Further observations on the syndrome, "testicular feminization"

JOHN McLEAN MORRIS, M.D.
New Haven, Connecticut
VIRENDRA B. MAHESH, PH.D., D. PHIL.
Augusta, Georgia

"TESTICULAR feminization" is a term suggested some years ago for a hereditary syndrome characterized by individuals with testes who present a female phenotype.[98] No entirely satisfactory explanation has as yet been offered for the completely female urogenital sinus derivatives, the lack of development of both Müllerian and Wolffian duct systems, the female secondary sex characteristics, and the scanty or absent sexual hair.

The name "testicular feminization" has been criticized as inappropriate. It was not originally offered with any special enthusiasm, but was merely to call attention to this disorder as a separate and definite entity, which was easy to recognize clinically, and to point out that it was not so rare and unusual as earlier authors seemed to think. Furthermore, evidence from castrated cases suggested that the testes were, at least in part, responsible for the feminization. A number of other names have been suggested including "feminizing testes," "hairless women with testes," and "male pseudohermaphroditism" with qualifications such as "familial," "hereditary," "with total feminization," "internus," "with female genitals and habitus," etc. For one reason or another none of these seems ideal.

From the Department of Obstetrics and Gynecology, Yale University School of Medicine, and Department of Endocrinology, Medical College of Georgia.

This study was supported in part by Grant Nos. FR 38-03 and AM 04429-03, National Institutes of Health.

Presented by invitation at the Eighty-sixth Annual Meeting of the American Gynecological Society, New Orleans, Louisiana, May 13-15, 1963.

Complete and incomplete syndromes

The syndrome has been somewhat confused by the fact that the name has been applied to certain types of cases which are not "testicular feminization" as originally described. Most frequently included are cases in which clitoral enlargement or a phallus is present. In the complete syndrome the clitoris is normal or small. There is no question that patients with minimal clitoral enlargement present a closely related entity, especially when associated with female secondary sex characteristics. There may also be a similar hereditary pattern, but there are two reasons for separating such cases.

One is that the secondary sex characteristics even with slight enlargement of the clitoris are unpredictable. They may resemble the syndrome under discussion (and in such instances probably have a similar etiology),[13, 75, 76, 105] they may be essentially male,[78, 83] they may be intermediate with sexual hair and breast development,[91] or they may have no hair and no breast development.[79, 87]

A second, and perhaps more significant, reason for separating cases with clitoral enlargement is that while both syndromes are hereditary, the complete feminization

syndrome and the syndrome with clitoral enlargement do not, as a rule, occur in the same family tree. Furthermore, in the patients with clitoral enlargement, there may be instances of varying degrees of genital abnormality in members of the same family. For example, König[88] reports a case of a family in which one child had a 1.5 cm. clitoris the thickness of a finger, another had a 2 cm. clitoris, and a third had hypospadias and cryptorchidism.

Thus, on genetic grounds, because secondary sex is variable, and because the genital abnormalities may vary with gradual progression to hypospadias, cases with clitoral enlargement should be considered separately. Präder[101] and Núñez, Fernández, and Casabón[100] have suggested that such cases, when associated with female secondary sex characteristics, be called "partial" or "incomplete testicular feminization."

Incidence

To the 82 cases previously collected,[98] an additional 99 cases reported in the literature (plus doubtless some inadvertent omissions) appear to meet the criteria originally described.[1-72] This includes only those with histologic proof of the testes and those old enough for secondary sex characteristics to have had an opportunity to develop. These are probably unnecessary restrictions as a chromatin-negative "female" without a uterus is almost surely an example of this syndrome. If prepubertal cases and those in which there was no biopsy are included, the number is significantly greater.

The actual incidence is difficult to determine because in many instances the patients have no symptoms other than amenorrhea. Considerably more than half of the reported cases had hernias or inguinal gonads. The true incidence of hernias may be lower, since those without hernias may have escaped medical attention. Inguinal hernias are considerably less common in young girls than in boys, and ovarian hernias are even rarer. Based on a study of hernias in apparent females, Jagiello and Atwell[84] estimate the prevalence of the syndrome as 1:62,400 males. Hauser,[23] in his excellent review, believes it is 10 times higher than Präder's[101] estimate of 1:20,000, and Netter and coworkers[46] claim that 15 to 20 per cent of intersexual individuals, with other than gonadal dysgenesis, are cases of this syndrome.

