenoma has been removed, with a successful result.

Case 1

A male Post Office counter-hand aged 27 was admitted to hospital on August 16, 1947, complaining of fits. The history, obtained from the patient and his wife, started in February, 1946. He then began to have attacks of sweating, trembling, and a feeling of unusual hunger. These occurred in bed in the morning or just before the midday meal. The symptoms were relieved by taking food and usually did not last more than about 10 minutes. At first they occurred infrequently, with symptomless intervals of as long as two or three months, but they grew more frequent, and by October, 1946, were occurring at the rate of one a week. By January, 1947, the attacks had become more severe. They began to occur when he was asleep, and his wife was unable to rouse him. Once he was incontinent, and on another occasion he bit his tongue. Attacks during the day started with blurring of vision, a feeling of dizziness, and

profuse sweating. His arms went useless and stiff, and he lost consciousness. Up to the time of his admission he had been having up to five or six attacks in one week.

There was nothing relevant in the past or family history. He had served in the Middle East during the war and had had sandfly fever. Examination revealed a healthy young man weighing 162 lb. (73.5 kg.). There were no abnormal physical signs, blood pressure was 120/80, and there was no swelling palpable in his abdomen. The urine contained neither albumin nor sugar. The following investigations were done to confirm the diagnosis of organic hyperinsulinism.

Starvation for 18 Hours.—During the last three hours he became drowsy, sweated, and eventually passed into coma. The injection of 5 g. of glucose intravenously resulted in an immediate return to consciousness. Blood sugars during the attack were 45 and 48 mg. per 100 ml.

Glucose-tolerance Test.—After three days on a diet of 350 g. of carbohydrate this test gave the following results. Fasting, 57 mg. per 100 ml. After 50 g. of glucose by mouth: 1 hour, 56 mg.; 2 hours, 125 mg.; 3 hours, 81 mg.; 4 hours, 60 mg.; 5 hours, 58 mg.

Rate of Removal of Intravenous Glucose.—An intravenous drip of glucose solution was begun at the rate of 28 g. per hour, and increased to 33 g. per hour after the third hour. During the first three hours the blood sugar did not rise above 96 mg., and thereafter the highest level reached up to 11 hours was 205 mg. per 100 ml.

The requirements of Whipple's triad were fulfilled in that the attacks came on while fasting, blood sugars during the attack were below 50 mg. per 100 ml., and consciousness was restored by the intravenous injection of glucose.

On September 16 one of us (J. P. H.) explored the pancreas through a transverse epigastric incision. A prolonged search failed to reveal any tumour, and it was decided to do a subtotal resection: about three-quarters of the gland was removed, only the head being left. After operation 24 hours of starvation did not produce any symptoms. A sugar-tolerance curve showed a rise after 50 g. of glucose to 190 mg. per 100 ml., but the blood sugar fell to 50 mg. at the fourth hour. Recovery from the operation was uneventful, and the patient left hospital on November 1.

For two months after operation there were no attacks whatever. Thereafter he had several episodes of sweating and difficulty in waking. By 4½ months after operation he had had three comas. Subsequently there were many minor attacks, which were aborted by taking carbohydrate: on one occasion he bit his tongue.

On readmission to hospital in September, 1948, the nature of the attacks had changed somewhat. The symptomatology was variable, but the sequence in a typical attack was as follows: he would at first continue to walk and talk, but behaved in a childish manner, and on recovery had no memory of his conversation. His face became red, his eyes staring and later wandering. He performed aimless movements with his hands and feet. During this period he would respond to commands. Thereafter his movements became more violent and there was rigidity of the limbs. Untreated attacks culminated in unconsciousness, with eyes wide open and pupils dilated. There was profuse sweating and facial pallor. He sometimes bit his tongue and was incontinent of urine, but the onset was always gradual and he never fell or sustained external injuries.

Blood sugars during attacks were between 40 and 50 mg. per 100 ml. Glucose-tolerance and intravenous glucose-disposal tests were similar to those before operation.

Glucose, by mouth, nasal tube, or intravenously, and adrenaline were effective in relieving the symptoms. Frequent extra feeds between meals and at night were necessary to reduce the number of attacks.

It was clear that a second operation would be necessary, but the patient had become very fat and weighed 215 lb. (97.5 kg.). To diminish the operative risk, efforts were made to reduce his weight. Any attempt to decrease the daily calorie intake was at once defeated by an increase in the amount of glucose needed to treat the hypoglycaemic attacks.

