FATAL HYPOGLYCAEMIA IN A DIABETIC PATIENT WITH PITUITARY NECROSIS

BY

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Pituitary necrosis, not associated with shock or haemorrhage, is occasionally encountered in post-mortem examinations. Plaut (1952), in a routine series of necropsies, found pituitary necrosis in 13 out of 149 cases, but does not correlate these findings with clinical findings. Kraus (1920, 1926a, 1926b) noted the relative frequency with which pituitary necrosis is found in diabetics, and particularly in young diabetics, and described certain "diabetic changes in the hypophysis." Kiyono (1926) could find no characteristic changes in the pituitary glands of diabetics, but described two cases in which there was necrosis. Another two cases of pituitary necrosis in young diabetics were reported by Baló (1923).

When pituitary insufficiency complicates diabetes mellitus, conditions exist analogous to those in the Houssay animal. Houssay (1936) showed that diabetes produced in an animal by pancreatectomy was alleviated by subsequent hypophysectomy. Such an animal was readily rendered hypoglycaemic by fasting, and showed pronounced hypersensitivity to insulin.

This phenomenon has been observed in the human subject on a few occasions. Apart from a brief reference by Calder (1932) to a case of Simmonds's disease which showed amelioration of pre-existing mild diabetes, nine cases have been reported (Lyall and Innes, 1935; Kotte and Vonderahe, 1940; Feldman *et al.*, 1947; Vandenbroeck and Férin, 1947; Bastenie, 1949 (quoted by Poulsen, 1953); Marzullo and Handelsman, 1951; Williams, 1952; Israel and Conston, 1952; Poulsen, 1953). The ages of these nine cases (three male, six female) ranged from 29 to 53, with an average of 39. Three cases showed a great improvement in the diabetes (including, in Poulsen's case, disappearance of diabetic vascular lesions in the eye) and remained alive. In each case there was clinical evidence of pituitary damage. Of the six fatal cases necropsy was performed in five, and pituitary necrosis found in every case. In the sixth case there was clinical evidence of pituitary insufficiency. In all the fatal cases there was a disappearance of signs of diabetes of either gradual or sudden onset, and in five of the cases death was associated with marked hypoglycaemia. In the remaining case the blood sugar was not estimated.

Irradiation of the hypophysis, leading to amelioration of diabetes, has been reported by Merle (1935) and by Balfour and Sprague (1949). Similar results following surgical removal of the hypophysis have been reported by Chabanier *et al.* (1936) and by Luft *et al.* (1952).

Another case of pituitary insufficiency in a diabetic is here reported.

Case Report

The patient, a man aged 36 at his final illness in 1952, had no illnesses of importance in childhood, and his development was quite normal. In 1933, at age 17, he was admitted to hospital in diabetic coma. After treatment he was maintained on a diet and insulin, and remained well until 1940, when he was admitted to hospital in hypoglycaemic coma. He responded to treatment with glucose, and thereafter the diabetes was controlled by three daily injections of soluble insulin. In November, 1951, he was admitted to hospital after having been knocked down by a vehicle while in a hypoglycaemic state. He was dismissed, apparently in good health, on a diet of 212 g. of carbohydrate (2,352 calories) and two injections of soluble insulin a day—40 units in the morning, and from 25 to 30 units in the evening.

He seems to have been free of symptoms and regularly at work until April 29, 1952, when he complained of headache and nausea. He took his food and insulin as usual, and went to bed at 11.30 p.m. Two hours later he was found in coma and having convulsions. He was given sugar orally, and he recovered. Throughout that day he remained well, but at 10.15 p.m. he was seen to be acting as though drunk, and an hour later was again comatose and sweating profusely. Oral sugar revived him. Next day he felt well and took his food and usual insulin. At 10 p.m. he was seen staggering along the road, and at 11 p.m. was found completely comatose. He was given sugar by mouth, and at 12 midnight he was sitting up in bed talking and smoking. He had some tea to drink containing 12 teaspoonfuls of sugar. He did not take any more insulin. Two hours later, at 2 a.m. on May 2, he was once again comatose and having convulsions. It was found to be impossible to give him anything by mouth. At 9 a.m. his doctor gave him 50 ml. of 50% glucose intravenously, and 50 ml. of 10% glucose subcutaneously. This had no effect. He was admitted to the Victoria Infirmary at 1 p.m., having then been in coma for 11 hours.

On admission he was seen to be slimly built, but well nourished. He was completely comatose and was sweating profusely. His limbs were spastic, and irregular twitching movements were present. Plantar responses were extensor. Pupils were equal and reacted to light. There was nothing abnormal in the chest or abdomen. Axillary and pubic hair showed normal distribution.

Treatment and Progress

Blood was withdrawn for sugar estimation, and 100 ml. of 50% glucose was given intravenously. No change occurred in his condition. Intravenous glucose was repeatedly administered throughout the afternoon until a total of 300 g. had been given. The blood sugar on admission was 8 mg.