The diagnosis should be considered in the female child with inguinal hernias, especially if the gonads are present; in primary amenorrhea, especially if examination fails to reveal a uterus; and in patients with an absent vagina, with absent axillary or pubic hair, or with germ cell tumors.

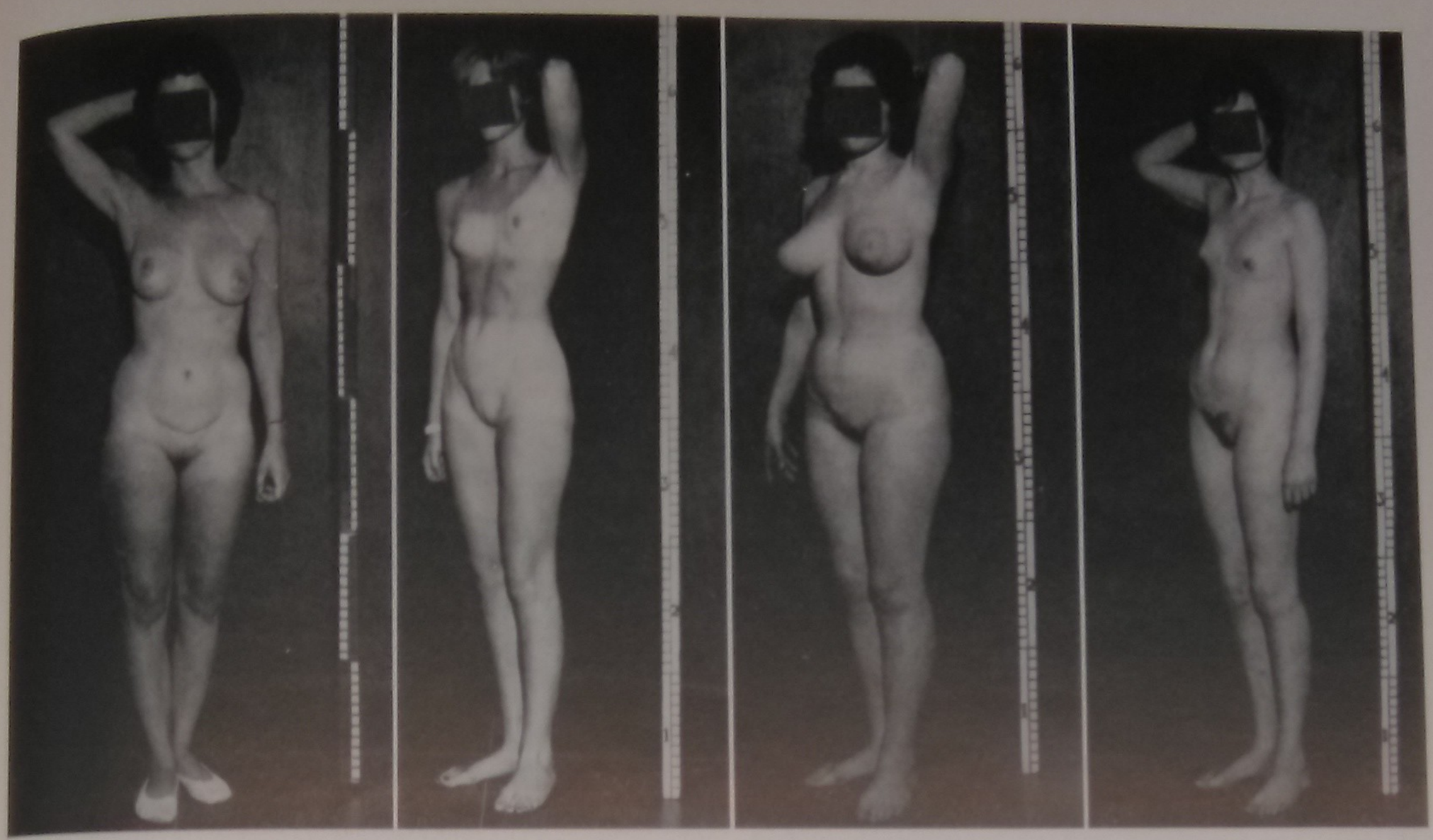
Because of the fact that many of these patients have a weakness in the abdominal wall in the inguinal area, a Pfannenstiel incision is, perhaps, preferable to facilitate any repair necessary or to expose any gonad lying in the abdominal wall.

A brief summary of three additional cases of the "complete" form of the syndrome is given below, as well as one case which should probably be considered an "incomplete" or "partial" form (Fig. 1).