Various dietary modifications, ephedrine, and thyroid extract were tried without success. Growth hormone did, however, produce an increase in preprandial blood-sugar levels, a decrease in the amount of carbohydrate necessary to prevent hypoglycaemic attacks, and some reduction of body weight (Black *et al.*, 1952).

On October 11, 1949, J. P. H. again opened the abdomen through a transverse incision, and carefully examined the head of the pancreas. When its posterior surface was exposed by mobilizing the second part of the duodenum a small, firm, rounded nodule was felt in it, and on incising the pancreatic tissue covering it a dark-red encapsulated tumour was exposed and shelled out. The incision in the pancreas was closed with sutures. A drain was put down to the pancreas through a stab wound in the right flank, and through this a temporary pancreatic fistula developed which healed without trouble in a short time.

Pathological Report (Mr. K. C. Richardson).—"The tumour is clearly an islet adenoma composed of cells resembling beta cells. There are a few ducts in the tumour and some islands of abnormal acinar cells. I have not detected any alpha cells. The islets in the fragments of normal pancreas attached to the tumour seem to be normal."

The operation was followed by a mild and transient hyperglycaemia with an insulin requirement of 18 units daily, falling to zero by the end of the third post-operative week. Glucose-tolerance curves have since remained normal, and there has not been any recurrence of hypoglycaemic symptoms. Removal of the tumour was promptly followed by loss of bloated appearance of the face, which had been present before, and a precipitate fall in body weight. Within three months of operation over 3 st. (19 kg.) had been lost, and a more gradual loss continued for a further three months. When last seen in February, 1951, the patient was well and working.

Case 2

A female schoolteacher aged 22 was admitted to St. Bartholomew's Hospital on January 20, 1950, in coma. She had been well till June, 1949, when after a walk of several hours she suddenly felt very tired and unsteady on her legs and was somewhat confused mentally. She managed to get to a café, and after drinking some coffee she recovered in about half an hour. She had three attacks during the next six months, each occurring about the time lunch was due. In one of them she was about to dismiss her class, but found that she could not speak, although she knew what she wanted to say; she then became confused and lost consciousness, the whole attack lasting about an hour. On December 24, after an attack in which she was unconscious for an hour and a half, she was admitted to a hospital. While in this hospital she had four further attacks of loss of consciousness, during which the pupils were dilated and the plantar responses extensor. During two of these attacks she vomited, and on coming round after one to two hours she had no memory of the attack. It was during a further and more severe attack that she was transferred to St. Bartholomew's, having been in coma for about 24 hours. There was no relevant past or family history.

On examination she was in deep coma, pulse 80 and regular, respirations 16, and temperature normal. The pupils were widely dilated and did not react to light, and the fundi were normal. The arms and legs were spastic; tonic neck reflexes could be elicited; the tendon-jerks were abnormally brisk; there was bilateral ankle clonus; and the plantar responses were extensor. The urine contained a trace of ketones but no sugar or albumin.

The blood sugar was 55 mg. per 100 ml.; a ventriculogram carried out to exclude a third-ventricle tumour demonstrated a normal ventricular system; and the electroencephalogram (E.E.G.) was grossly abnormal, with diffuse slow activity, more pronounced on the right than on the left. She was given 15 g. of glucose intravenously and 45 g. six hours later, and a gastric drip was continued for the next 10 days, about 220 g. of glucose together with milk being given through it each 24 hours. Blood sugars, esti-

mated at intervals, varied between 105 and 390 mg. per 100 ml. Recovery from coma was slow: on January 21, 1950, there were periods of weeping and laughing, but she did not respond to commands; on January 23 she understood simple commands and followed people with her eyes; and on the 24th she understood more complicated requests and was able to sip fluids from a spoon. The right plantar response was flexor for the first time, but it was now apparent that she had a left hemiplegia, and the left plantar remained extensor.

A glucose-tolerance test on February 15 gave the following results. Fasting, 86 mg. per 100 ml. After 50 g. of glucose by mouth: $\frac{1}{2}$ hour, 140 mg.; 1 hour, 160 mg.; $1\frac{1}{2}$ hours, 142 mg.; 2 hours, 120 mg.; 3 hours, 69 mg.; 4 hours, 65 mg.; 5 hours, 60 mg.