FIG. 1.—Showing intravenous therapy and insulin treatment, degrees of acetonuria and glycosuria, and blood-sugar levels.

per 100 ml. After one and a half hours this had risen to 148 mg., but the patient showed no improvement. Periodic convulsive attacks lasting 10 to 15 minutes occurred, separated by periods of relative calm lasting 24 to 40 minutes. At 4 p.m. a catheter was inserted and, from this time, frequent analyses of urine were made. Blood-sugar estimations were carried out regularly. At 6 p.m. continuous intravenous fluid was started, beginning with 5% dextrose in normal saline. Penicillin, 1,000,000 units, was given, followed by 500,000 units twice daily. Later in the day the convulsions became less severe, but generalized twitching movements persisted. At no time did he respond to cutaneous or aural stimuli.

May 3.—Throughout the day the patient's condition remained unchanged. The skin was moist and twitching movements were still present. Overnight the blood sugar had fallen to severe hypoglycaemic levels (11 mg. per 100 ml.), but subsequently rose and was maintained at between 300 and 400 mg. per 100 ml. Lumbar puncture was performed at 11 a.m.

May 4.—There was no improvement in his clinical state. A heavy glycosuria persisted, and on account of the appearance of ketonuria, increasing in amount, 10-unit doses of soluble insulin were given, up to a total of 60 units. The blood sugar, which throughout the earlier part of the day was maintained at between 200 and 300 mg. per 100 ml. suddenly fell to extremely low levels (14 mg.) with disappearance of ketonuria and glycosuria. Glucose, 150 g. was administered intravenously. The blood sugar then rose to between 100 and 200 mg. Lumbar puncture was repeated at 3.30 p.m.

May 5.—The patient's condition was still unchanged. During the afternoon twitching movements became less marked, and by 6 p.m. were no longer present. Hyperventilation developed and acetone appeared in the breath. Glycosuria and ketonuria increased, and the blood sugar rose to 651 mg. In spite of this hyperglycaemia, sweating remained profuse. Small doses of insulin up to a total of 25 units were again given, resulting in a fall of blood sugar to 78 mg.

May 6.—The limbs were now flaccid. Sweating was still occurring. The blood-sugar levels fluctuated between 118 and 561 mg. per 100 ml. The patient died at 11.10 a.m.

During this period in hospital there was an irregular pyrexia, with a terminal rise to 104.4° F. (40.2° C.). The blood pressure was maintained at about 115/75 until two hours before death, when it fell to 90/50.

The biochemical findings in blood and C.S.F. are summarized in Tables I and II. The fluctuations in blood-sugar readings, with details of therapy, are shown in Fig. 1. The Wassermann reaction of the blood and C.S.F. was negative.

TABLE I.—*Biochemical Findings in the Blood*

Date and Time	Urea (mg./100 ml.)	Chlorides (mg./100 ml.)	Alkali Reserve (Vol. CO ₂ %)	Potassium (mg./100 ml.)	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K-A Units)
2/5/52 4 p.m.	46	416	48.1	18.9	—	—	—
3/5/52 11 a.m.	27	591	52.8	—	—	—	—
4/5/52 1.30 p.m.	39	627	45.3	18	9.7	1.15	8.2

TABLE II.—*Biochemical Findings in the C.S.F.*

Date and Time	Glucose (mg./100 ml.)	Chlorides (mg./100 ml.)	Protein (mg./100 ml.)	Cells (per c.mm.)	Granulocytes (%)	Lymphocytes (%)
3/5/52 11 a.m.	80	749	44	35	80	20
4/5/52 3.30 a.m.	208	767	54	23	76	24

Necropsy Report

Necropsy was carried out, four hours after death, by Dr. J. E. Craik, of the Department of Pathology, Victoria Infirmary. There was no evidence of bruising of the scalp or of an old fracture of the skull. The C.S.F. was increased in amount but was clear. There was oedema of the brain with flattening of the convolutions and a slight pressure cone on the inferior surface of the cerebellum, but not on the medulla or pons. The cerebral blood vessels were unusually healthy for a diabetic: they were thin and did not contain any plaques of atheroma. The brain weighed 1,510 g.

The cut surface was moist, but there were no petechiae or larger haemorrhages. No softening or macroscopic abnormalities could be found.

The respiratory, circulatory, digestive, and genito-urinary systems showed no macroscopic abnormalities. The pancreas weighed 55 g.

The suprarenal glands were much enlarged, the right weighing 12 g. and the left 10.5 g. On section it was seen

FIG. 2.—Low-power view of pituitary, showing two areas of necrosis. (H. and E. x7.)

FIG. 3.—High-power view of anterior pituitary, showing recent necrosis to the right and normal pituitary cells to the left. Outlines of necrotic cells are still preserved, but nuclei are small and pyknotic, and the cytoplasm is losing its specific staining reactions. (H. and E. x100.)

that they had undergone simple hyperplasia, the proportions of cortex and medulla being normal. The pituitary and thyroid appeared normal.

