The function of the endocrine glands in diabetes mellitus

A clinical study of 107 cases

By

Paul Horstmann

For a number of years following the discovery of insulin it has been commonly accepted that diabetes mellitus in man is due to a deficient pancreatic secretion of insulin. A new and important fact in the problem of the etiology of the disease appeared when Houssay (1930, 1931) and Houssay & Biasotti (1930) showed that hypophysectomy in pancreatectomized animals greatly alleviated the diabetes, thus suggesting that the pituitary gland secretes a diabetogenic factor. Later (1937) Young was able to produce a permanent diabetic state in dogs by injections of anterior pituitary lobe extracts. Further, it was demonstrated that this kind of diabetes is most readily produced in adult dogs, in which the onset is preceded by an increase in weight, while injections of pituitary extracts in puppies cause acceleration of growth, diabetes occurring only with intense treatment; in the latter case growth ceases (Young, 1941 b, 1944, 1945).

These experiments led to the investigation of the significance of other endocrine glands in the pathogenesis of the disease. The results of animal experiments were reviewed by Houssay (1937). The most outstanding facts, in addition to
the importance of the pituitary gland, are as follows: Thyroid extract may cause diabetes in partly pancreatectomized dogs but not in normal dogs. Sometimes the diabetes continues after stopping thyroid feeding (metathyroid diabetes, Houssay, 1944). Thyroidectomy increases the sensitivity to insulin, but does not cure diabetes. Adrenalectomy produces hypersensitivity to insulin, and this is also seen if the medulla only is removed. Pancreatic diabetes is alleviated by adrenalectomy. Ingle (1941, a) showed that administration of 17-hydroxy-11-dehydrocorticoesterone to normal rats caused hyperglycemia and glycosuria (adrenal steroid diabetes). Conn et al. (1948) were able to produce a temporary diabetes mellitus in man by injections of purified pituitary adrenocorticotrophic hormone. They conclude that »so far as pure pituitary fractions are concerned, adrenocorticotropic hormone has been found to have the greatest diabetogenic effect of any tested to date.«

Evidence of diabetes mellitus in man caused by endocrine disturbances other than pancreatic deficiency is scanty. Acromegaly resulting from an eosinophile adenoma of the pituitary gland is fairly often associated with diabetes (yet, according to Wilder (1940), only in 6 to 9 per cent of all cases). Also, pituitary basophilism is fairly frequently combined with diabetes. Alleviation of diabetes by destruction or removal of the pituitary gland (the Houssay phenomenon) has been reported four times in man (Lyall & Innes (1935), Chabanier et al. (1936), Kotte & Vonderahe (1940), Feldman et al. (1947)).

Tumours (adenomas) of the adrenal cortex are sometimes complicated by diabetes. Russi et al. (1945) found that diabetes occurred five times as frequently in subjects with cortical adenomas as in a general group of 9000 autopsies. Sprague et al. (1943) report a case of tumour of the adrenal cortex in which the complicating diabetes was cured following extirpation of the tumour. Diabetes is sometimes seen in patients with a pheochromocytoma. Duncan et al. (1944), Green (1947) and Goldner (1947) report such cases in which the diabetes disappeared following removal of the tumour.

Sprague et al. (1948) describe a case of assumed »steroid
diabetes», associated with Cushing’s syndrome, in a 14-year-old boy.

On the other hand, diabetes and Addison’s disease may be found in the same patient. According to Feldman et al., in 1947, 16 cases showing this combination were on record. Another case is reported by Ernberg (1947), and, recently, Knowlton & Kritzler (1949) found reports of 22 instances of this combination in the literature. Either of these diseases may be the first to appear.

It is generally agreed that the incidence of diabetes is greater among patients with hyperthyroidism than in the population as a whole. That hyperthyroidism greatly aggravates a preexisting diabetes is a well known fact. On the other hand, Weinstein (1932) believes that diabetes is particularly rare in myxoedema, but this is denied by Shepardson & Wever (1934). Wilder et al. (1934) report a case in which removal of a morphologically normal thyroid gland markedly increased the glucose tolerance of a patient with severe diabetes. The increase in tolerance roughly paralleled the decrease in the metabolic rate. Similar observations have been reported by Thune Andersen (1933).