A series of liver-function tests (van den Bergh, thymol turbidity, and Takata-Ara) were within normal limits; the plasma proteins were 6.75 g. per 100 ml.; and the blood potassium was 19.2 mg. per 100 ml.

The patient remained in hospital till March 19, but no further attacks of loss of consciousness occurred. Her mental state was abnormal, memory was poor, she was emotionally facile, was generally apathetic, and was uncooperative in her physiotherapy. The complete left hemiplegia gradually improved, but on discharge there was still a marked left hemiparesis and she needed a stick when walking. She was seen at intervals as an out-patient, and in the middle of April had a further attack of confusion and difficulty in speaking lasting half an hour. During June and July attacks occurred about once every three weeks, usually in the later afternoon, and lasted from half to two hours; they would start and end fairly suddenly and there was amnesia for the attack. On August 21 she was dull and apathetic at lunch-time and would not eat; she then slumped into a chair, lost consciousness, and was incontinent of urine. This attack lasted four hours, and following it she was readmitted to St. Bartholomew's Hospital, where her blood sugar was found to be 75 mg. per 100 ml. This time the effects of fasting were studied (August 25, 1950).

During the next two weeks several further attacks of hyperinsulinism occurred spontaneously, in one of which there was a generalized tonic-clonic convulsion. Blood sugars in two of these attacks were 42 and 48 mg. per 100 ml.

A glucose-tolerance curve on September 13 gave the following results. Fasting, 66 mg. per 100 ml. After 50 g. of glucose by mouth: 40 minutes, 106 mg.; 1 hour 20 minutes, 116 mg.; 2 hours 40 minutes, 63 mg.; $3\frac{1}{2}$ hours, 61 mg.; 4 hours, 60 mg.; 5 hours, 50 mg.; 6 hours, 46 mg.

Period of Fast	Clinical State	Blood Sugar (mg./100 ml.)	E.E.G.
14 hours	Drowsy, unresponsive to stimuli, dribbling saliva	28	Grossly abnormal. Many high-voltage $1\frac{1}{2}$ -a-second waves and $\frac{4}{6}$ -a-second waves
15 "	Unchanged	28	Less abnormal. $1\frac{1}{2}$ -a-second waves less marked and of low amplitude. Some runs of normal 10 a second activity
16 "		35	
17 $\frac{1}{2}$ "	Still "drowsy, but improving. More responsive	50	Deteriorated; similar to the 14-hour record
18 $\frac{1}{2}$ "	Aware of environment. Answers questions	50	Improved; slow waves less evident. Some fast activity of low voltage
19 "	After an attempt to exercise her, sudden deterioration. Drowsy, unresponsive to stimuli	—	Deteriorated; much slow activity of high voltage
20 "	Drowsy; responds only to strong stimuli	64	As previous record
20 $\frac{1}{2}$ "	No change clinically	79	
15 ml. of 25% glucose given intravenously	Normal within a few minutes	180	Practically normal record

There seemed no doubt that the patient had a functioning islet-cell tumour, and on September 20 one of us (R. S. C.) explored the pancreas, the anaesthetic being thiopentone, gas, oxygen, and curare. For 14 hours she had a gastric drip containing at first 5% and later 15% glucose, and during operation and for 24 hours afterwards 5% glucose intravenously. The abdomen was opened through a right paramedian incision and the pancreas mobilized. A thorough examination of the head was made first, which involved a mobilization of the duodenum by dividing the peritoneum on the lateral side. A gland was dissected out first, adjacent to the common bile duct. Later a nodule was palpated in the substance of the head, and on incision over the posterior surface of the gland a purple-coloured tumour 0.75 cm. in diameter presented, and was removed easily by blunt dissection. The cavity in the gland was obliterated by interrupted catgut sutures and the wound closed. Recovery was uneventful.

Pathological Report (Dr. Cureton).—"A portion of greyish-white tissue measuring 1 by 0.75 cm. and weighing 0.59 g. Sections show this to be an islet-cell adenoma. Specific staining shows that it is almost exclusively composed of beta cells, most of which preserve their granules. One section only shows numerous primitive-looking ducts."

