A CASE OF KLINEFELTER'S SYNDROME COMPLICATED BY DIABETES AND DIABETIC GLOMERULOSCLEROSIS

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Klinefelter's syndrome was first described in 1942.[1] Heller and Nelson[2] pointed out that there were 3 consistent features of the syndrome, namely small testes, azoospermia and high urinary gonadotrophin, while the other features described, including gynaecomastia, were variable. In 1958 Ferguson-Smith[3] found that only sterility and small testes were constant features and suggested the name primary micro-orchidism for the syndrome.

Although the syndrome is being more often diagnosed, to the best of our knowledge no other case of primary micro-orchidism complicated by diabetes mellitus and ultimately diabetic glomerulosclerosis has been described. It is felt that in this case the course of the diabetes was influenced by the hypogonadism. Moreover, the patient was given testosterone by implant as substitution therapy for his

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hypogonadism, as was suggested by Heller and Nelson.[4] This therapy appears to have had an unfavourable effect on the progress of the diabetes.

CASE REPORT

The patient, a European male, then aged 51 years, was first admitted to the Johannesburg General Hospital on 23 November 1955 in diabetic ketosis. He was a deaf-mute and the details of his past history were obtained from his wife and his brother. As far as is known, his mother had a normal pregnancy and he was a healthy full-term baby. At the age of 6 months he had a pyrexial illness accompanied by irritability. He recovered, but at the age of 2 years he was found to be deaf and in due course was sent to a school for the deaf. At no stage was he mentally retarded. Little is known about his puberty, but as an adult he found it necessary to shave only once or twice a week. At the age of 25 years he married. According to his wife he was potent but intercourse only took place once every month or two and conception did not occur.

At the age of 40 years he began to lose weight progressively and was found to have diabetes mellitus. He was referred to the Johannesburg General Hospital Diabetic Clinic in 1950 at the age of 46 years. As he lived in a rural area his attendance at the clinic was irregular and in consequence his glycosuria was difficult to control. However, he was never ketotic.

His family consisted of mother, father, 3 brothers and a step-brother. One brother died, perhaps of tuberculosis, at the age of 21 years. The other brothers, all older than the patient, are alive and well and have substantial families. There was no family history of diabetes.

On examination he was seen to be a tall, thin, pale man who looked younger than his stated age. His skin was soft and his axillary and pubic hair was scanty, of fine texture, and of female distribution. His proportions were eunuchoid, with a female distribution of fat. The penis was normal but the testes prepuberal in size. His body measurements (in inches) were as follows: Height 72½, span 76, vertex-pubis 33½, pubis-heel 39. Blood pressure 110/72 mm. Hg. Heart not enlarged; all the peripheral pulses palpable. Liver palpable 2 fingers below costal margin; smooth and not tender. No oedema. Visual fields normal. No signs of peripheral neuritis.

Laboratory investigations. Blood sugar 400 mg./100 ml., blood urea 36 mg./100 ml., haemoglobin 17·1 g./100 ml., PB iodine 8·3 μg./100 ml. (normal 3·5 - 8·0, usual values 4 - 6). 17-Ketosteroids (as dehydro-iso-androsterone) 6·8 mg./24 hours (normal 7 - 30 mg./24 hours, usual values 10 - 25). Urine: Sugar 4+, acetone present, no albumin, occasional pus cells, growth of coliform bacilli on culture.

The patient was discharged on insulin therapy (30 - 40 units IZS per day) and did not attend at the hospital until his second admission.

Second admission. He was readmitted on 1 March 1957 for control of his diabetes. The fundi now showed micro-aneurysms and hard exudates. There was a loss of sensation over both lower limbs and in the area supplied by L2 - S1. The following additional *laboratory investigations* were carried out: Haemochromatosis was excluded by the serum-iron level (which was normal) and liver biopsy. A testicular biopsy showed small and large islands of Leydig cells and a few hyalinized tubules. A skin biopsy was reported as being chromatin positive. The Robinson-Kepler-Power test was negative. 17-Ketosteroids 16·6 mg./24 hours. FSH 12 - 24 mouse units/24 hours (normal 6 - 48, usual values 6 - 12). Serum albumin 3·8 g./100 ml., globulin 2·8. Traces of albumin in urine. X-ray of the skull showed a normal pituitary fossa.

Third admission. The patient was readmitted on 2 July 1957 in a diabetic coma. He had developed a severe urinary-tract infection which gave rise to a diabetic pneumaturia.[5] The diabetes and the urinary-tract infection were successfully controlled with antibiotics and insulin. 300 mg. of testosterone propionate were implanted subcutaneously before discharge early in August.