Only inconclusive evidence exists regarding the significance of the parathyroid glands in human diabetes (Olmer & Paillas, 1936, and Zunz & La Barre, 1933). The problem of the function of the gonads in human diabetes will be considered later.

There is very little histological work on the endocrine glands in diabetes. In 1914, Fry described in pituitary glands from diabetics 1) an increase in the chromophile cells; 2) conversion of chromophile granular cells into colloid or granular masses; 3) areas of degeneration which may be of such size that few of the cellular elements remain in the anterior lobe. Examining the endocrine glands of diabetics, Kraus (1923) found the pituitary gland to be smaller than normal, with a reduction in the number and size of the acidophile cells, while the chromophobe cells were present in increased number. The adrenal glands were smaller than normal in young subjects.
but, on the contrary, larger than normal in older people. The thyroids showed various changes, but not in any definite direction, while the parathyroids were remarkably small. Regarding the gonads, a few men showed decreased spermatogenesis, and, in women, the ovaries, in some cases, presented deficient follicular ripening.

OWN INVESTIGATIONS

The scope of the present work was to investigate whether non-selected clinical cases of diabetes, submitted to a special examination showed any signs of abnormal functions of the endocrine organs apart from the pancreas. Of course marked endocrine disturbances were not to be expected, but it appeared possible that the clinical and laboratory findings might support, or be inconsistent with the endocrine etiologies suggested by animal experiments and by the occasional cases seen in human pathology.

In the period from May 1947 to August 1948 107 diabetic in-patients in the Medical Department of the City and County Hospital in Odense were examined. This hospital is the centre of medical treatment in the northern part of the island of Fyn in central Denmark. The district served, covers an area of 1144 square km, with a population of 168000, 100000 of these living in the City of Odense, and the remainder partly in smaller towns, partly in the country. Practically all inhabitants are of Danish origin, foreign immigration being insignificant.

The patients included in the investigation were questioned with special reference to signs of endocrine disorders in the history. A clinical examination was performed and the height, weight, blood pressure, blood sugar, basal metabolic rate, total serum cholesterol and serum calcium were determined. Urine analyses were made, the sella turcica X-rayed, the eyes were examined and in more than half the cases the urinary hormonal excretion was estimated.

Statistical evidence.

One woman had a basophile adenoma of the pituitary
gland. Because of the probable special etiology in this case it is omitted in the final analysis. Of the remaining 106 diabetics, 45 were males, 61 females (42 and 58 per cent respectively). 31 males and 34 females received insulin treatment.

As the sex distribution, married or unmarried state, age at the beginning of the disease, and height and weight measurements are considered important in the subject under discussion, these results were obtained from all diabetics treated in the department in 1945 and 1946 and have been added to the data, thus bringing the number of diabetics investigated up to 241. This allowed of a more reliable statistical analysis.

Of the total number of 241, 102 were males, 139 females (42 and 58 per cent respectively), exactly the same proportion as in the cases specially examined.

Table 1.
241 cases of diabetes mellitus, grouped according to age at the beginning of the disease.

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Age at onset of the disease is seen in Table 1. Evidently these figures must be seen in relation to the size of the various age groups in the general population. This is done by calculating the numbers of hospitalized diabetics per 1000 inhabitants in each age decade. This, of course, does not represent the annual morbidity rate of diabetes in the population, (as these are only the hospitalized diabetics, over a three year pe-
period, and the disease appeared at a different time in the different cases), but it is in all probability proportional to that figure. Statistical information from the census of 1940 has been used.

**Relative figures**

![Graph showing incidence of diabetes among men and women according to age at the beginning of the disease.](image)

**Fig. 1.**

Incidence of diabetes among men and women according to age at the beginning of the disease.

The results are shown in Fig. 1. It appears that the incidence of the disease is quite different in the two sexes. In men the morbidity is approximately the same throughout life, with the exception of a moderate rise in the age group 50—59 years. In women, the incidence of the disease varies considerably throughout life, being the same as in the male sex during the first 20 years of life, lower than in men from the age of 20 to 40 years, and then gradually rising to a maximum in seventh decade, when the incidence in women is four times as high as that of men of the same age and more than eight
times that of women at the age of 20 to 40 years. In the oldest age groups the morbidity again decreases in both sexes.