The patient's post-operative recovery was uneventful. She was seen as an out-patient in February and in September, 1951, and on the latter occasion she had returned to work as a schoolteacher and was doing this without difficulty. There had been no further hypoglycaemic attacks, her memory and intellectual ability had improved, and her parents said that she was now co-operative and easy to deal with, whereas before operation she had been unco-operative and irritable. There was still a mild spastic left hemiparesis. In September, 1952, her condition remained the same and there had been no recurrence of hypoglycaemic attacks.

Case 3

A female groom aged 20 was admitted to St. Bartholomew's Hospital on November 1, 1951, complaining of attacks of confusion. Details of the first attack, on July 7, 1951, and of the second, a few weeks later, are vague: they each occurred about three hours after breakfast and consisted of a short period of difficulty in concentration and drowsiness lasting for a few minutes. The third attack occurred on a Sunday morning: the patient did not come down to breakfast, and her mother found her in bed, sweating profusely, not apparently aware of what was said to her, and resisting any efforts to persuade her to get up. The attack passed off in an hour and she was normal again. The fourth attack was on October 3, at the beginning of lunch: she seemed dazed, answered only in monosyllables, put her head into her hands, and burst into tears. She was helped up to bed and was normal within an hour. The fifth and most severe attack was on October 17. After a dance on the previous evening she seemed perfectly well, but on the morning of the 17th was found unconscious in bed. She was seen in consultation by Dr. Philip Buckley, who noted that she was flushed and sweating; her temperature was 96.4° F. (35.8° C.), pulse 90 and regular, and blood pressure 140/95. She was stuporous and resisted examination. The knee-jerks were absent, the ankle jerks feeble, and the plantar responses extensor.

She was transferred to St. John's Hospital, Chelmsford, under Dr. Buckley's care, and at 4 p.m. there was no essential change in her condition. The C.S.F. pressure was 90 mm., there was 1 lymphocyte per c.mm., the protein was 25 mg. per 100 ml., the chlorides were 730 mg. per 100 ml., the sugar content was reduced, and the W.R. was negative. The white blood count was 9,250 per c.mm. (polymorphs 95%, lymphocytes 5%, transitional leucocytes 1%). X-ray films of the chest and skull were normal. The blood sugar was 60 mg. per 100 ml., and she was given 20 ml. of 50% glucose intravenously; there was no immediate response, but within 20 minutes she sat up and seemed quite normal except for

some slurring of speech and general bewilderment. Apart from these attacks she had been normal in every way, and had no memory of the attacks.

The patient was a dissimilar twin, and the past history was uneventful except for two minor head injuries due to falls from a horse. There was no family history of epilepsy.

When examined on admission to St. Bartholomew's she was normal mentally, and there were no abnormal signs in the nervous or other systems. Blood pressure was 160/95, and the urine contained neither sugar nor albumin.

As hyperinsulinism seemed the probable diagnosis the crucial test was to induce an attack by fasting: accordingly she had no food on November 4 from 9 a.m. onwards; by 10 a.m. on November 5, after a 25-hours fast, she was drowsy and confused, could give no history, appeared vacant and flushed, and her speech was slurred. She was not, however, sweating noticeably. The pupils were widely dilated but reacted normally to light, and both plantar responses were extensor. At this time the blood sugar was 45 mg. per 100 ml. She was given 50 g. of glucose by mouth and within 20 minutes was fully awake and alert; she seemed normal mentally, her pupils were considerably smaller, and the plantar responses were flexor.

A sugar-tolerance test was carried out after this fast, with the following result. Fasting, 45 mg. per 100 ml. After 50 g. glucose by mouth: 1 hour, 190 mg.; 2 hours, 130 mg.; 3 hours, 89 mg.; 4 hours, 54 mg.; 5 hours, 48 mg.; 6 hours, 46 mg. A barium meal showed no deformity in the duodenum.

An E.E.G. on November 8 (in fasting state—blood sugar 45 mg. per 100 ml.) showed unstable alpha rhythm of very irregular amplitude, with spread into the frontal areas. Excessive generalized slow waves were present in all areas. Overbreathing slowed the alpha rhythm and greatly increased the slower frequencies, which often became paroxysmal and of increased amplitude. After 22 ml. of 33.3% glucose intravenously there was a marked reduction in the slow frequencies, and the alpha rhythm became more steady in amplitude and was reasonably stable.

