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HYPOPITUITARISM WITH CONSECUTIVE DEVELOPMENT OF DIABETES MELLITUS

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The first convincing demonstration of the importance of the anterior part of the pituitary gland in diabetes mellitus was given in 1931 by Houssay and Biasotti, when they showed that the diabetes which followed pancreatectomy in dogs could be alleviated by hypophysectomy; and the "Houssay dog" formed the basis for a great deal of experimental work in the years that followed. It was also found that if anterior pituitary extracts were injected into dogs thus operated on the diabetes reverted to its former severity. Later, Young (1937) found that administration of pituitary extract to adult dogs for a certain length of time led to the development of diabetes mellitus. The occurrence of hyperglycaemia and glycosuria in a proportion of patients with acromegaly had of course been recognized for many years.

In the last twenty years the role of the pituitary and of other endocrine glands in the aetiology of diabetes has become increasingly obvious, so much so that Hims-worth (1949) declared that diabetes could no longer be regarded as a single entity but as a syndrome. Nevertheless there are many points still not fully understood, among which should be mentioned the part played by the glands of internal secretion in the production of some of the complications of the disease.

The Houssay phenomenon, first described in dogs, has been reported in man on various occasions. In each of these cases pituitary insufficiency has developed in patients known to have had diabetes for a varying length of time; the pathological lesions have been diverse and have included infarction, tumour, and abscess. It is extremely rare, however, for the sequence of events to be reversed, and we have been able to find only one previous report of such a condition.

Case Report

The patient was first seen by us in September, 1953, at the age of 45, when he was referred by his doctor with a request for gastro-intestinal investigations. He stated that

for about ten years he had suffered from recurrent attacks of pain in the epigastrium and right hypochondrium accompanied by vomiting; he also complained of backache for three years, with difficulty in stooping, and a sensation of locking in the small of the back. As he was extremely deaf his wife amplified the history and revealed that since her marriage to him in 1943 she had known that he was sexually underdeveloped. She stated that during their married life her husband had seldom shown any desire for intercourse, and when he attempted coitus he was unable to achieve erection. The patient himself was quite co-operative during interrogation, but seemed unaware of the significance of many of the questions. He did, however, volunteer the opinion that "it was all the result of self-abuse"; he stated that during his middle teens he had occasionally masturbated and had had seminal emissions. This was the only fact ever obtained that might give some hint regarding the duration of the pituitary deficiency.

In 1947 he was examined by an ophthalmologist because of iritis and early keratitis in the right eye, and the blood Wassermann reaction was found to be strongly positive; his brother's W.R. was also positive, and a presumptive diagnosis of congenital syphilis had been made at that time. The patient's wife had known him for about eight years before marriage and thought that "he had always looked much the same." In view of this story he was admitted for endocrinological study.

In appearance the patient looked pale; his face was smooth and hairless, and the skin of the body generally rather dry. No axillary sweating was observed; there was no cutaneous or mucosal pigmentation. Hair was completely absent from axillae, chest, abdomen, and thighs, but a few fine downy hairs were present on the pubic region. Both testes were in the scrotum, but were soft and only the size of a pea; the penis approximated to that of a pre-pubertal boy (see Fig. 1).

The lungs, cardiovascular system, and alimentary system were clinically normal. The blood pressure was 140/80. No neurological abnormality was noted except that the left pupil was a little larger than the right; both reacted to light and on convergence. The fundi were normal. Moderate dorsal kyphosis and an exaggerated lumbar lordosis were present.

Mentally he was a placid, amiable individual, and took little interest in his surroundings or in his own condition. He showed no diffidence in exposing his body for examination.

