Disorders of Sexual Function in Male Diabetics

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Disturbances of fertility in diabetics were frequently observed in the pre-insulin era. Pregnancy of diabetic women occurred only rarely.[1] Impotency was a frequent complaint of men suffering from diabetes mellitus.[2] The change in the course of the disease and the conditions of life of the diabetic after the discovery of insulin[3] often led to the assumption that sexual disorders in diabetics had become less frequent.[4-8] This assumption conflicts, however, with the few surveys done during the past twenty-five years.[9-12] In the study of 198 male diabetics by Rubin and Babbott[13] in Philadelphia, 55 per cent of the patients suffered from erectile impotence. In the study by Neudorfer,[11] of eighty-five married male diabetics who were examined, twenty-four were found to be sterile.

MATERIAL AND METHODS

Our own investigations were started after severe disturbances of potency and fertility had been observed in male juvenile-type diabetics. These patients had been kept in as good control as possible and had been regularly checked in our outpatient clinic.

The following studies were made: A. Data on sexual development, libido, potency and fertility of a selected group of male diabetic outpatients were obtained. B. Patients with clinical evidence of sexual disorder were admitted to the hospital for extensive laboratory investigation of endocrine and particularly testicular function.

Frequency of impotence. After exclusion of unmarried patients and patients suffering from other severe general disorders, 314 patients were left for study. All had developed diabetes mellitus before age sixty. After periods ranging from months to years following the discovery of diabetes, 160 patients (51 per cent) had observed disturbances of sexual function, whereas 154 patients (49 per cent) had not noted significant decrease in sexual function. Thirteen patients who had experienced transient impotence of short duration at the time of initial symptoms of diabetes are not included in this study.

The complaints related to disturbed sexual function varied in quality as well as in intensity, the predominant ones being periodic or constant erectile impotence. Even in the group of patients thirty years or younger, 29.4 per cent complained of diminished potency. This percentage increased for the higher age groups of patients, reaching 72.6 for diabetics sixty years of age and older (figure 1). These results agree with the findings of Rubin and Babbott.[13]

Figure 2 compares the cumulative distribution of erectile impotence in 512 diabetics (198 of Rubin and Babbott[13] and 314 of our own) and the 4,108 presumably healthy males of Kinsey et al.[14] Quite obviously, male diabetic patients have sexual disturbances not only at an earlier age, but two to five times more often than other healthy men (Rubin,[15] Schöffling[16]).

Figure 3 gives the mean frequency of marital intercourse in relation to age, from the time of first manifestation of diabetes, as recalled by the 314 patients in our series. In each age group the mean frequency is less after the development of diabetes than it was just before the discovery of diabetes. In agreement with the data of Bergqvist[12] and Rubin and Babbott,[13] 48.1 per cent of our patients with erectile impotence reported no decrease in libido.

Although we could not establish a relationship between the age of the patients with and without impotence and their age at the time of diagnosis of diabetes (figure 4, left and center), we could clearly prove a difference in the duration of the diabetes in the two groups (figure 4, right). In the group of patients without impotence, diabetes had a mean duration of only 4.3 yrs. as compared to a mean duration of 9.3 yrs. in the group with impotence. In more than 50 per cent of the patients with impotence, diabetes had been present for less than five years at the time of interrogation, 18.2 per cent suffered for six to ten years and 21.4 per cent of the patients had been diabetic for more than ten years prior to our investigation (figure 4, right).

Of the cases suffering from impotence, 58.5 per cent received insulin, 34.3 per cent were treated with sulfonylureas and 6.9 per cent received dietary treatment only. There were no significant differences in dosage of insulin or sulfonylureas between the groups of patients with and without impotence. The average dose of insulin was virtually the same, i.e., 45.7 and 43.3 U. per day, respectively. As far as could be determined, metabolic control was approximately the same

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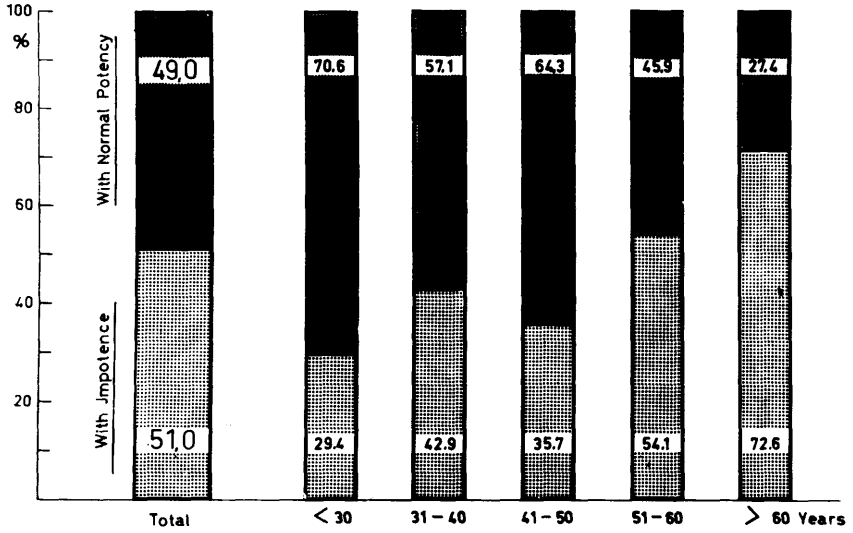

FIG. 1. Percentage of diabetics with and without impotence in total group of 314 patients and in the different age groups.