Fourth admission. He was re-admitted on 26 August 1957 in hypoglycaemic coma. There was now a notable pallor. Furthermore, the lower extremities were oedematous and there were small areas of gangrene at the tips of the toes. It was noted that he had begun to grow a beard. Blood pressure 162/84 mm. Hg. *Laboratory investigations:* Haemoglobin 10·6 g./100 ml. Serum albumin 3·0 g./100 ml. Urine: Albumin 2+; 17 hydroxycorticosteroids 9·9 mg./24 hours measured as free cortisone (normal 2·9 - 12·0 mg.).

Fifth admission. The patient was readmitted on 1 November 1957 in a state of acute dyspnoea of 3 days' duration. He was found to have the signs of congestive cardiac failure, with marked swelling of the body and legs. The blood pressure was 160/90 mm. Hg and the diabetic retinopathy was more severe. The peripheral neuritis was also more extensive in the legs. The urine contained 4+ albumin. A marked deterioration in the clinical condition was noted since the previous admission. After a transfusion of packed cells he was discharged to a convalescent home. He required constant supervision because his diabetes was now extremely 'brittle' and he continually lapsed into hypo- and hyperglycaemic coma.

TABLE I. COURSE OF CASE

	Date of Admission					
	Nov. 1955	*Mar.* 1957	*Jul.* 1957	*Aug.* 1957	*Nov.* 1957	*Jun.* 1958
Blood pressure (mm. Hg)	110/70		150/90	160/85	160/90	190/100-200/110
Retinopathy	nil	+	++	+++	+++	+++
Oedema	nil	nil	nil	++	+++	++++
Albuminuria	nil	nil	+	++	++++	++++
Serum albumin (g./100 ml.)		3·8	—	3·0	—	2·1
Haemoglobin (g./100 ml.)	17·1	17·0	—	10·6	10·0	10·0
Treatment	Insulin	Insulin	Insulin. Antibiotics	Insulin. Testosterone implant	Insulin. Packed cells	Insulin

Final admission on 5 June 1958. On this occasion the patient was admitted with gross generalized oedema and was extremely dyspnoeic. The blood pressure was now 190/100 mm. Hg and this rose to 200/110 in hospital. The serum albumin fell to 2·1 g./100 ml. and the haemoglobin to 10 g./100 ml. At first he responded to treatment but he developed a severe broncho-pneumonia and died on 21 September 1958.

Autopsy Findings

The autopsy was performed 36 hours after death on a White male of eunuchoid proportions. Both pubic and axillary hair was sparse but facial and scalp hair appeared normal. Oedema of the upper and lower extremities. Penis oedematous but normally developed. First toe of right foot showed early gangrene; pressure sore over left heel.

Heart enlarged (435 g.). All valves competent and cusps normal. Mild degree of atheromatosis of coronary arteries. Aorta and large arteries also showed moderate atheroma. Lungs showed bronchopneumonia. Left kidney weighed 245 g. and right kidney 220 g.; both firm and pale, and capsules thickened; large abscess in right renal medulla. Bladder wall trabeculated and showed haemorrhagic cystitis. Testes small and firm; both about the same size (longest axis 1·5 - 2 cm.). Adrenals markedly enlarged. Thyroid pale and nodular. Pituitary macroscopically normal. Pancreas soft but normal in appearance.

Histology

All the tissues were fixed in 10% formalin or formol-saline. Sections were stained with haemotoxylin and eosin and additional stains were used where necessary.

The testes showed the histological features of chromatin-positive primary micro-orchidism. There were large and small aggregations of pleomorphic Leydig cells with pink cytoplasm, large nuclei, and prominent chromatin. These cells contained no glycoprotein (periodic acid Schiff—PAS—negative) but a moderate amount of intracellular fat was demonstrated (oil red 0). The fat was not identified histochemically. With reticulum stains, a fibrillar network of reticulum in the Leydig-cell aggregations was demonstrated.[6] In a few focal areas there were spindle-shaped cells with large trachychromatic nuclei. The tubules were small, coiled, and lined by a single layer of cells on a poorly defined membrana propria. A combined elastic Masson stain[7] failed to demonstrate any increase of the elastic tissue or thickening of the tunica propria. There was no evidence of spermatogenesis in any of the tubules.

The thyroid gland showed the histological features of an adenomatous colloid goitre.