The average height and weight of 75 diabetic men over 20 years of age were 171.2 cm and 73.5 kg. The corresponding values of 107 diabetic women were 157.7 cm and 68.1 kg. These figures may be compared to those found by Schmidt (1929), who measured 218 male and 215 Danish (psychiatric) patients. The average values found by Schmidt for height and weight were respectively 169.62 ± 0.48 cm and 67.38 ± 0.82 kg in men and 157.24 ± 0.41 cm and 60.20 ± 0.92 kg in women. Thus the height of adult diabetics did not significantly differ from the values found by Schmidt, while the weight was significantly higher. The weight distribution curve is asymmetric, deviating towards the overweight side, but showing only one maximum. The mean ages of Schmidt's patients were 43.6 and 47.6 years, while the mean ages in the present cases of diabetics were 49.5 and 54.6 years, in men and women respectively. This difference of age, however, only accounts for an increase of weight of 1 kg. at most, according to standard height and weight tables.

Admittedly, measurements on psychiatric patients cannot be considered identical with the values found in the normal population, but similar figures from Danish «normal patients» do not exist (measurements on recruits or on special classes of the population cannot be used).

Of the total of 102 men and 139 women, 68 per cent of the men and 74 per cent of the women were married or had been married previously. Of the general population in 1940, 48.9 per cent of the men and 53.3 per cent of the women were married or had been married previously. The difference between the diabetics and the general population with regard to marriage must be considered significant. An explanation of this is entirely lacking, but the fact that the age distribution of diabetics is different from that of the population as a whole must be taken into consideration (cf. Joslin, 1946).

The results given below are deduced from the 106 patients which were specially examined.
Sex glands.

With regard to sex function the most prominent symptom in the male diabetic is a lack of libido and a decrease in sexual potency. 17 of 19 patients questioned on this point showed these symptoms. It may be present even in well controlled diabetes, and once established it may continue in spite of adequate treatment of the diabetes.

20 diabetic men over 45 years had a total of 75 children or 3.8 each.

In women menstruation was as a rule not disturbed. Only one woman had had periods of amenorrhoea before the appearance of diabetes. Two had undergone radio-therapy for cancer of the uterine cervix. The menarche occurred at an average age of 14.6 years (50 cases), ranging from 12 to 20 years, while the menopause took place at an average age of 47.6 years (33 cases), ranging from 40 to 55 years. The values must be considered normal for Danish women.

In 30 of 61 women the diabetes appeared after the menopause. As seen from the diagram, there is no marked increase at the time of the menopause, the highest incidence being found later. Nor is there any marked increase of cases around the menarche.

34 women, who had passed the menopause at the time of examination, had borne a total of 154 children, or 4.5 each, and had 12 abortions. Only one of these 34 women had never given birth to a child.

Analysis of the urinary hormonal excretion was carried out in 28 men and 28 women (Table 2). The results were as follows:

The excretion of gonadotrophic hormones was within the normal limits in both sexes, being in nearly all cases lower than 50 m. u./24 hours. The excretion of oestrogen was also without any definite abnormality, though 9 out of 20 men excreted less than 20 m. u./24 hours. In most of the women the excretion of oestrogen was normal for the particular age. Only one, 34-years old, sexually mature woman, excreted no oestrogenic hormone. The patient had had a mild pulmonary
Table 2.
Urinary hormonal excretion per 24 hours in diabetics.

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Figures marked with an asterisk indicate a considerably decreased 17-ketosteroid excretion. Normal values: gonadotrophin < 50 M. U./24 hrs.; oestrogens (men) 20—50 M. U./24 hrs.; oestrogens (women) 20—200 M. U./24 hrs.; 17-ketosteroids see Fig. 2. The analyses have been carried out in the State Serum Institute, Copenhagen, under the supervision of C. Hamburger, M. D.
Excretion of 17-ketosteroids in 26 male and 19 female diabetic subjects. The black line shows the average output in normal subjects, and the stippled area gives the zone within which 97—98 per cent of normal values are falling, according to Hamburger (1948).