Radiological and Laboratory Studies.—X-ray examination of the skull showed that the pituitary fossa was normal. The lumbar spine showed generalized osteoporosis with osteoarthritic change between the spines of L3 and 4; there was slight wedging of the bodies of D11 and 12 with minimal osteoarthritic changes; the appearances suggested old fracture. No abnormality was noted in the epiphyses of the long bones. 17-Ketosteroid excretion, 2 mg. a day. Fasting blood sugar, 85 mg. per 100 ml. Glucose-tolerance test, normal (see Fig. 2). Serum electrolytes: sodium, 315 mg.; potassium, 18 mg. chlorides, 640 mg. per 100 ml. Serum cholesterol, 200 mg. per 100 ml. Serum proteins, total 6.1 g. per 100 ml. (albumin 4.2 g., globulin 1.9 g.).

FIG. 1.—Photograph of patient; body hair absent and genitals underdeveloped.

Haemoglobin, 90% (Haldane). Wassermann reaction, strong positive. Meinicke reaction, strong positive. Kepler's test: overnight urine, 720 ml.; 8.30 a.m., 55 ml.; 9.30 a.m., 45 ml.; 10.30 a.m., 58 ml.; 11.30 a.m., 52 ml.; 12.30 p.m., 53 ml.; A = 2.9.

FIG. 2.—Results of glucose-tolerance tests.

A diagnosis of anterior pituitary insufficiency was made on the basis of the above findings; and as the hypogonadism appeared to be the main manifestation the patient was given testosterone, 25 mg. thrice daily, this dosage being later reduced to twice daily. (Cortisone was not then available.) This was continued by his own doctor for about six weeks; at the end of this time there was little appreciable change, though the

patient asserted that he now had to shave daily. Objectively, however, one felt that "the wish was father to the thought." Three months later there was still no significant physical change, and after this he was not seen again at the out-patient clinic for almost two years.

In May, 1955, he came to the diabetic centre with the classical symptoms of diabetes mellitus—thirst, polyuria, nocturnal muscle cramps, and loss of weight—which had been present for four months. There was no family history of diabetes. Clinical examination was essentially the same as before, but he was about 10 lb. (4.5 kg.) lighter. The urine gave a strong reduction of Benedict's solution, but no ketones were present. The blood sugar two hours after an average breakfast was 480 mg. per 100 ml. A diet containing 200 g. of carbohydrate was prescribed, with 15 units of soluble insulin (S.I.) in the morning and 10 units in the evening.

One week later the blood sugar two hours after breakfast was 185 mg. per 100 ml. and the urine was sugar-free. He was now placed on insulin zinc suspension (I.Z.S.) 24 units daily. After a further seven days the blood sugar two hours after breakfast was 120 mg. per 100 ml. and the urine was sugar-free. He had had no hypoglycaemic symptoms, but the insulin was reduced to 18 units I.Z.S. Two weeks later the blood sugar was 220 mg. per 100 ml. under the same conditions, and there was no sugar in the pre-breakfast sample of urine. It was not considered necessary to alter the insulin dosage.

During the next three weeks he began to develop attacks of hypoglycaemia but did not report to the clinic as advised. On June 29 he was admitted to hospital in severe hypoglycaemia at 8.30 p.m.; 60 ml. of 50% dextrose was given intravenously with good effect. One hour later he relapsed, but recovered on injection of 20 ml. of 50% dextrose followed by glucose orally. Seven hours later he was again hypoglycaemic and again responded to the intravenous administration of 20 ml. of 50% dextrose. At 10 a.m. on the morning after admission—that is, about 14 hours after the last dose of insulin and two hours after a light breakfast—blood sugar was only 130 mg. per 100 ml. The urine remained sugar-free, without insulin, for the next three days on a diet containing 160 g. of carbohydrate. On July 4 the fasting blood sugar was 160 mg. per 100 ml. with no glycosuria; three hours after breakfast it was 320 mg. per 100 ml. and the urine contained 1.5% sugar. However, in view of the recent severe hypoglycaemia this high figure was not considered sufficient reason for recommending insulin, especially as there was no clinical evidence of deterioration.

