ISLET-CELL ADENOMA OF THE PANCREAS

REPORT OF A CASE

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An adenoma of the islet-cells of the pancreas was first reported by Nicholls in 1902 as a post-mortem finding but no clinical details of the case were recorded. Harris formulated the concept of hyperinsulinism in 1924, 3 years after Banting and Best isolated insulin. In 1927 Wilder and his co-workers were the first to demonstrate an insulin-secreting tumour. The first successful removal of an adenoma was undertaken by Graham in 1929. The diagnostic triad is associated with the names of Whipple and Frantz (1935). This consists of the development of hypoglycaemic symptoms after prolonged fasting or exercise, the dropping of the blood-sugar level below 50 mg.% and the relief of symptoms by the

administration of glucose. Webster[2] has, however, reported a case in which fatal coma ensued with a blood sugar of 64 mg%. Other similar cases have been reported in the literature.

Review of the Literature

A review of the literature on spontaneous hypoglycaemia due to islet-cell tumours of the pancreas shows about 500 reported cases including a case by Lowenthal[1] in South Africa. Extensive reviews of various aspects of the subject are given by Briedahl, Priestley and Rynearson (diagnosis, findings at operation and results),[3] Kelly (diagnosis),[4] Peyster and Gilchrist (medical and surgical treatment),[5] Whipple (pathology, clinical picture, diagnosis, treatment),[6] Howard (surgery),[7] Parfitt (comparison of irreversible coma with that in the insulin treatment of schizophrenic patients),[8] Black *et al.* (review of British cases),[9] Bickerstaff *et al.* (clinical manifestations and diagnosis),[10] Brearley and Laws (carcinoma of the Islets of Langerhans with hypoglycaemia)[11] and Crain and Thorn (medical review).[12]

The interest of the present case lies in the patient's age, epilepsy, family history and associated arteriosclerosis and dementia.

CASE REPORT

History

Mr. H. J. v. H. was first admitted to a mental hospital on 7 June 1946. He was then 68 years old, single, and had been a peasant-farmer all his life. There was a history of *grand mal* epilepsy of 3 years duration. After a fit he became violent and aggressive and this behaviour led to his certification. Neither fits nor abnormal behaviour were observed in hospital and he was discharged on 14 June 1946.

In addition to the above, the patient gave a history of 'minor' attacks of some years duration in which he stated that he felt weak for a few minutes. Apart from a suprapubic scar no physical abnormality was detected in a healthy man. He was described as an abstainer from alcohol.

He was readmitted on 6 December 1946, 6 months later, for similar behaviour, but this was now pre- and post-ictal, the pre-ictal behaviour being described as 'maniacal' by his general practitioner. On admission this time he was grossly confused. During 1947 he had 30 seizures followed by marked restlessness and confusion. Between seizures he was retarded and could give only a poor account of himself. He was, however, quite quiet, cooperative and usefully occupied. During 1948 he had 43 seizures, and apart from this he was confused most of the time. During 1949 the patient had 19 seizures, the confusion was less but his memory for current events was poor, his emotional responses were blunted and his comprehension was impaired. He showed no evidence of an epileptic 'temperament' and was described as being of 'childish behaviour of a good-natured type' and a willing worker.

In 1950 it was noted that fits could be aborted by feeding the patient as soon as his otherwise correct habits became faulty. Apart from the fits the patient had spontaneous attacks of hypoglycaemia and these always responded to glucose. He remained free from seizures until the middle of 1952 and from July 1952 to December 1953 he had 34 seizures. An overt aura of opening and closing his mouth was noticed. He became progressively apathetic and attended only to his own needs. He also became progressively deaf. During 1954, 1955 and 1956 he had 13 seizures and in 1957 he was reported to have bilateral cataracts. His peripheral vessels were arteriosclerotic. His blood pressure was within normal limits. His liver-function tests were found to be normal, his urine was normal and a fasting blood sugar after 16 hours was normal. He was given glucose regularly by day and night and this reduced his hypoglycaemic attacks to 3, but on one occasion intravenous dextrose was required. By the end of 1957 he was deaf, blind, resistive, and interested only in his tobacco. He had to be dressed and his intimate habits were faulty. He spent his day sitting in a chair. On 12 July he went into hypoglycaemic coma and required intravenous glucose to restore him to consciousness. About 12 hours later he began to lapse into stupor and 24 hours later signs of a left hemiparesis were evident. He died, in coma, on 13 July 1958.

Post-mortem examination 36 hours after death showed marked generalized arteriosclerosis. There was a large thrombus in the right lenticulo-striate artery and accompanying cerebral softening. His clinoids were well calcified. There was marked nephrosclerosis and the kidneys were cystic with little normal tissue present. Numerous gallstones were present. In the head of the pancreas a well encapsulated tumour ¾ in. in diameter was found. The pathological report reads: 'The pancreas shows the presence of a "nesidiocytoma" (islet-cell adenoma). This is unfortunately not sufficiently well preserved to demonstrate the cell-type but the clinical history suggests that it must be an insulin-secreting adenoma.'