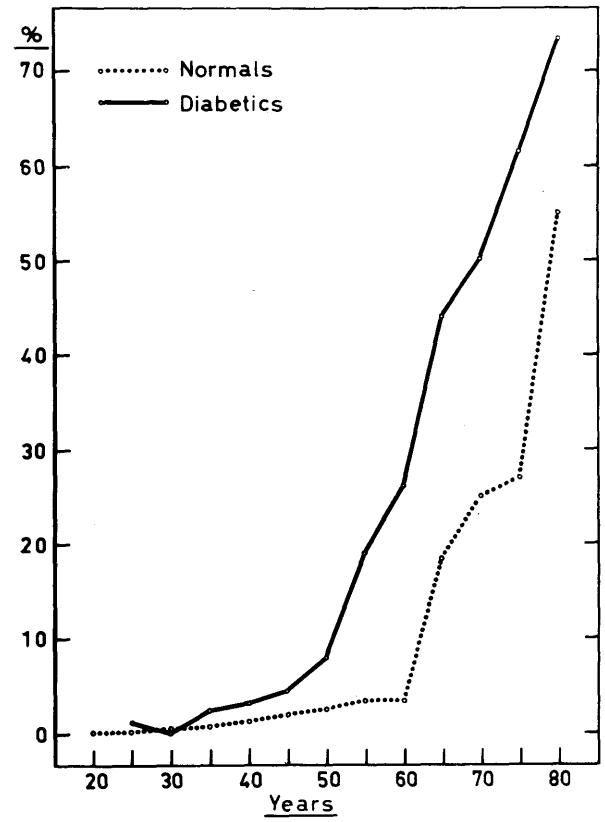

FIG. 2. Cumulative incidence of erectile impotence in 512 diabetics (Rubin and Babbott, Schoffling and others) and 4,108 normals (Kinsey and others).

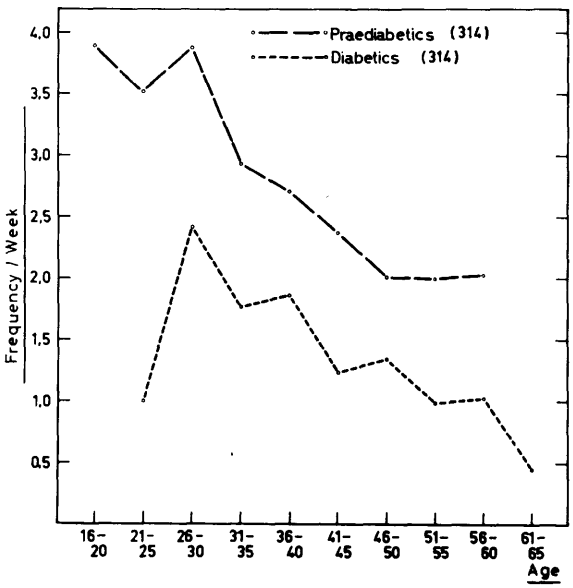

FIG. 3. Patients' recall of average frequency of coitus in 314 diabetics, by age groups, just before diagnosis of diabetes (prediabetics) and at inquiry (diabetics).

in the two groups.

Diabetic angiopathy was found in 20.6 per cent of the patients with impotence and in only 6.2 per cent of the patients without impotence. On the other hand, the incidence of general arteriosclerosis was approximately the same in the two groups, i.e., 20.9 and 18.8 per cent, respectively. We lack precise data on the incidence of diabetic neuropathy in the two groups.

Chronic hepatic disease was found in 3.7 per cent of the patients with impotence and 3.9 per cent of the patients without impotence; 15 per cent of the first group and 5.8 per cent of the second group reported past liver disease (mostly hepatitis). No evidence could be found, however, of active hepatic disease in any of the patients.

To further our investigations, 510 male married diabetics of all ages were queried regarding fertility.