On July 7 an oral glucose-tolerance test showed a typical diabetic curve (Fig. 2). Subsequently a number of investigations previously carried out in 1953 were repeated. 17-Keto-steroid excretion, 1.5 mg. a day. Serum electrolytes:

sodium, 300 mg.; potassium, 17 mg.; chlorides, 590 mg. per 100 ml. Serum cholesterol, 200 mg. per 100 ml. Kepler's test: overnight urine 480 ml.; 9.30 a.m., 40 ml.; 10.30 a.m., 65 ml.; 11.30 a.m., 50 ml.; 12.30 p.m., 45 ml.; A=3.4.

A modified Thorn test was carried out by injecting 50 units of corticotrophin in a single dose intramuscularly on four successive days; eosinophil counts were made hourly for 12 hours on the day prior to this series of injections and four times on each day that the hormone was given, the injection being made at 8 a.m. daily. The details of these eosinophil counts and of a normal control are shown in Table I. After the second dose of corticotrophin ketonuria

TABLE I.—Results of Modified Thorn Test
Eosinophil Count of Patient before Corticotrophin and of Normal Control

	Patient (c.mm.)	Control (c.mm.)		Patient (c.mm.)	Control (c.mm.)
7 a.m. . .	268	260	2 p.m. . .	125	178
8 " . .	259	237	3 " . .	90	103
9 " . .	246	218	4 " . .	100	72
10 " . .	228	182	5 " . .	97	82
11 " . .	92	165	6 " . .	198	198
12 noon . .	102	57	7 " . .	191	244
1 p.m. . .	58	56			

Eosinophil Counts of Patient during Corticotrophin Administration

Day	Time	Count (c.mm.)	Day	Time	Count (c.mm.)
1	9.30 a.m.	100	3	9.30 a.m.	89
	11.30 "	100		11.30 "	22
	2.30 p.m.	100		2.30 p.m.	22
	4.30 "	100		4.30 "	22
2	9.30 a.m.	10	4	9.30 a.m.	77
	11.30 "	Nil		11.30 "	100
	2.30 p.m.	"			
	4.30 "	"			

occurred for the first time, though the blood sugar did not show any very significant increase; glycosuria was between 2 and 3% in a 24-hour specimen of urine, having previously been between 0.5 and 1%. Insulin was therefore given in doses of 10 to 15 units before each of the three main meals of the day, and the ketonuria disappeared by the third day of this regime.

Fig. 3 illustrates the result of radio-iodine tracer studies; thyroid function was almost negligible, and the pick-up in the gland was so low that a survey was not feasible. The

FIG. 3.—Radio-iodine tracer studies. ●—● Before thyrotrophin. ×—× After thyrotrophin.

investigation was repeated after 5 units of thyrotrophin had been injected daily for four days, but no appreciable increase in thyroid function was produced nor was there any change in the clinical condition. Estimation of the B.M.R. before administration of thyrotrophin gave a figure of minus 20%; this test was not repeated after thyrotrophin. Other findings are shown in Table II.

There was no follicle-stimulating hormone or interstitial-cell-stimulating hormone in a 24-hour sample of urine.

TABLE II.—Findings Before and After Administration of Thyrotrophin

	Before	After
Plasma content per litre at 3 hours ..	0.72%	2.39%
" " " " " 51 " ..	0.32%	0.16%
" ratio " " " " " ..	0.446	0.07
Thyroid clearance rate (litres/hour) ..	1.45	0.61

An intravenous insulin-tolerance test (Fig. 4) showed much increased sensitivity to a very small dose of insulin (0.03 unit per kg. body weight). Twenty-four hours after this dose of insulin the blood sugar was still only 135 mg. per 100 ml.

FIG. 4.—Insulin-tolerance test.

The diagnosis having now been firmly established, we were anxious to study the effect of hormone therapy (a) on the manifestations of the pituitary insufficiency and (b) on the diabetes. It had already been observed that ketosis rapidly developed when corticotrophin was administered, and it was anticipated that this would recur when other hormones were exhibited, and that insulin sensitivity would decrease.