On November 16 the pancreas was explored by R. S. C. A more extensive search had to be made which involved not only the mobilization of the head of the pancreas, as in Case 2, but also an incision of the peritoneum along the inferior border of the pancreas after entering the lesser sac. It was only after turning up this lower edge of the gland that the tumour was seen embedded in the posterior surface of the tail, lying just above the splenic vein. An enucleo-resection was carried out with preservation of the splenic vein. The space left was obliterated with interrupted sutures of catgut as in Case 2 and the pancreas replaced. The wound was closed without drainage. This was an error in technique, for in three weeks a left subphrenic abscess formed in the lesser sac. This was drained through a left lateral incision and the fluid contents showed large quantities of diastase. Following this, recovery was uneventful, and the patient was discharged six weeks later.

Pathological Report (Professor Blacklock).—"The tumour measures 2.5 cm. in its greatest diameter and is 0.5 cm. thick. It is well encapsulated, fragments of the pancreas being still adherent to the capsule. The tumour is rather plum-coloured on the surface, though on section there are paler fleshy areas in it. The tumour weighs 1.85 g. Microscopically the growth consists of masses of small cells resembling the cells of the islet tissue of the pancreas. The tumour is fairly well encapsulated and is a typical islet-cell tumour."

There were no hypoglycaemic attacks after the removal of the islet-cell adenoma, and a glucose-tolerance curve on January 14, 1952, gave a fasting level of 86 mg. per 100 ml., rising to 115 mg. per 100 ml. after 50 g. of glucose and falling to 74 mg. per 100 ml. two hours later.

When seen in May and in November, 1952, she was very well, had had no further hypoglycaemic attacks, and had returned to her work as a groom.

Discussion

Symptoms

The important feature in the early stages, and often throughout the whole course of the illness, is paroxysmal attacks, of which two main types occur. The less serious type was well illustrated by the early attacks in Case 1, and is thought to be due to excess liberation of adrenaline in response to a rapid fall in the blood-sugar level. These attacks consist in sweating, trembling, general weakness, and nervousness, and often palpitations and precordial discomfort without impairment of consciousness. The more serious type of attack is due to a disturbance of cerebral function resulting from the low blood sugar, and these attacks vary greatly in type, not only from patient to patient but in different attacks in the same patient. They may consist of short confusional episodes often associated with automatic behaviour, major epileptic attacks with convulsions, periods of stupor in which bilateral extensor plantar responses may be found, or prolonged coma with, in a severe attack such as occurred in Case 2, signs of decerebrate rigidity. Cerebral attacks were the presenting symptom in Cases 2 and 3, while in Case 1 they began a few months after the onset of attacks, due to excess adrenaline secretion. Attacks of either type tend to occur some hours after a meal and are not uncommon early in the morning, as was well illustrated in Case 3, in which the two severe attacks occurred before breakfast. In general, attacks occur with gradually increasing frequency and severity, though periods of complete freedom may occur as in Case 2, in which after an extremely severe and prolonged attack there was a period of freedom lasting three months.

If the condition is not treated, more permanent changes may develop; in particular there may be a change in personality, with intellectual deterioration and emotional changes. Case 2 presented a curious mental state with poor memory, affective lability, apathy, and a general lack of co-operation, all of which features improved after the removal of the islet-cell adenoma, and within a few weeks of operation her parents thought that her mental condition had returned to normal, and shortly afterwards she resumed her work as a schoolteacher. Comparable mental changes occurred in the patient from the Maudsley Hospital reported by Fraser *et al.* (1938).

Transient focal neurological disturbances such as hemiparesis or aphasia may occur during the attacks of hyperinsulinism, and, more rarely, permanent neurological changes may develop: Case 2 had a complete left hemiplegia following a prolonged hypoglycaemic attack, and, though gradual improvement took place over the course of months, she still had a mild residual hemiparesis: a similar occurrence has been recorded by Crain and Thorn (1949). These rare permanent neurological sequelae are presumably due to actual death of nerve cells resulting from prolonged hypoglycaemia.