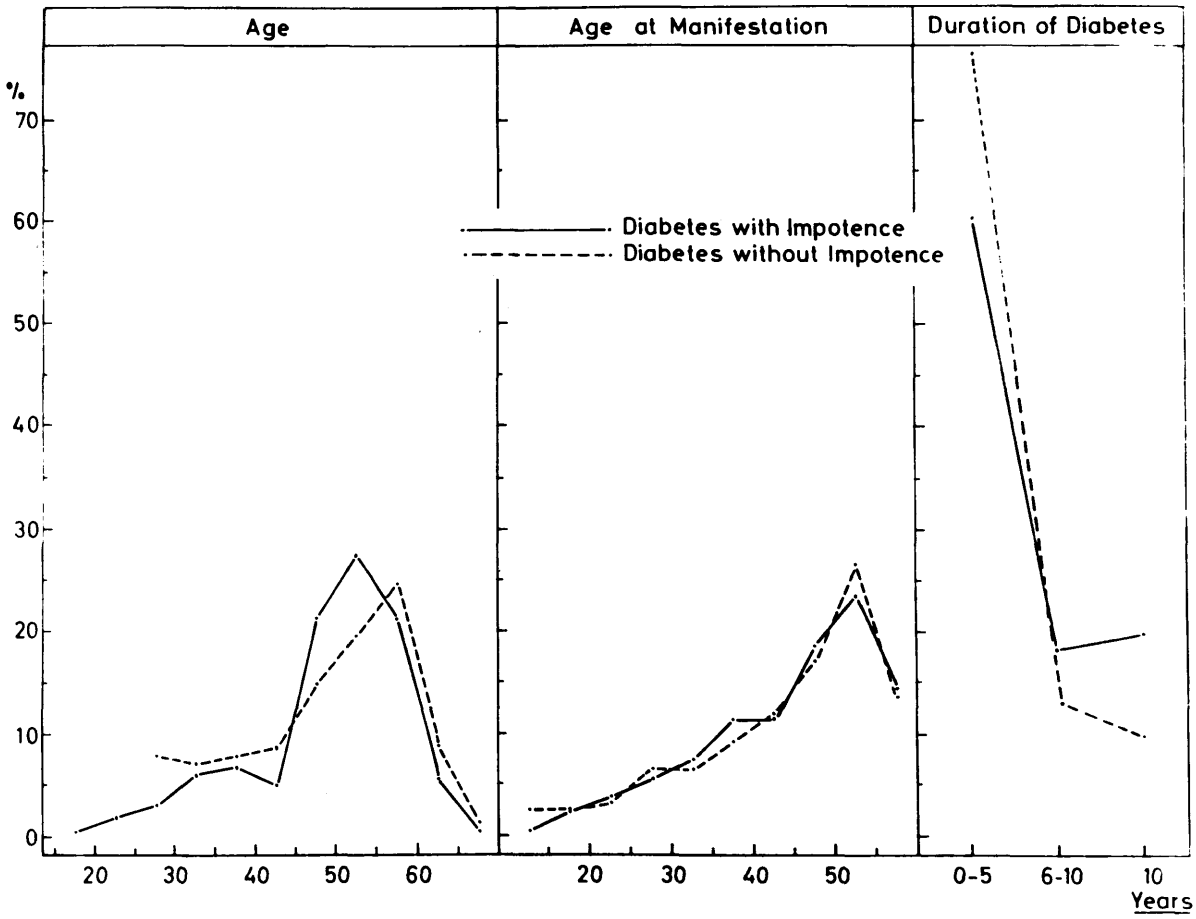

FIG. 4. Age at time of interrogation, age at time of diagnosis of diabetes and duration of diabetes in the 160 diabetics with and the 154 without impotence.

As expected, healthy wives of diabetics with diminished potency conceived less frequently than the wives of diabetic husbands with normal potency, i.e. 1.59 and 1.81 conceptions per family, respectively. Further inquiry showed that more of the healthy wives of diabetics—particularly those suffering from disturbed potency—had miscarriages than did wives of healthy nondiabetic men who had been interrogated for reasons of comparison, i.e., 15.5 and 11.1 per cent, respectively. Our investigations confirm the findings of Babbott, Rubin and Ginsburg.[17]

CLINICAL EXAMINATIONS

Size of testes and prostate. Extensive physical examinations of sixty diabetics with impotence[16] revealed a definite reduction in the size of the testes in fourteen patients and reduced consistency of the testes in thirty-nine cases. Decreased size of the prostate, which is known to be a fairly reliable indication of gonadal insufficiency, was found in twenty patients. Calcification of the vas deferens, as reported by Wilson and Marks,[18] was not found in our patients.

ENDOCRINOLOGICAL EXAMINATIONS

Volume of seminal fluid. According to MacLeod and Gold[19,20] and Joel,[21] the average seminal fluid volume of healthy men is 3.3 ml. Less than 1.0 ml. ejaculate has been universally accepted as being abnormal.[21,22] Investigations of the ejaculate of forty-eight diabetics in our series revealed that seven of the patients consistently had a volume less than 1.0 ml., and ten patients had no ejaculate.