All 4 patients presented female phenotype, sexual characteristics, and psychological orientation. All were chromatin negative, karyotypes on blood samples, and were XY (kindness of Dr. Herbert Lubs). Intravenous pyelograms were normal, and x-rays of the pelvis were interpreted as gynecoid.

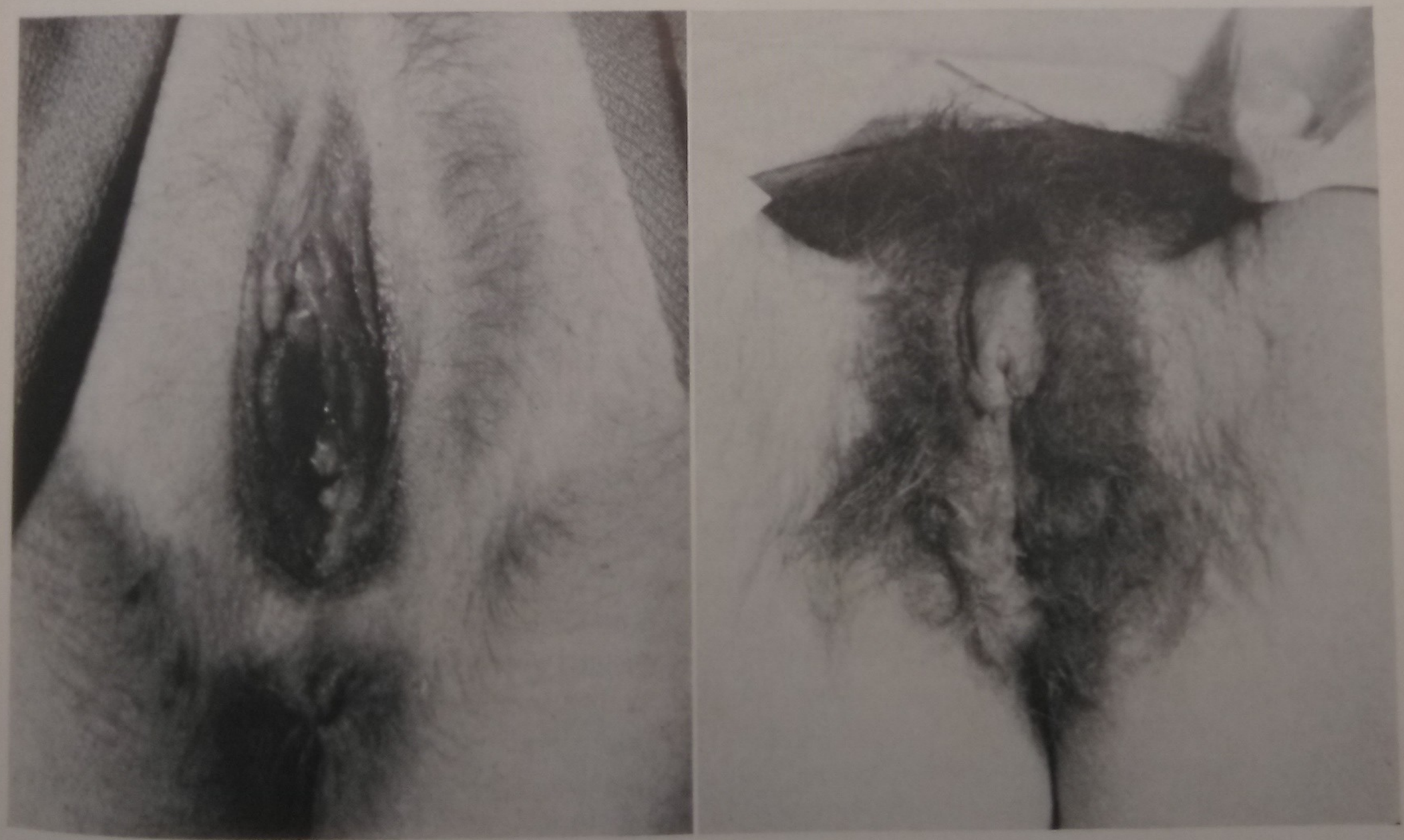
In the first 3 cases the external genitals were of adolescent female type with small clitoris and undeveloped labia minora, shallow vaginas approximately 4 to 5 cm. in depth, absent uterus, and intra-abdominal "testes" which were removed by operation. There was female breast development but only insignificant axillary or pubic hair. The postoperative administration of 20 mg. of methyltestosterone daily (in conjunction with estrogen) for periods up to 8 months produced minimal if any change.