Lawrence *et al.* (1942) have studied the cerebral changes in six fatal cases of hypoglycaemia—three diabetics suffering from insulin overdosage, two patients dying during insulin treatment for schizophrenia, and one islet-cell adenoma unsuspected during life—and they found similar changes in all six patients. There was widespread degeneration and necrosis of nerve cells with microglial and macroglial proliferation, the most severe changes being in the cerebral cortex, the caudate nucleus, and putamen, with only slight changes in the cerebellum and brain stem. These changes are very similar to those found in cerebral anoxia and are thought to be due to failure of the normal oxidative processes in the cells from lack of glucose. Although these pathological changes are probably the basis for permanent neurological sequelae, it is difficult to understand why a hemiplegia should occur: one would expect that both hemispheres would be equally affected by prolonged hypoglycaemia, with a resulting double hemiplegia rather than a unilateral hemiplegia, and it is possible that vascular factors are also important.

Lower motor-neurone lesions may also occur as a result of hypoglycaemia and confuse the diagnosis. Silfverskiöld (1946) described two patients with islet-cell adenomas: one developed gross wasting and weakness of the hand muscles, without fibrillation, and weakness of both ankles following a prolonged hypoglycaemic attack; and the other had a bilateral flaccid foot-drop in similar circumstances. Lidz and others (1949) removed an islet-cell adenoma from a patient with severe mental changes, cerebellar ataxia, and extensive muscle-wasting in both legs, without fibrillation: after operation the mental condition and ataxia improved while the muscle-wasting remained unaltered. Tom and Richardson (1951) showed that the cause of a lower motor-neurone lesion of this type was destruction of spinal anterior horn cells occurring during prolonged hypoglycaemia in a patient in whom an islet-cell tumour was found at post-mortem examination. In their case the diagnosis had not been made during life, largely because of the confusing feature of severe localized muscle atrophy in the legs.

Diagnosis

Whipple (1938, 1944) has suggested three criteria for the diagnosis of functioning islet-cell tumours: (1) attacks of nervous or gastro-intestinal disturbance occurring in the fasting state; (2) during the attacks hypoglycaemia with a blood sugar below 50 mg. per 100 ml.; and (3) relief of symptoms immediately by the ingestion of glucose. Whipple's triad is of great value in attacks deliberately induced by a period of fasting as a diagnostic measure, but there may be deviations from it in the attacks which occur spontaneously. In some patients the time relationship of attacks to fasting is by no means obvious, as attacks may occur three hours or so after a meal without any sensation of hunger. More confusing is the fact that the blood sugar may have risen above 50 mg. per 100 ml. while the patient is still unconscious: this was illustrated in Case 3, whose blood sugar was 60 mg. per 100 ml. when she was stuporous and had bilateral extensor plantar responses. Prompt recovery from the attack is usual when glucose is given either by mouth or intravenously, but if the hypoglycaemia has been severe and prolonged this rapid recovery may not occur. Case 3 had been comatose for about 24 hours when she was admitted to St. Bartholomew's and her blood sugar was 55 mg. per 100 ml., but, in spite of intravenous glucose and a gastric drip containing glucose, her recovery was very slow, and it was at least 48 hours before she became conscious.

The most useful confirmatory test is to fast the patient for 12 to 24 hours: if an attack occurs the blood sugar must be estimated and then the effects of oral or intravenous glucose observed. Under these controlled circumstances Whipple's three criteria hold good in the majority of cases. In each of our three patients attacks occurred after 14 hours, and in Case 3 after 24 hours; in each case blood sugars below 50 mg. per 100 ml. were recorded and the attack was rapidly stopped by administration of glucose. We have used this fasting test in a number of other patients whose histories suggested the possibility of hyperinsulinism, most of whom were in fact suffering from epilepsy or hysteria, without an attack being induced and without the blood sugar falling to below 80 mg. per 100 ml.

Differential Diagnosis

Spontaneous hypoglycaemia is known to occur in a variety of conditions. These include organic hyperinsulinism, liver disease, functional hypoglycaemia, certain diseases of the endocrine glands, and a miscellaneous group of which starvation and severe renal glycosuria are examples. None, except the first three, is likely to enter into the differential diagnosis of islet-cell tumour. Hypoglycaemic crises are not a feature of anorexia nervosa, and hypoglycaemic symptoms are absent or unobtrusive. Addison's disease and Simmonds's disease will be recognized by their other clinical manifestations. In practice, then, the problem which confronts the clinician is to distinguish between liver disease, functional hypoglycaemia, and a tumour of the islets of Langerhans.