Examination of sperm. Sperm counts, motility and morphology were studied in thirty-eight cases. The findings were classified according to MacLeod and Gold,[19,20] Nowakowski,[23] Tyler and Singher[24] and others. "Slight subfertility" was evident in six patients, "severe subfertility" in eight patients and "infertility" in three patients. Aspermia existed in one patient.

Seminal fluid fructose. The concentration of fruc-

tose in the seminal fluid of thirty-six patients was determined according to the original method of Roe,[25] modified by Davis and McCune.[26] Since the concentration of fructose in semen bears a direct relationship to secretion of testosterone, a decreased fructose concentration implies testicular androgen deficiency (Nowakowski and Schirren[27]). The normal fructose concentration in human semen ranges from 1,200 to 5,000 γ/ml. Normal values were found in eighteen (50 per cent) of our patients, while fourteen patients had values between 600 and 1,200 γ/ml. and four had values below 600 γ/ml. (figure 5).

Gonadotropin determinations. The urinary excretion of pituitary gonadotropin was determined in thirty-one diabetics with impotence, twelve diabetics without impotence and fifteen normal men. Concentration of urinary gonadotropin was at first accomplished by ultrafiltration according to the modification of Gorbman's original method[28] described by v. Massenbach and v. Eickstedt.[29] Later, the permutit adsorption method of Taubert and Weller[30] was adopted. The final step of both procedures is based on the increase in weight of the infantile mouse uterus.

The average daily gonadotropin excretion of the fifteen normal men was from 20 to 40 MUU (mouse-uterus-units). Twenty of twenty-six determinations in twelve diabetics without decreased potency were within the normal range (figure 6, left). Determinations of gonadotropin in thirty diabetics with impotence revealed only two patients with values over 32 MUU; nine patients (eleven determinations) showed values between 8 and 16 MUU, and no gonadotropic activity

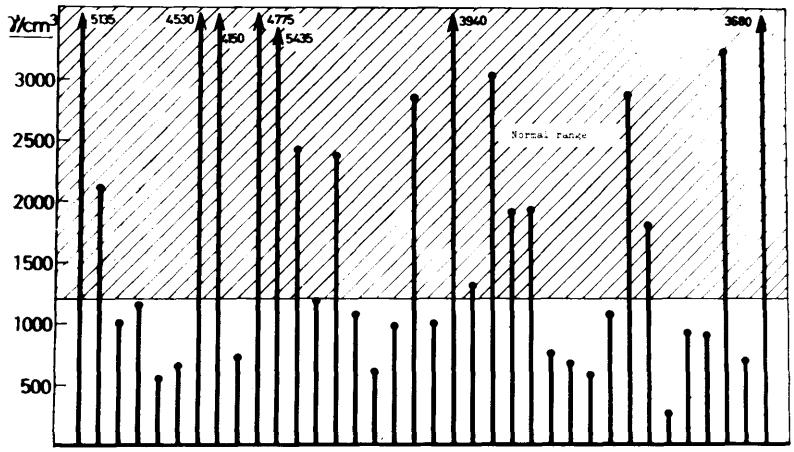

FIG. 5. Fructose concentration in the ejaculate of thirty-six diabetics with impotence (sixty-seven tests).

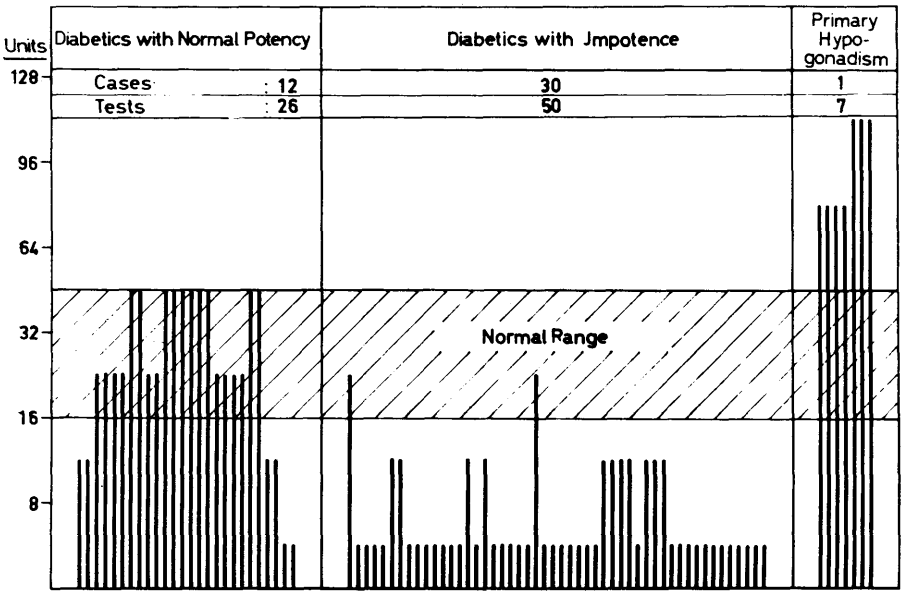

FIG. 6. Urinary excretion of pituitary gonadotropin in diabetic patients with and without impotence and in a diabetic patient with primary hypogonadism.

was found in the remaining nineteen cases (thirty-six determinations) (figure 6, center). The right part of the same figure shows seven high values between 80 and 112 MUU in a diabetic with primary hypogonadism.