The following regime was begun on October 2; (a) thyroxine, 50 µg. twice daily, (b) testosterone, 25 mg. twice daily, and (c) cortisone, 12.5 mg. twice daily. Within 48 hours of beginning this treatment the patient complained of some thirst and polyuria, and moderate ketonuria appeared. On October 3 the fasting blood sugar was 300 mg. per 100 ml. On October 4 it was 600 mg. per 100 ml. and 5 units of S.I. was therefore given before each of the three main meals on that day. It was felt that caution was necessary with the initial doses of insulin because of previous experience; but it was soon found that larger doses would be required for control; this was achieved eventually with 40 units of S.I. daily, divided into three doses. Before his discharge from hospital the insulin was readjusted to 20 units before breakfast and 15 units before supper, and the daily carbohydrate increased to 200 g. Thyroxine was discontinued and thyroid extract, ½ gr. (32 mg.) three times daily, substituted for it. Testosterone was reduced to 25 mg. once daily; cortisone was continued in a dosage of 12.5 mg. twice daily. While still in hospital marked improvement was already manifest in the patient's general condition; he became much more alert and interested in his surroundings. The most noticeable physical change was the development of a strong growth of beard.

He subsequently attended the diabetic clinic, at first twice weekly, and later once weekly. The dose of insulin varied between 16 and 20 units a day, and he took 25 mg. of cortisone daily. Apart from growth of the beard, there was little sign of increased gonadal activity, but the pubic hair did show a slight increase in quantity.

He has remained well up to the time of writing apart from one illness, and is at work each day as a canteen manager. In February and March, 1956, he suffered from an attack of infective hepatitis, for which he was admitted to hospital. During this illness cortisone was discontinued and his dietary carbohydrate increased considerably. He was given 16 units

of insulin daily (in two doses). In spite of his large carbohydrate intake, and even though he was kept in bed, he had one severe hypoglycaemic reaction; this developed rapidly about 10 o'clock one evening, and, although the nursing staff gave him some oral glucose, he quickly became unconscious and convulsions occurred. The injection of 30 ml. of 50% dextrose intravenously brought recovery, and he was then able to swallow a further 15 g. of sugar. Analysis of a sample of blood (taken before the injection of dextrose) showed a sugar content of 35 mg. per 100 ml.

Recovery from the hepatitis has apparently been complete, and liver-function tests have not so far revealed any evidence of residual liver damage.

Discussion

In the foregoing description certain points deserve special comment. Firstly, as mentioned earlier in this article, previous reports of the Houssay phenomenon in man have recorded the effects of pituitary failure on a pre-existing diabetes, the chief result being, as would be expected, marked increase in sensitivity to insulin, both endogenous and injected. It is therefore somewhat surprising to find that diabetes mellitus in typical form may occur in a person who shows clear evidence of pituitary hypofunction.

Secondly, the history of this patient indicates that hypopituitarism has been present for probably twenty years and possibly more. In spite of this the diabetes has arisen in circumstances which would appear to be antagonistic to it.

Thirdly, the pituitary insufficiency has apparently declared itself in relation to only some of the other endocrine glands. The thyroid and the gonads show definite evidence of prolonged lack of stimulation by the hypophysis, and the thyroid has lost its ability to respond to the administration of thyrotrophic hormone.

The results of the therapeutic use of cortisone, thyroxine, and testosterone are of interest. The most striking effect has been the growth of the beard, although this is also frequently observed in cases of primary hypogonadism. Up to the time of writing axillary and chest hair has not appeared, nor has there been more than a very slight increase in pubic hair. The external genitalia have not increased in size and there is still complete absence of libido. The patient's mentality and outlook have improved; he is more active physically and has taught himself to lip-read.

The diabetic state reacted to hormone therapy in the expected fashion. Ketonuria appeared for the first time when corticotrophin was given and was abolished by insulin; it occurred again under the influence of cortisone and was again abolished by insulin. Sensitivity to insulin was also much less than before.

Summary

A case of hypopituitarism is reported in which diabetes mellitus developed after at least twenty years of deficient pituitary function. The clinical findings and laboratory investigations are described, with special reference to the behaviour of the diabetic state under the influence of various hormones.

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