No difficulty arises with the hypoglycaemia of severe damage to the liver parenchyma with jaundice, but hypoglycaemia occasionally results from minor degrees of liver damage. Conn and others (1938) reported six cases of hypoglycaemia due to an ascending infection of the biliary tract. One of his patients, a man aged 47, had repeated hypoglycaemic crises ending in unconsciousness. These always occurred between 3 and 7 a.m. A biopsy taken at operation showed cholangitis with early biliary cirrhosis. The gall-bladder contained stones and pus, and its removal was followed by complete disappearance of hypoglycaemic attacks. Whipple's triad may fail to distinguish between organic hyperinsulinism and hepatic hypoglycaemia. It is therefore advisable to include radiological examination of the biliary tract and tests of the liver function in the investigation of patients with spontaneous hypoglycaemia.

Difficulty is likely to arise in differentiating organic hyperinsulinism in its early stages from functional hypoglycaemia, which is by far the commonest of all the causes of spontaneous hypoglycaemia. The distinction is an important one, because the treatment of the former is surgical whereas in the latter medical treatment is effective and surgery is to be avoided. It can usually be made with reasonable certainty on clinical grounds. Functional hypoglycaemia is of the stimulative type: the blood sugar is normal even after prolonged fasting, and hypoglycaemic attacks do not occur during the night or before breakfast. They are confined to the daytime and occur two to four hours after meals. The clinical course of organic hyperinsulinism is progressive, the hypoglycaemic crises becoming increasingly severe and frequent, whereas functional hypoglycaemia is not progressive. Undoubtedly the crucial test is the fasting test, which leads to hypoglycaemic symptoms in organic hyperinsulinism but not in functional hypoglycaemia. The glucose-tolerance test is less reliable. The fasting blood sugar is normal in functional hypoglycaemia and the blood sugar falls to subnormal levels two to four hours after the administration of glucose. A sharp rise to 200 mg. per 100 ml. or more immediately after the glucose is characteristic of the hypoglycaemia which sometimes follows operations on the stomach.

Glucose-Tolerance Tests

Glucose-tolerance tests are of less value in the diagnosis of islet-cell tumours than is a fasting test. Very varied results have been recorded in the literature (Crain and Thorn, 1949), but this may be partly due to the fact that they have been carried out under varying conditions of diet. Duncan (1947) has suggested that a standard diet containing 350 g. of carbohydrate in 24 hours should be given for the three days before a six-hour glucose-tolerance test. Under these conditions a patient with a functioning islet-cell tumour usually has a subnormal fasting blood sugar; the highest peak rarely exceeds 120 mg. per 100 ml. and the level falls to subnormal values within two hours, and these low values continue during the third to sixth hours. In our first case a standard diet was given before the glucose-tolerance test: the blood sugar rose to a peak of 125 mg. per 100 ml. and subnormal levels were not reached until the fourth hour. In the other two cases a standard diet was not given, and in fact the tolerance curve in Case 3 was carried out after a 24-hour fast. In this patient the blood-sugar level rose to 190 mg. per 100 ml. at the first hour and did not fall to a subnormal level (54 mg. per 100 ml.) till the fourth hour. In Case 2 glucose-tolerance tests were carried out on two occasions with a seven-months interval between them: the first curve was practically within normal limits except that after three hours the level was 69 mg. per 100 ml. and remained in the sixties at the fourth and fifth hours; the second test fulfilled all Duncan's criteria.

Electroencephalography

It is recognized that marked E.E.G. changes occur during hypoglycaemia: Hofer *et al.* (1946) studied 11 of Whipple's patients who had functioning islet-cell tumours. The most typical abnormality was high-voltage slow activity occurring

in synchronous bursts all over the head, with considerable improvement in the record after intravenous glucose. He found no clear-cut correlation between the degree of E.E.G. abnormality and the blood-sugar level in the five patients in whom this was studied. In our second patient the E.E.G. was recorded at intervals from the fourteenth to eighteenth hours of a fast, with blood-sugar estimations. The findings of high-voltage slow activity agreed with those of Hoefer *et al.*, and, although from the sixteenth to twentieth hours the blood sugar was rising slowly, there was no progressive improvement in the E.E.G. record or in the clinical state till intravenous glucose was administered, when both the E.E.G. and the clinical condition rapidly returned to normal. In Case 3 when the blood sugar was 45 mg. per 100 ml. the E.E.G. showed generalized slow waves which were greatly increased by overbreathing, and considerable improvement occurred in the record following intravenous glucose. The E.E.G. does not afford any great help in the diagnosis of these patients, but it is perhaps worth stressing that diffuse abnormality in an E.E.G. record of a patient in stupor or coma does not necessarily indicate a primarily intracranial cause for the coma, as both the coma and the abnormal E.E.G. may be the result of disordered brain metabolism from conditions such as hypoglycaemia.