Histological examinations. Biopsies of the testes were performed on twenty-four diabetics with sexual disturbance. The histological changes found in the various samples were so similar that they can be discussed together. The most frequent finding was atrophy of the tubules. The basal membrane of the canaliculi was thickened in most of the cases studied (figure 7). During examination of the various layers of testicular epithelium, we found that spermatogonia were present in surprisingly normal quantities and did not show any suspicious changes in the nuclei or cytoplasm. We observed, however, a reduced number of spermatocytes of the first and second order in the early stages of development, as described by Warren and LeCompte,[31] especially of spermatids and spermatozoa (figures 7, 8, 9). Whereas in several cases all of the stages of development could be found in some of the tubules, the germinal epithelium of other patients showed only spermatogonia and occasional spermatocytes of the first order. Frequently no mature spermatozoa were present in the lumen of the tubules, only their discarded precursors (figure 9).

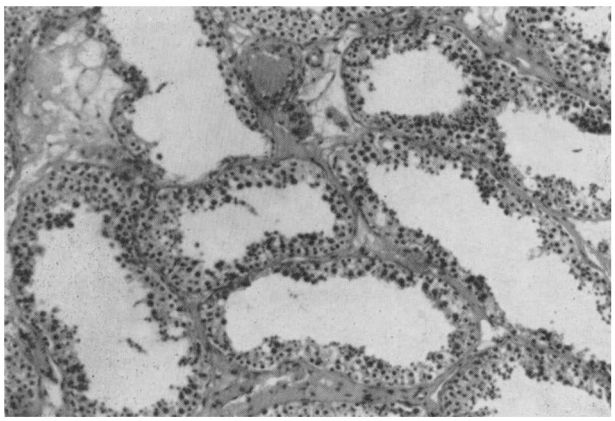

FIG. 7. Patient Bi. O., thirty-nine years. Atrophy of the tubules, reduction of the testicular epithelium with stop in maturation. Testis-Specimen (biopsy), Hemalum-Orange G-Anilinblue-phosphormolybdenum acid-stain. X 90.

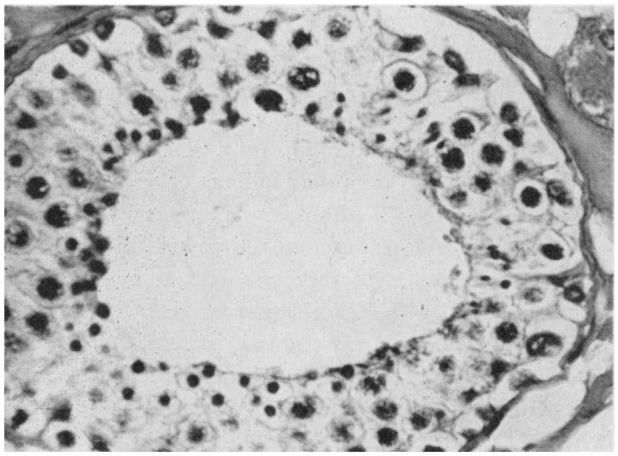

FIG. 8. Patient Fr. H., fifty-six years. Thickening of basement membrane, stop in maturation in the testicular epithelium, small borderline against the lumen. Testis-Specimen (biopsy), Hemalum-Orange G-Anilinblue-phosphormolybdenum acid-stain. X 405.

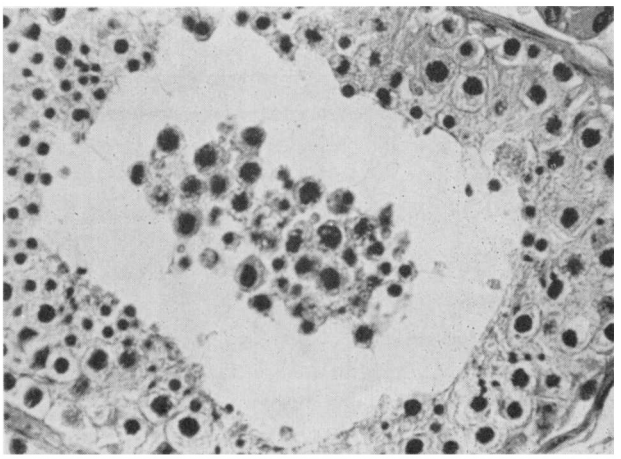

FIG. 9. Patient Bi. O., thirty-nine years. Thickening of the basement membrane, stop of the maturation in the testicular epithelium, desquamation of immature cells. Testis-Specimen (biopsy), Hematoxylin and Eosin-stain. X 405.