Histology.—In the pancreas, islets of Langerhans were extremely scarce; in a search through two blocks of tissue only one islet was found. It was probably a little on the large size, but otherwise appeared normal. The thyroid showed histological evidence of hyperfunction. The acini varied greatly in size, some being so small as to be almost solid. They were lined by thick cubical epithelium, which was often folded. Colloid was well coloured but did not fill the acini completely, and often there was peripheral vacuolation. Both suprarenals were large, but the hyperplasia was proportional in the medulla and all the layers of the cortex. There was no histological abnormality. The pituitary showed peculiar patchy necrosis in the most anterior part of the anterior lobe. The necrosis was early;

FIG. 4.—High-power view of anterior pituitary, showing older necrosis with gross granulocytic and lymphocytic infiltration. The architecture of the pituitary is almost completely destroyed. (H. and E. x100.)

in some patches the cells were still well preserved but had pyknotic nuclei; in some the cells were only just discernible; and in others the cells were lost, but the general architecture of the pituitary was still preserved (see Figs. 2, 3, and 4). It was thus obvious that the various patches of necrosis were not of the same age, though none was of more than a few days' duration. In the brain, sections from the pons showed various degrees of degeneration of ganglion cells. A few appeared normal. Most showed moderate or severe chromatolysis up to complete loss of nuclei. Shrinkage of ganglion cells was a feature, most being surrounded by a clear zone. There was no evidence that glial proliferation had begun. In the liver, glycogen was increased, as was to be expected. Otherwise the histological appearances were normal.

Comment

The notable feature of this case is the sudden development of a series of severe hypoglycaemic episodes in a diabetic patient who seems to have been under at least moderately satisfactory control for 19 years. The last of these episodes, which terminated in coma lasting four and a half days and death of the patient, began two hours after he had been treated successfully for an insulin reaction, and in spite of the fact that additional glucose, but no insulin, was given. In hospital, extremely large doses of glucose were required to raise the blood-sugar level, which, however, fell spontaneously to a severe hypoglycaemic level. Later, when small doses of insulin were given to combat ketosis, the blood sugar fell to unexpectedly low levels even while glucose was being administered by intravenous drip. This state of affairs suggests suddenly acquired extreme insulin sensitivity, and the explanation for this may lie in the pathological changes found in the pituitary.

Death in this case resulted from extended hypoglycaemia. Since the brain can utilize only glucose for its metabolism, if this is virtually absent from the blood for a considerable period irreversible changes may be expected in the brain cells. These changes have been studied by Baker and Lufkin (1937), Baker (1938), Sahs and Alexander (1939), and Lawrence, Meyer, and Nevin (1942). The duration of hypoglycaemia required for these changes is not known exactly, although Lawrence *et al.* state that hypoglycaemic coma of one to three hours is compatible with recovery. In the above case the patient had been in coma for 11 hours before admission, and remained in coma despite the rise of blood sugar. Cellular changes in the brain similar to those reported by these observers were, in fact, present.

Summary

Pituitary necrosis is occasionally encountered in routine necropsies. Its occurrence in diabetic subjects is noted.

The Houssay phenomenon is described, and cases are cited of this phenomenon occurring in man.

Irradiation of the hypophysis and hypophysectomy as a treatment of diabetes is mentioned.

Another case of pituitary insufficiency in a diabetic is reported.

Extended hypoglycaemia as the ultimate cause of death is discussed.

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FRIEDREICH'S ATAXIA COMBINED WITH DIABETES MELLITUS IN SISTERS

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The combination of Friedreich's ataxia with diabetes mellitus in families has been mentioned mainly in Continental literature. Schlezinger and Goldstein (1940), in the only comprehensive survey in the English language, list 18 patients from the literature with two of their own. The comparative rarity of the association prompts us to record its occurrence in two sisters.

Case 1

A woman aged 28 was admitted to hospital on September 15, 1950. She had been a full-term normally delivered infant. During her childhood her family noticed that she tended to stumble, to walk on her toes, and to be unable to play or skip normally. The stumbling increased, until at the age of 14 she could just walk along a narrow passage by supporting herself with her hands on the walls, and at this time she could not sit upright in a chair. From the age of 22 she had been partly confined to bed, being able to get around only by holding on to objects in her room, and from 27 she had been wholly bedridden. In 1948 she had been investigated for joint pains and was found to have diabetes mellitus. She was put on a diet without insulin, to which she had since adhered. Menstruation had been scanty, only two to three days every three months, following menarche at 16.

Physical Examination.—The patient sat slumped in a chair and was unable to walk even with assistance. No abnormal signs were found in the heart, lungs, or abdomen. The blood pressure was 108/80. *Skeletal system:* Scoliosis and bilateral pes cavus were present. *Central nervous system:* The patient was fully co-operative. Well-marked head-nodding, particularly during questioning, slurred and slow speech, and coarse lateral and rotary nystagmus were noted. The pupils were equal and reacted briskly to light and on accommodation. The fundi were normal. Right eye 6/12, left 6/6. Colour vision was normal. Other cranial nerves were normal. The upper limbs showed gross hypotonia, ataxia, dysmetria, dysidiadochokinesia, intention tremor, and diminished power, particularly of grip. The biceps, triceps, and supinator jerks were present and equal, though diminished, and there was no wasting or sensory change apart from absent postural sensibility of the fingers. The legs showed hypotonia, incoordination, dysmetria, and