The fourth patient differed slightly from the others. The external genitals appeared female, but the clitoris was at the upper limits of normal, rather than small. It had a rather large frenulum. The distance between clitoris and a patulous urethral meatus was excessive (5.5 cm.). The perineum was



Case 1 Case 2 Case 3 Case 4

Fig. 1. The first 3 cases represent the complete form of the syndrome. Case 4 is an "incomplete" form and appears to have a different etiologic background.



Case 2 Case 4

Fig. 2. Effect of androgen in producing pubic hair growth and marked clitoral enlargement in Case 4 as compared to Case 2.

high, and on opening this area by operation a small 5 cm. vaginal pouch was encountered. The gonads were quite small and at the time of operation were found in the abdominal wall only by following the gonadal vessels.

A further difference was that she had less in the way of female secondary sex characteristics. Pubic hair growth in adolescence appeared to be related to exogenous hormone administration, and this also may have influenced breast development. Postoperative androgen-estrogen administration in the same dosage employed in the other three patients produced not only sexual hair, but definite virilization (Fig. 2).

Case reports

Case 1. M. H. (Referred by Dr. Paul Drucker) aged 21, had sisters aged 27, 24, and 18, and no brothers. Although the patient and all three sisters allegedly had occasional menstruation, a letter from 1 sister indicates that all probably have the same syndrome and are without menses or sexual hair. The mother's brother and 2 sisters plus the maternal grandmother's three brothers and 2 sisters were apparently normal, although 1 of the latter was childless. Breast development occurred at 15. Laparotomy and gonadal biopsies 6 months prior to admission showed testes. The patient was married with active and satisfactory sexual relations in spite of a shallow vagina. She weighed 123 pounds, was 66½ inches tall, with a span of 66⅝ inches. Color vision was normal.

Urinary steroids (mg./24 hr.): 17-ketosteroids, 19; 17-ketogenic steroids, 11; pregnanediol, 0.8; and pregnanetriol, 0.4. Creatinine excretion, 945 mg. per 24 hr. F.S.H. $> 13 < 52$ M.U.U. per 24 hr.

Case 2. P. L. (Referred by Dr. Virginia Stuermer), aged 18, had one brother and 2 sisters ages 14 and 11 who were, apparently, normal. Maternal family history was negative. The maternal menarche was at 13 years with sexual normal hair. Left inguinal hernia repair was done at 5. Breasts developed at age 12. She weighed 145 pounds and was 70 inches tall with a span of 74¼ inches and slightly eunuchoid build. Color vision was normal.

Urinary steroids (mg./24 hr.): 17-ketosteroids, 15; 17-ketogenic steroids, 7.9; pregnanediol, 1.3; pregnanetriol, 0.5. Creatinine excretion, 1,194 mg./24 hr. F.S.H. preoperative, $> 13 < 52$, M.U.U. per 24 hr., postoperative, > 208.

Case 3. J. R. (Referred by Dr. Joseph Belsky), aged 18 had one sister aged 16, who was normal and two half-brothers by her mother's second husband. Maternal sexual hair was normal with menarche at 11. The mother and both half-brothers showed moderate red-green color blindness. The father remarried the mother's sister, who was normal. The two uncles were normal. Right inguinal herniorrhaphy was performed at 11. The breasts developed a year or more later than her classmates', but final endowment was generous. The areolae were large but the nipples small. In spite of insignificant sexual hair, forearm hair was slightly increased. She weighed 159 pounds and was 68 inches tall, with a span of 71 inches. She was partially red-green color-blind.

Urinary steroids (mg./24 hr.): 17-ketosteroids, 21; dehydroepiandrosterone, 5.3; etiocholanolone, 5.3; androsterone, 6.0; 11-ketoetiocholanolone, 1.8; and 11 β-androsterone + 11 β-etiocholanolone, 0.4; 17-ketogenic steroids, 5.5; pregnanediol, 1.6; pregnanetriol, 1.2. Creatinine excretion, 1,219 mg./24 hr. F.S.H. (M.U.U./24 hr.) preoperative $> 13 < 52$, postoperative > 208.