Urinary steroids. Determinations of urinary 17-ketosteroids and corticoids were performed in 103 normal men, forty-two diabetics without impotence and fifty-seven diabetics with impotence. The 17-ketosteroids were determined according to the method of Zimmermann[32] and the corticoids according to the method of Staudinger and Bauer.[33] Average values for the three groups of patients are shown in figure 10. Whereas the results of our other studies described thus far are consistent with hypogonadotropic, i.e., secondary, testicular insufficiency in diabetics with impotence, the steroid analyses yielded results which at first appeared inconsistent with hypogonadotropic hypogonadism. The 17-ketosteroid excretion of the impotent diabetics of all ages was elevated (23.2 ± 8.6 mg.). The mean values of healthy men and of diabetics without potency disorders differed significantly from those of the impotent diabetics (17.7 ± 6.4 mg., $P<0.001$, and 17.5 ± 7.7 mg., $P<0.02$, respectively). The total corticoid

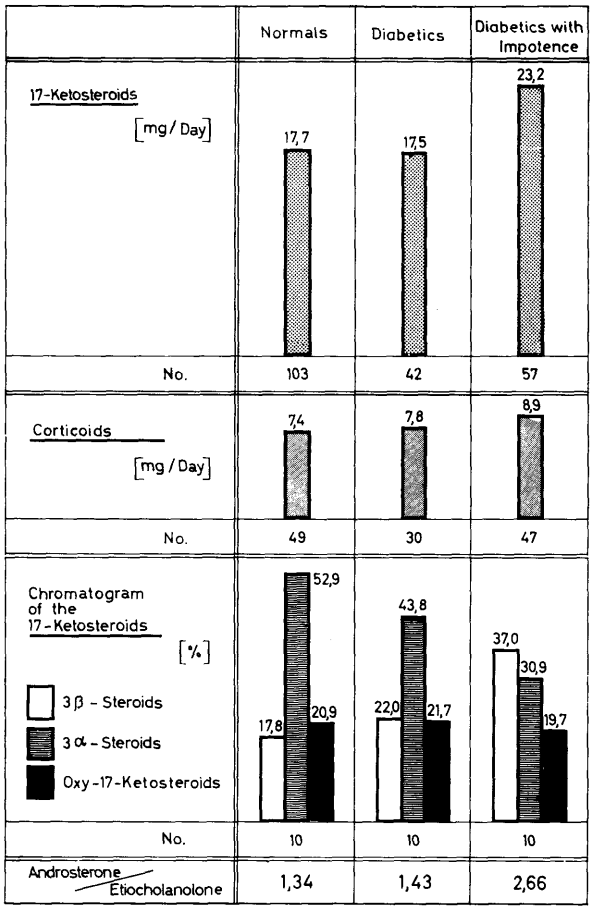

FIG. 10. Average values of urinary 17-ketosteroids, corticoids, and the steroid fractions in healthy men and in diabetics with and without impotence.

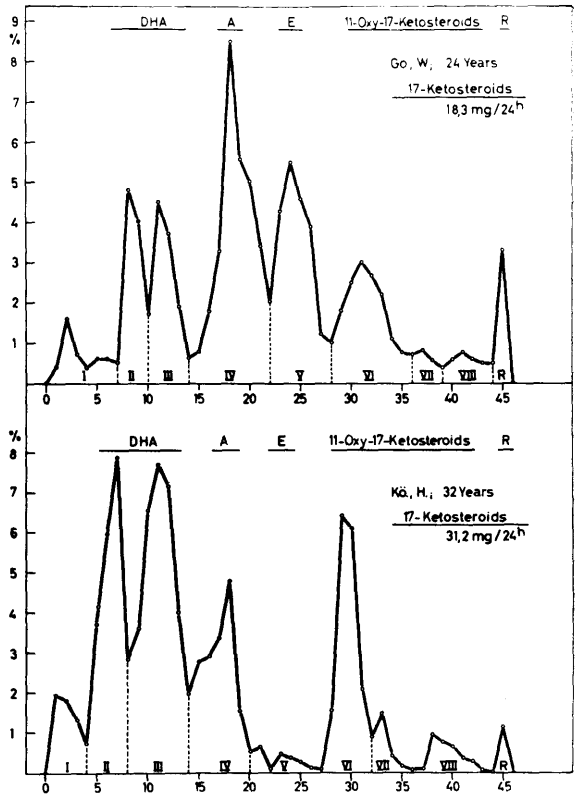

FIG. 11. Chromatogram of the 17-ketosteroids in a healthy man (above) and a diabetic with impotence (below).

excretion was also slightly increased in the impotent patients (figure 10).