Ordinates: mg/24-hours. Abscissae: age of the subject.

tuberculosis, but did not show any signs of hormonal dysfunction clinically.

The excretion of 17-ketosteroids was different in the two sexes (Fig. 2). Seven out of 26 diabetic men showed an excretion of 17-ketosteroids less than was found by Hamburger (1948), in 97 per cent of normal men, though the same technique was used. All men with such abnormally low excretions were between the ages of 20 and 50. If only this particular age group is considered, then the deviation is still more marked, 7 of 13 subjects showing this low excretion, and 4 of the remainder being below the average. On the other hand, one 35-year old man showed an abnormally high excretion of 17-ketosteroids at the time immediately following a severe coma.
Further investigation of this case was impossible, as the patient was unwilling to continue his stay in the hospital.

In children, old people and in women, the excretion of 17-ketosteroids appeared within the normal limits, though not very high in the 4 middle-aged women in whom the analysis has been performed. The one woman with the abnormally low ketosteroid excretion was the same patient, who did not excrete any oestrogen.

_Hypophysis._

X-ray examination of the sella turcica was performed in 40 men and 54 women. In no case was any definite enlargement found, nor were there any signs of other pathological changes, apart from partial or complete closure of the sella in four cases, due to calcification of the diaphragma sellae. In no case did the eye examination reveal any signs of intracranial tumour. No clinical signs of acromegaly were found in any case.

That the urinary gonadotrophin excretion was normal (i.e. not increased) in both sexes has already been mentioned.

_Thyroid gland._

Enlargement of the thyroid gland was found in three cases, one case of exophthalmic goitre, and two cases with a non-toxic goitre. All these patients were women. Another woman was treated with methylthiouracil for hyperthyroidism; she had no goitre.

_Adrenal glands._

In no case was any definite sign of adrenal disease found. The hair growth was normal, and there were no cases of marked hypertrichosis. »Bearded women« were found no more frequently among diabetics than in the general population. The 17-ketosteroid excretion is considered to be mainly of adrenal origin in women, and in children and old people of the male sex; as already stated the 17-ketosteroid excretion was in these groups within the normal limits.
Parathyroid glands.

Serum calcium determinations were carried out in 101 cases. The values varied from 8.3 mg per 100 ml. to 12.5 mg per 100 ml. with the majority around 10.0 mg per 100 ml. Seventy-one of the 101 values found were between 9.7 and 10.6 mg per 100 ml. The result does not suggest any abnormality of the parathyroid function in diabetes mellitus.

Basal metabolic rate.

The total basal metabolism was determined by the apparatus of Krogh. The determinations were carried out in the morning, after 14 hours' rest, and before giving food and insulin. No special diet was given, the patients being on the diet considered adequate in each case. A total of 272 determinations were made on 36 men and 47 women. The average basal metabolic rate was 109.6 ± 1.7 per cent in men, and 110.8 ± 1.6 per cent in women. The average basal metabolic rate is thus apparently slightly but significantly raised under these conditions.

These results, which are based on the oxygen consumption, are in complete agreement with those found by Joslin (1937) before the introduction of the undernutrition treatment (+ 12 per cent), and by Holten (1925) (+ 10.2 per cent).

Total serum cholesterol.

Determination of total cholesterol was carried out in 42 men and 59 women. The values varied from 42 to 470 mg per 100 ml. If, according to Hunt (1940) 230 mg per 100 ml. is considered the upper limit of the normal, 15 of 42 men and 30 of 59 women showed abnormally high values (36 and 51 per cent respectively). The percentages for men and women over 50 years were still higher, 44 and 59 per cent respectively.

DISCUSSION

The remarkably low urinary excretion of 17-ketosteroids, which is found in diabetic men of middle age, and to a lesser degree in women but not in children or in old people suggests
an inhibition of the function of the testes, since the 17-ketosteroid excretion in adult men is partly of testicular and partly of adrenal origin, while in women, children and old people it is mainly derived from the adrenals. Should further work support these results (and continued investigations have so far confirmed them), we may see in this finding an explanation of the impotence so common in diabetic men. In contrast to this, menstrual irregularities are nowadays uncommon in well controlled diabetic women. This is in agreement with the normal oestrogen excretion found in diabetic women.