Case 4. P. S. (Referred by Dr. Louis Claiborne), was aged 19. Both the patient and her mother were only children. The maternal menarche and sexual hair were normal. She had two great-aunts with children, one without and one great-great-aunt was thought to be amenorrheic. Plastic procedure was performed to the genitals at the age of 5 (? separation of labial fusion). At the age of 15 there was only questionable commencement of breast development with slightly enlarged nipples but no glandular tissue. There was no axillary hair and insignificant pubic hair. The patient was placed on 10 mg. of methyltestosterone and 1.25 mg. of conjugated estrogens (Premarin), and within 30 to 50 days there was sudden growth of pubic hair, though no axillary hair appeared. There was no further hair growth. Breast development also commenced at this time. In spite of prolonged estrogen therapy, the breasts remained rather small, and somatic growth continued with x-ray evidence of retarded bone age. The patient reached a height of 70½ inches, with a span of 70 inches, and weighed 143 pounds. There was a slight acromegalic tendency with a rather prominent jaw. In this case the color vision was normal.

Urinary 17-ketosteroids 3.9 to 9.8 mg./24 hr.

F.S.H. (M.U.U./24 hr.): preoperative > 104 < 208, postoperative > 208.

Postoperatively this patient was placed on 20 mg. of methyltestosterone and 2.5 mg. of conjugated estrogens daily, the same dosage as the others. She failed to keep several appointments for check-ups, but on her own renewed the prescriptions. When seen 7 months later there was acne and slight facial hair, deepening of the voice, axillary hair, abundant pubic hair, and definite clitoral enlargement (Fig. 2).

Morphology of the gonad

While the gonads in this syndrome are usually described as being similar to undescended testes, there appear to be some definite morphologic differences:

1. The tubules seem to resemble those of a considerably less mature testis than would be expected from the age of the individual (Fig. 3). They are often indistinguishable from those found in tubular adenomas. While such nodules are found in the undescended testis, in this age group the undescended testis shows a predominance of tubules containing apparently mature Sertoli cells (Fig. 4). One might further expect to encounter some germ cell development, which is rare in this syndrome even when the gonads are extra-abdominal or labial. The tubules vary and in some instances may be considerably more developed than those illustrated. Electron microscopy of the gonads in Case 3 by Dr. Gerald Gordon and Dr. Klaus Bensch[81] showed the fine structures to be similar to those of the fetal testis. The tubules appeared to be lined principally by primitive germ cells with some Sertoli cells present.

2. A second feature is the Leydig cells, which may be absent or replaced by rather heavily collagenized interstitial tissue in portions of the gonad, only to be found in large aggregates to the exclusion of other gonadal elements in other areas, particularly near the hilus of the gonad (Fig. 5). Often the undescended testis at this age will show an increase in Leydig cells, but not to this degree and, furthermore, one does not encounter such broad expanses of the cells. Leydig cells are also found along the mesogonadal nerves in much the same fashion that the hilar Leydig cells of the ovary are encountered (Fig. 6).

3. There may be areas of nonspecific fibrous stroma resembling ovarian stroma (Fig. 7). In some instances this has been such a feature that the diagnosis of ovotestis has been considered. There are, however, no follicular derivatives present, and in some places immature Leydig cells are present among the fibroblasts. These ovarianlike areas are not found in the undescended testis.

Dr. Ronald Sniffen, who has written authoritatively on the testis,[103] kindly reviewed the slides of these gonads. He concluded that these gonads were "histologically distinguishable from undescended testes in males of the same age." It may not be entirely correct, therefore, to classify these patients as bona fide male pseudohermaphrodites, as there is, apparently, some element of gonadal dysgenesis present. However, the testis in some other forms of male pseudohermaphroditism may be slightly atypical. Furthermore the morphologic differences seen may be an adolescent change, as the prepubertal gonad in this syndrome resembles a normal prepubertal testis.

The effect of hormones on the development of gonad itself is not well understood, but observations, such as that of Burns[73] that estradiol may induce sex reversal of the morphogenesis of the embryonic testis in animals, suggest that some of the abnormalities noted in the structure of the gonads of testicular feminization might be on an endocrinologic basis, such as an androgen defect at puberty. However, as the gonad is also the probable source of hormone in question it may be a little hard to know which is cause and which effect.