Together with Robe and Pallaske, we carried out chromatographic fractionation of the 17-ketosteroids of thirty patients, according to the method of Dingemanse et al.[34] modified by Pond.[35] A normal curve (top) of a nondiabetic healthy man is compared with one (bottom) of a diabetic person with hypogonadism (figure 11). The relative amount of dehydroisoandrosterone originating from the adrenal cortex was found to be increased in diabetics with hypogonadism as compared to the values of normal individuals, whereas androsterone and etiocholanolone, i.e., the decomposition products of testosterone, were distinctly reduced. The average relative values of the fractionation are also summarized in figure 10. The β-steroids, which originate only from the adrenal cortex, were increased to 37.0 ± 10.3 per cent, almost double their normal percentage ($P<0.001$). The α-steroids were decreased to 30.9 ± 10.6 per cent in comparison to 52.4 ± 10.1 per cent for healthy individuals ($P<0.001$) (figure 10). The relative amounts of 11-oxygenated 17-ketosteroids were approximately equal for the three groups.[36]

THERAPY

After examining the first patients in 1955 we realized that the cause of the impotence and infertility in male diabetics was most probably hypogonadotropic hypogonadism. At that time, we treated our patients with chorionic gonadotropin only. The results were neither persistent nor outstanding. Therefore, since 1956 we have used a combined therapy with chorionic gonadotropin and testosterone in young diabetics, because restoration of potency was just as important to these patients as the elimination of their in- or subfertility. Only one forty-year-old patient did not respond to the treatment; in all other patients we were able to eliminate or significantly improve the disorder with this treatment. Impotence disappeared, and semen analyses, sperm counts and size of prostate were improved. Since then four patients with initially severe hypogonadism have produced one child each. It was most surprising that in some patients an effect was

maintained for several months after treatment was terminated.

Between 1956 and 1958 combined therapy usually was intramuscular administration of 300 mg. testosterone-caprinoylacetate (Testosid-Depot Boehringer, Mannheim) per month and 1,000-3,000 U. chorionic gonadotropin (Primogonyl Schering, Berlin) per week. For the past two years, a test preparation of the Schering Co., Berlin, has been available to us which contains 1,000 U. of chorionic gonadotropin and 25 mg. testosterone proprionate combined in oily solution. We administer one or two injections weekly, depending upon the severity of the disorder. Treatment over a period of six months has often been successful; some patients, however, require treatment for one to one-and-a-half years. The therapy is considered to be completed when, after withdrawal of the hormones for several months, satisfactory potency remains and repeated sperm analyses reveal no abnormalities.

A majority of diabetic patients with complaints of impotence are over forty-five years of age. Since combined therapy with chorionic gonadotropin and testosterone is expensive, and since most patients of this age are more interested in potency than in fertility, we now treat them with testosterone only. This therapy is continued for two to twenty-four months, followed by a rest period of six to twelve months to determine whether or not additional substitution is necessary. In 76 per cent of our patients, the potency disorder has improved within three to five months. There was significant improvement in sperm counts and morphology in 62 per cent of those who responded with increased potency. Interruption of treatment for several months was possible only in 26 per cent of the elderly patients.

DISCUSSION

Our investigations, as well as those of Rubin and Babbott,[13,15] demonstrate that sexual disturbances in male diabetics are common. Half of our group of 314 patients suffered from sexual disturbances at the time of examination. Our data demonstrate that pathologic decrease of potency may occur at any time after manifestation of diabetes and is not always a late complication of the disease.

Contrary to Rubin,[15] we observed only thirteen patients with a temporary loss of potency at the time of discovery of the diabetes. Since potency improved in these patients when their diabetes was controlled, they are not considered in the present report.

Inasmuch as almost 80 per cent of the diabetics with impotence had no apparent angiopathy and almost 40 per cent did not require insulin for control, we could not conclude that there is necessarily a relationship between degenerative complications of diabetes and requirement for insulin on the one hand and the appearance of impotence on the other. Neither was there any evidence that the impotence and decreased fertility in these patients was caused by other diseases. A possible role of emotional factors in the impotent could not be assessed.

As far as could be determined, the groups of patients with and without impotence did not differ with respect to control of diabetes. However, this does not exclude control as a possible factor.

Associated with impotence, it was our strong impression that the size and consistency of the testes and the size of the prostate were frequently less than normal. In addition, sperm counts were often low and there was an increased percentage of nonmotile or dead sperm. Klebanow and MacLeod,[37] however, did not observe a reduction in sperm count, although they did note decreased sperm motility in 50 per cent of the patients they studied.

We found that eighteen of thirty-six diabetics with testicular dysfunction and reduced or absent sexual potency had androgen deficiency, as indicated by low concentrations of fructose in the semen.