The above results are in accordance with the findings of Miller & Mason (1945). These authors noted that diabetic patients of all ages excreted a smaller amount of 17-ketosteroids than do normal persons. The trend toward a lowered excretion was most marked in men but was also found in women.

White (1946) observed a tendency to higher 17-ketosteroid excretion in diabetic children than in normal controls.

While older statistics on sex incidence in diabetes invariably show the disease to be more common in men than in women (e.g. v. Noorden, 1917) this seems to be reversed in modern times. This trend has been noted in the United States by Joslin (1946), in Norway by Hansson (1947) and is also found in Sweden (Dahlberg et al., 1947). Joslin believes that the reason for this is that women can more easily obtain adequate treatment, because of the higher appreciation of women in modern communities. Another explanation may be sought in the present increasing average duration of life. The high incidence of diabetes in women is particularly marked in the seventh decade, while the difference between men and women with regard to the incidence of diabetes is only slight during the first six decades as a whole.

The varying diabetic morbidity in women during life is another conspicuous fact. In childhood, the morbidity is the same in the two sexes, between 20 and 40 years the incidence in women is lower than in men, while the female sex is predominant among diabetics over 40 years, with a maximum in
the seventh decade. In still older people the morbidity decreases in both sexes. This peculiar distribution, which is practically the same as that found by Joslin (1937) in a very large number of cases, suggests the possibility that the female sex hormone protects to some extent against diabetes.

Some reports concerning the effects of oestrogens on diabetes have accumulated in the literature. Several workers report alleviation of menopausal diabetes in women following oestrogen treatment, with decreasing glycosuria and lower insulin requirement (Cantilo, 1941; Gessler et al., 1939; Gitlow & Kurschner, 1943; Mazer & Israel, 1937; Morton & McGavack, 1946; Schoene, 1940; Spiegelman, 1933; Thaddea & Hampe, 1940). Negative results have also been reported (Collens et al., 1936; Kaufmann, 1929; Lawrence & Madders, 1941). Conflicting evidence has also been obtained in animal experiments (Barnes et al., 1933; Ingle, 1941 b; Nelson & Overholser, 1929; Young, 1941 a; Zunz & La Barre, 1939; Foglia et al., 1947). The question cannot as yet be considered as decided.

A hypothetically abnormal pituitary activity might reveal itself in the gonadotrophic hormone excretion, enlargement of the sella turcica, growth abnormalities and in the basal metabolic rate. None of these findings have shown any definite signs of pituitary involvement in the disease. The sella turcica and the urinary gonadotrophic excretion was normal. The skeletal growth, as measured by the body height, was normal. The frequently increased height of the prediabetic child, described by White (1927), or the tendency to dwarfism sometimes noted in diabetes in children are not reflected in the average height of the usual diabetic.

The slightly raised basal metabolism is evidence that the condition is not similar to pituitary basophilism, since the basal metabolic rate is usually lowered in Cushing's disease. It might be compatible with a hyperactivity of the acidophile cells of the pituitary gland, but it could of course be explained in several other ways. Whether it is due to thyroid hyperactivity is unknown.
SUMMARY

A total of 107 non-selected consecutive cases of diabetes mellitus were examined with reference to the functions of the endocrine glands. The results were as follows:

The incidence in men was found to be approximately the same during the various stages of life, with the exception of a moderate increase in the sixth decade. In contrast to this, the incidence in sexually mature women is lower than in men of the same age, while in the more advanced years the incidence in women greatly surpasses that in men. This suggests that the female sex hormone may to some degree protect against diabetes.

The urinary excretion of 17-ketosteroids was extraordinary low in men between 20 and 50 years, low but within normal limits in women of the same age, and normal in children and old people. It is considered likely that the excretion of 17-ketosteroid of testicular origin is particularly decreased in male diabetics of middle age, thus giving an explanation for the impotence so common in these patients. The excretion of gonadotrophin and oestrogen was normal in both sexes.

No definite signs of abnormal pituitary, thyroid, parathyroid or adrenal activity were revealed.

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