The pituitary gland contained an excessive proportion of acido-

phil cells. No other abnormal change was observed with haemotoxylin and eosin. Cell counts were carried out on sections taken from various levels stained by the PAS technique. Approximately 3,000 cells were counted. The methods used were as follows: Four hairs were fixed to the diaphragm of the ocular lens and cells on the edge of the hair were counted in a random number of fields under oil immersion. A more accurate random sample was obtained by selecting fields by means of the 'random numbers table', the stage scales being used as coordinates. The cells were divided into acidophils, basophils, amphophils, hypertrophic amphophils and chromophobes, according to the morphological criteria outlined by Russfield.[8] The results obtained are shown in Table II and compared with two other cases of micro-orchidism.

TABLE II. PITUITARY CELL TYPES: COMPARISON BETWEEN THE PRESENT CASE AND TWO RELEVANT CASES (AVERAGE NORMAL VALUES IN BRACKETS)

Cell Type	*Present Case*	*Burt* et al.[15]	*Bell* et al.[20]
Basophil	8·3	10·2 (12·2, 1·86)[9]	34·7 (11·0)
Acidophil	59·3	33·4 (31·7, 1·74)[9]	23·5 (37·0)
Chromophobe	15·0	37·8 (51·3, 1·58)[9]	41·8 (52·0)
Amphophil	10·8	17·7 (4·5, 0·58)[9]	
Hypertrophic amphophil ..	6·6	0·9 (0·3, 0·03)[9]	
Stain	PAS	PAS	H & E

The pancreas contained a slight excess of intralobular and interlobular connective tissue, but no comment could be made on the islets or parenchymal tissue owing to post-mortem change.

Kidneys. Necrotizing papillitis was present in the right kidney. In addition, there was bilateral chronic pyelonephritis, the glomeruli showing the capillary hyaline spheres of diabetic glomerulosclerosis and the laminated argyrophylia described by Allen[10] as characteristic of diabetic glomerulosclerosis. The vessels showed moderate hyaline thickening.

The lungs showed the histological features of bronchopneumonia. Pus cultured from the lung yielded an abundant growth of *Staphylococcus aureus*.

Liver. The central veins of the liver were dilated and the sinuses were congested. There were also focal areas of necrosis.

Sex typing. The original ante-mortem slides were reviewed by Dr. Murray Barr,[11] who made the following comment: '(The blood showed) female-type neutrophils with a frequency of 1%. They did not have typical drumsticks. This is a low incidence but is sometimes found with the Klinefelter syndrome where there are typical female nuclei in oral smears and skin biopsy'. He found that the techniques used for fixation and staining of the skin were unsuitable for chromatin study.

DISCUSSION

The clinical presentation of this infertile, eunuchoid, male phenotype with small testes was typical of Klinefelter's syndrome. The histological features of the testes confirmed the clinical diagnosis. Although the genetic sex could not be established satisfactorily, the clumping of the pleomorphic Leydig cells and the presence of 'ghost' tubules without lumina and without any evidence of spermatogenesis were in favour of a female genetic sex.[11,12] However, the recent work of Ford[13] suggests that a person with the Klinefelter type of gonadal dysgenesis cannot be termed a genetic female because of the XXY sex-chromosome composition. Whatever the sex it would not influence the occurrence of diabetes and the fluctuations in its course, which are the main features to be discussed.

The patient was first diagnosed as a diabetic 11 years before his first admission to hospital. Until he was admitted the only sign of diabetes was glycosuria. This had been difficult to control, largely owing to the patient's enforced lack of cooperation. He had never been ketotic and there were no complications at that stage, but 11 years after the proven onset of the disease the clinical picture changed from one of a stable diabetic to one of a labile diabetic who frequently lapsed into coma. It should be noted that at no stage did his insulin requirements increase appreciably. With this change the vascular complications of the disease appeared and developed rapidly over a period of 16 months. The nephropathy in particular had a rapidly progressive course.

The interest of this case lies in the fact that a gonadal dysgenesis of the Klinefelter type was complicated by diabetes and ultimately diabetic glomerulosclerosis. The unusual clinical course of the diabetes can be explained by interpreting the relation of the hypogonadism to the anterior pituitary. This relationship has been noted by Russfield,[14] who showed that hypogonadism may be the initiating factor in pituitary hyperfunction and that the deficiency of one endocrine end-organ may lead to pituitary hyperplasia and even neoplasia. Moreover, Burt *et al.*,[15] who studied the post-mortem findings in an uncomplicated case of Klinefelter's syndrome and who also reviewed 21 other cases of hypogonadism, found a high incidence of adrenal or thyroid hyperplasia in these patients. They concluded that these glands may participate in the 'endocrine imbalance' in this syndrome.