Characteristic laboratory abnormalities accompanying reduced testicular activity in our patients were low or absent pituitary gonadotropin in the urine and abnormalities of gonadal morphology, with thickening of the basement membrane of the tubules, defective spermatogenesis and a reduced number of Leydig cells. The first observation is in agreement with the findings of Bergqvist[12] and the second with those of Warren and LeCompte.[31]

Whereas these observations are consistent with hypogonadotropic hypogonadism, steroid investigations gave seemingly inconsistent results. Contrary to Miller and Mason,[38] as well as Horstmann,[39,40] we observed an increased urinary excretion of certain steroid metabolites. The results of chromatographic fractionation of urinary 17-ketosteroids suggest that the cause of the high steroid excretion is an increased production of adrenal androgenic hormones of low virilising potency. This conclusion is supported by animal experiments reported in an earlier paper.[36]

Our endocrinological investigations, as well as the encouraging results of hormone therapy, have shown that there is an endocrine basis for the sexual disabilities of diabetics, and that testicular hypofunction in these patients cannot be regarded as an indefinable

complication of the metabolic disease. The cause of the gradual failure of pituitary gonadotropic function which occurs in a large number of male diabetics remains unknown.

SUMMARY

Among 314 male diabetic patients who developed diabetes before age sixty, 160 (51 per cent) complained of erectile impotence. Mean known duration of diabetes was 9.3 yrs. in the impotent group and 4.3 yrs. in the group without this complaint. Wives of the diabetics in the former group had had fewer conceptions and more miscarriages than wives of patients in the latter group.

Endocrine studies of patients with impotence revealed that two thirds had decreased urinary excretion of pituitary gonadotropin. On the other hand, urinary excretion of 17-ketosteroids was increased. Chromatographic fractionation of 17-ketosteroids revealed that the augmented excretion reflected an increase in metabolites of adrenal steroids of low androgenic potency, while metabolites of testosterone were decreased. One third of the impotent patients studied had low sperm counts, and one half had low concentrations of fructose in the semen, indicative of androgen deficiency. Testicular biopsy in twenty-four patients revealed thickening of the basement membrane of the tubules and abnormal spermatogenesis.

In most of the patients under forty years of age impotence was corrected by combined therapy with chorionic gonadotropin and testosterone. Wives of four of these patients became pregnant after prolonged periods without conception. Patients over forty were usually treated with testosterone alone, with improvement of sexual potency and general well-being.

Results of the endocrine studies, and response to treatment, suggest that impotence and infertility in male diabetics are frequently due to hypogonadotropic hypogonadism. The mechanism of impairment of pituitary gonadotropic function is unknown.

SUMMARIO IN INTERLINGUA

Disordines del Functiones Sexual in Diabeticos de Sexo Mascule

In un gruppo de 314 mascule patientes diabetic in qui le diabete se habeva declarate ante le etate de sexanta annos, 160 se plangeva de impotentia erectil (51 pro cento). Le valor medie pro le cognoscite duration del diabete in le gruppo impotente esseva 9,3 annos. Illo esseva 4,3 annos in le gruppo sin le mentionate gravamine. Uxores del diabeticos in le prime del duo gruppos habeva habite minus conceptiones e plus malpartos que le uxores del patientes in le secunde gruppo.

Studios endocrinologic del patientes con impotentia revelava que duo tertios habeva un reducite excretion urinari de gonadotropina pituitari. Del altere latere, le excretion urinari de 17-cetosteroides esseva augmentate. Le fractionation chromatographic del 17-cetosteroides revelava que le augmentate excretion reflecteva un augmento de metabolitos del steroides adrenal de basse potentia androgenic, durante que le metabolitos de testosterona esseva excernite in quantitates reducite. Un tertio del impotente patientes studiate habeva basse numerationes spermatozoic, e un medietate habeva basse concentrationes de fructosa in le semine, lo que indica un carentia androgenic. Biopsias testicular in 24 patientes revelava spissification del membrana basilar in le tubulos e anormalitates del spermatogenese.

In le majoritate del patientes de minus que 40 annos de etate, le impotentia esseva corrigite per un combinate therapia con gonadotropina chorionic e testosterona. Le uxores de quatro de iste patientes deveniva pregnante post prolongate periodos sin conception. Le patientes de plus que quaranta annos de etate esseva tractate usualmente con testosterona sol, con le resultato de un melioration del potentia sexual e del ben-esser in general.

Le resultatos del studios endocrinologic e le responsas evocate per le tractamento suggere que impotentia e infertilitate in diabeticos mascule es frequentemente le effecto de hypogonadismo hypogonadotropic. Le mechanismo per le qual le gonadotropismo pituitari es compromittite non es cognoscite.

ACKNOWLEDGMENT

This work was supported in part by the Deutsche Forschungsgemeinschaft.

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