Family History

1. Brother, W. J. v. H., who was admitted on 24 March 1948 at the age of 64. He was reported to have suffered from epilepsy since 1937 when he was 53 years old. He died 4 months after admission having been confused nearly all the time.
2. Brother, J. M. v. H., who was admitted in 1956 when he was 70 years old. He suffered from senile psychosis and died of bronchopneumonia within 5 months of admission.

DISCUSSION

Family history. Brain[13] states that in a series of 200 epileptic patients there was a family history of this disease in 28%. Lennox, quoted by McV. Hunt,[14] showed that epilepsy occurs among the near relatives 5 times more frequently than in the general population. Kallmann and Sander[15] give the morbidity of epilepsy among siblings as 3·7-3·99% as opposed to an incidence of ·4% and ·28% (in separate studies) in the general population.

If it is accepted that the tendency to seizures may be inherited, and since one sibling of this patient was epileptic, it might be suggested that our patient had a latent epileptic tendency until the necessary trigger, which produced full seizures, became operative. In his particular case there is the hypoglycaemia of an islet-cell adenoma, arteriosclerosis and senility.

With regard to senility, Kallmann[16] gives the expected morbidity rate for the siblings of seniles as 6·5% as opposed to an incidence of 1% in the general population.

Age. This man was 65 years old when his seizures began although the history of attacks of weakness for several years prior to this suggests that he may have been hypoglycaemic then. The age of Parfitt's[8] cases ranged from 30 to 60 years. In an analysis of 20 cases of carcinoma of the islets of Langerhans with hypoglycaemia (Brearley and Laws)[11] the mean age of the patients was 44 years, although there were 3 cases over the age of 65 years. Sixty-five years is also the generally accepted age above which senile psychosis may be diagnosed. The onset of the patient's fits is certainly coincident with the senium. While he showed no evidence of senile dementia on admission, he certainly began to show signs of dementia 3 years later. What part the senile changes *per se* played in his dementia cannot now be determined and the course of a senile psychosis may vary from a few months to years. It will be recalled that his brother, J. M., was admitted at the age of 70 years and died within 5 months.

Epilepsy. The question of the family tendency towards epilepsy has already been discussed. The certifying doctors in December 1946 described maniacal behaviour terminating in a fit and this particular feature in spontaneous hypoglycaemia has been commented on by Briedahl, Priestley and Rynearson.[3] Parfitt[8] gives the incidence of fits in hypogly-

caemia as 50% with a wide variation. He also quotes Crain and Thorn's series in which 28% of 193 cases had fits. On the other hand, it is this type of behaviour, which is not unknown in epileptic psychosis, where the 'mania' can be instantly terminated by an electric convulsive treatment. The incidence of epilepsy in arteriosclerosis is given as 15-20% by Mayer-Gross, Slater and Roth.[17]

Arteriosclerosis. The autopsy showed grossly calcified brittle arteries. A thrombus in one of these was the cause of the patient's death. The extensive renal changes would indicate that the arteriosclerosis had been of many years duration. The incidence of epilepsy in this condition has already been referred to. The rapidity of dementia in this condition is as variable as it is in senile psychosis. Hemiplegia, noted in this patient's terminal phase, occurred in 10% of Crain and Thorn's cases (Parfitt[8]). Black *et al.*[9] reported a case in 1954. Bickerstaff *et al.*[10] suggest that in epilepsy of late onset, in the absence of cerebral tumor, the diagnosis of cortical atrophy or cerebral arteriosclerosis is too easily made and that hyperinsulinism should be excluded in all such cases. Dimsdale[18] analysing 200 cases of epilepsy occurring over the age of 20 found cerebral arteriopathy in 7 cases, all in the over 40-year age group. There were no cases of spontaneous hypoglycaemia in her group.

Dementia. Dementia due to long-standing epilepsy is a daily feature in mental hospitals, where one frequently sees cases with gross dementia who are subject to infrequent fits. The relationship between intellectual deterioration, arteriosclerosis and senility has already been mentioned. Parfitt[8] notes that hypoglycaemia *per se* can produce transient or permanant signs of intellectual deterioration; he gives the incidence as 2%. In Crain and Thorn's series the incidence of irreversible personality changes was about 5% (Parfitt). Webster[2] considers irreversible brain damage among the main dangers of pancreatic adenoma. Black *et al.*[9] report a case with temporary mental abnormality which improved after surgical removal of the tumour.

Nielson and Thompson[19] state that if cortical cells have passed a certain point in sugar deprivation they may require a long time for recovery, even weeks. The episodes of confusion noted in this patient's history may well be evidence of the states implied by Nielsen, but they may also have represented mild hypoglycaemic states or evidence of the signs of temporary intellectual deficit mentioned by Parfitt.[8] However, such episodes are also independently compatible with epilepsy and arteriosclerosis.

SUMMARY

A case of spontaneous hypoglycaemia resulting from an islet-cell adenoma of the pancreas in a man dying at the age of 80 years is reported. The case is discussed from the point of view of his advanced age, epilepsy, family history, arteriosclerosis and dementia.

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