It is therefore possible that the diabetes in this patient was initiated by the anterior pituitary gland which was hyperactive as a result of the hypogonadism. Young[16] produced permanent diabetes in a series of classical experiments by the administration of pituitary extract. More recently, Lazarus and Volk[17] produced permanent diabetes in partially pancreatectomized dogs by administration of growth hormone. The long latent period between the onset of pituitary overactivity and the development of the diabetes has been described by Joslin,[18] who points out that in most cases of acromegaly 15 years elapse before diabetes mellitus manifests itself. Whether or not the diabetes was initiated by the pituitary gland, there is experimental evidence that pituitary activity might be expected to influence the course of the disease.

It is likely that the diabetes was of the insulin-deficient type, and the change from hyperglycaemia to ketosis which took place in the last 3 years of the patient's life may have been induced by an excess of growth hormone. It is well known that growth hormone sometimes produces ketosis where insulin is lacking. This has been amply verified experimentally by Gillman *et al.*[19] in baboons deprived of pancreas and pituitary. Furthermore, the anti-insulin effect of growth hormone was demonstrated by Cori and Cori[20] and has since been confirmed by De Bodo *et al.*[21] and other workers.

There is thus good evidence that pituitary hyperfunction can both initiate diabetes and affect its course. It is therefore possible that it may have played a part in the unusual clinical presentation shown by the present patient. In fact, there was biochemical and post-mortem evidence that mild pituitary hyperfunction was present in this case. The levels of serum protein-bound iodine and follicle-stimulating hormone in the urine were above normal. The post-mortem findings of enlarged adrenal glands and the histological picture of an adenomatous thyroid, while by no means conclusive, tend to support the clinical evidence. The question arises which section of the cellular population of the pituitary is responsible for the hyperfunction. The classical view is that the acidophils produce growth hormone. There

was a marked increase in the percentage (59·3) of acidophils in this case as compared to the normal. The increased proportion of acidophils is in contrast to findings in other cases of hypogonadism such as Klinefelter's syndrome,[15,22] in human castration,[8] and in old age.[23] In all these instances an increase in basophils and/or amphophils only has been observed. The administration of androgens probably accounts to some extent for this acidophil increase, because androgens cause granulation of the amphophils and increase the well granulated acidophils.[8] Russfield[8] has suggested that all the trophic hormones of the anterior pituitary are secreted by the amphophil and hypertrophic amphophil series. According to this view the increase in the proportion of these cells which has been found in the present case (10·8% amphophils) suggests pituitary hyperfunction. The cellular changes in the pituitary thus appear to be compatible with an increase of growth hormone.

The testosterone implant appeared to have an unfavourable effect on the diabetes and it is possible that this, too, was related to the function of the pituitary gland. It has been shown experimentally that androgens have an adverse effect on diabetes[24] and this is possibly mediated through the pituitary gland. As pointed out above, androgens may produce a histochemical change in the cells of the pituitary gland and probably this corresponds to a 'shift' in hormone production. Talbot[25] found a drop in 11-oxycorticosteroids in 2 cases of Cushing's syndrome in which testosterone propionate was administered. This shift in hormone production is not a new concept. Russfield[8] has suggested that it may occur in cretins and in gonadal agenesis where there is failure of growth. There is reason to suppose that shifts in hormone production do occur with the administration of exogenous hormones.

The aetiological agent responsible for the vascular complications of diabetes mellitus is not known. ACTH and the adrenal steroids have often been suggested but much doubt has been cast on the role of these steroids as an important factor, both in the development of diabetes[26] and in the vascular complications.[27,28] By contrast, growth hormone has a well established diabetogenic effect.

It is possible that the improvement in retinopathy and nephropathy following ablation of the pituitary gland[29-31] are due to the removal of the source of growth hormone. In our patient the rapid downhill course terminally may well have been associated with a further increase of this hormone.

Although the theory advanced to explain the clinical course in this case conforms with the findings and with certain evidence in the literature it is obviously impossible to be dogmatic. The diabetes mellitus may have run a natural course and perhaps neither the hypogonadal state nor the testosterone implant had any bearing on the disease. However, the observations in this case may be confirmed by future studies in similar cases. It is of interest that Stewart[32] also holds the opinion that there is possibly an increase of growth hormone in this type of gonadal dysgenesis and advances as his evidence the eunuchoid measurements of his cases in the presence of early epiphyseal closure.

SUMMARY

A case of primary micro-orchidism with diabetes mellitus and subsequently diabetic retinopathy and nephropathy is presented. The unusual course of the diabetes is discussed in relation to the finding of pituitary hyperfunction. In addition, comment is made on the possible effect of the administration of testosterone on the development of vascular complications.

We wish to thank Prof. G. A. Elliott for permission to publish details of this case. We are indebted to Prof. B. J. P. Becker and Dr. T. H. Bothwell for their interest and criticism and to Mr. D. Treurnich for technical assistance.

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