Treatment

The treatment of hyperinsulinism due to an islet-cell adenoma is by surgical removal of the tumour when possible. Once other causes of hypoglycaemia have been excluded and the diagnosis of organic hyperinsulinism has been made, the pancreas should be explored without delay because of the possibility of malignancy, the risk of permanent damage to the central nervous system, and increasing obesity. An intravenous infusion of 5 or 10% glucose solution is set up beforehand and continued throughout the operation. Transient hyperglycaemia may follow operation: it occurred in Case 1 and was easily controlled by soluble insulin, given twice daily.

Medical treatment is notoriously unsuccessful but may be the last resort if operation is refused or if there is a malignant growth with metastases. A predominantly protein-and-fat diet with little carbohydrate, though useful in functional hypoglycaemia, will not prevent the occurrence of severe hypoglycaemic attacks from an islet-cell tumour. A large carbohydrate intake and frequent meals are necessary to prevent attacks. Attempts to destroy the beta cells by alloxan have not been encouraging, and severe toxic effects may result. Extracts of adrenal cortex and of the anterior pituitary have proved disappointing. Growth hormone was tried in Case 1: it produced some elevation of the blood-sugar level, but not enough to be of practical value. It is possible that a combination of adrenocorticotrophin and growth hormone may prove to be more effective.

Surgical Treatment

In all three cases there was a solitary tumour, removal of which brought complete relief of symptoms. A right paramedian incision was used in two cases and a transverse incision in the third, a very adequate exposure of the whole pancreas being obtained in each case.

If the tumour is not seen or felt on any part of the anterior surface of the pancreas, a thorough search must be carried out. The posterior surface of the head is examined by dividing the peritoneum on its lateral side of the duodenum, mobilizing the second part of the duodenum. In Cases 1 and 2 the tumour was felt in this position and was exposed in this way: enucleation was effected after incising the pancreatic tissue over it. An enlarged lymph node was found lying adjacent to the common bile duct in Case 2. The undersurface of the body and tail are examined by making an incision along the inferior border of the pancreas, after entering the lesser sac. In Case 3 the tumour was found on the posterior surface of the tail.

The tumours were enucleated from the pancreas and the cavity obliterated with catgut sutures. It is wise to put a

drain down to the area through a stab incision in the right or left loin, to prevent a collection of blood and ferment and to avoid abscess formation. If a pancreatic fistula forms, as in Case 1, it will close spontaneously and the surrounding skin can be prevented from becoming sore by applying suction. In Case 3 the leak produced a subphrenic abscess as a result of not draining.

From the cases reported it seems that these tumours are small (1–2 cm.), red or purple in colour, and firm in consistency compared with ordinary pancreatic tissue. They are often buried in the gland and can occur anywhere from the head to the tail. In Case 1 the search was given up at the first operation and in Case 3 it was almost given up. A lymph node may be mistaken for the tumour on palpation, but the appearance (Case 2) is quite different. No sign of malignancy was found, which from reports is a rare occurrence.

Summary

Three cases of spontaneous hyperinsulinism due to an islet-cell adenoma are described. The removal of the adenoma in each case resulted in relief of symptoms, whereas a resection of three-quarters of the pancreas in one patient had caused only temporary improvement.

The symptomatology is discussed, and it is stressed that permanent neurological damage may occur in a prolonged hypoglycaemic attack.

The crucial diagnostic test is a period of fasting of up to 24 hours. In attacks produced in this way Whipple's diagnostic triad is fulfilled, which is not invariably true in spontaneous attacks.

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Four field medicines issued to British troops during the Crimean War have been added to the Pharmaceutical Society's historical museum. The bottles, labelled "The British Pharmacy, Smyrna," contain powdered rhubarb, milk of sulphur and cream of tartar, calcined magnesia (for indigestion), and ipecacuanha wine (for coughs).