Incidence of neoplasia

The incidence of neoplasia in these gonads is difficult to ascertain, since the majority of cases reported in the literature have only reached their late teens or early twenties, and, furthermore, in considerably more than half of these the gonads were removed. Only 1 malignant tumor has been reported among

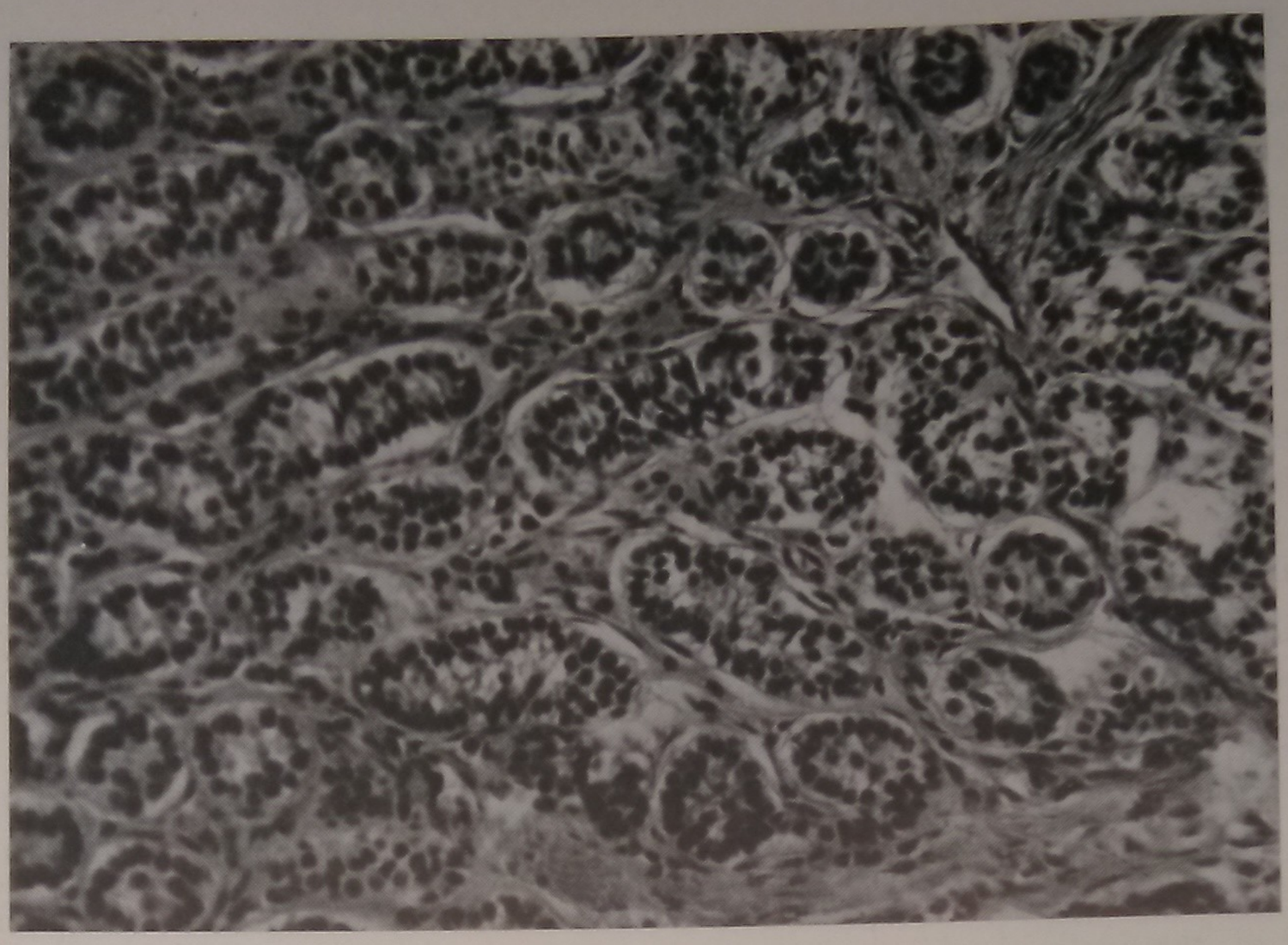


Fig. 3. Testicular tubules (Case 3). Note immaturity. (×300.)

Fig. 4. Tubules in undescended testes of otherwise normal 19-year-old male. Compare with Fig. 3. (×300.)

teen-age patients, and 2 malignant tumors in those in their twenties, but in the 50 reported cases 30 years of age or older there have been 11 malignant tumors, chiefly germinomas. In addition there were 15 tubular adenomas (up to 24 cm. in diameter), and 10 cysts large enough to be an indication for operative intervention.

This 22 per cent incidence of malignant tumors is obviously abnormally high because in many instances it was the indication for operation that brought the patient to the attention of the physician. However, even allowing for this fact, the incidence of neoplasia appears sufficient to continue to advocate removal of the gonads with substi-

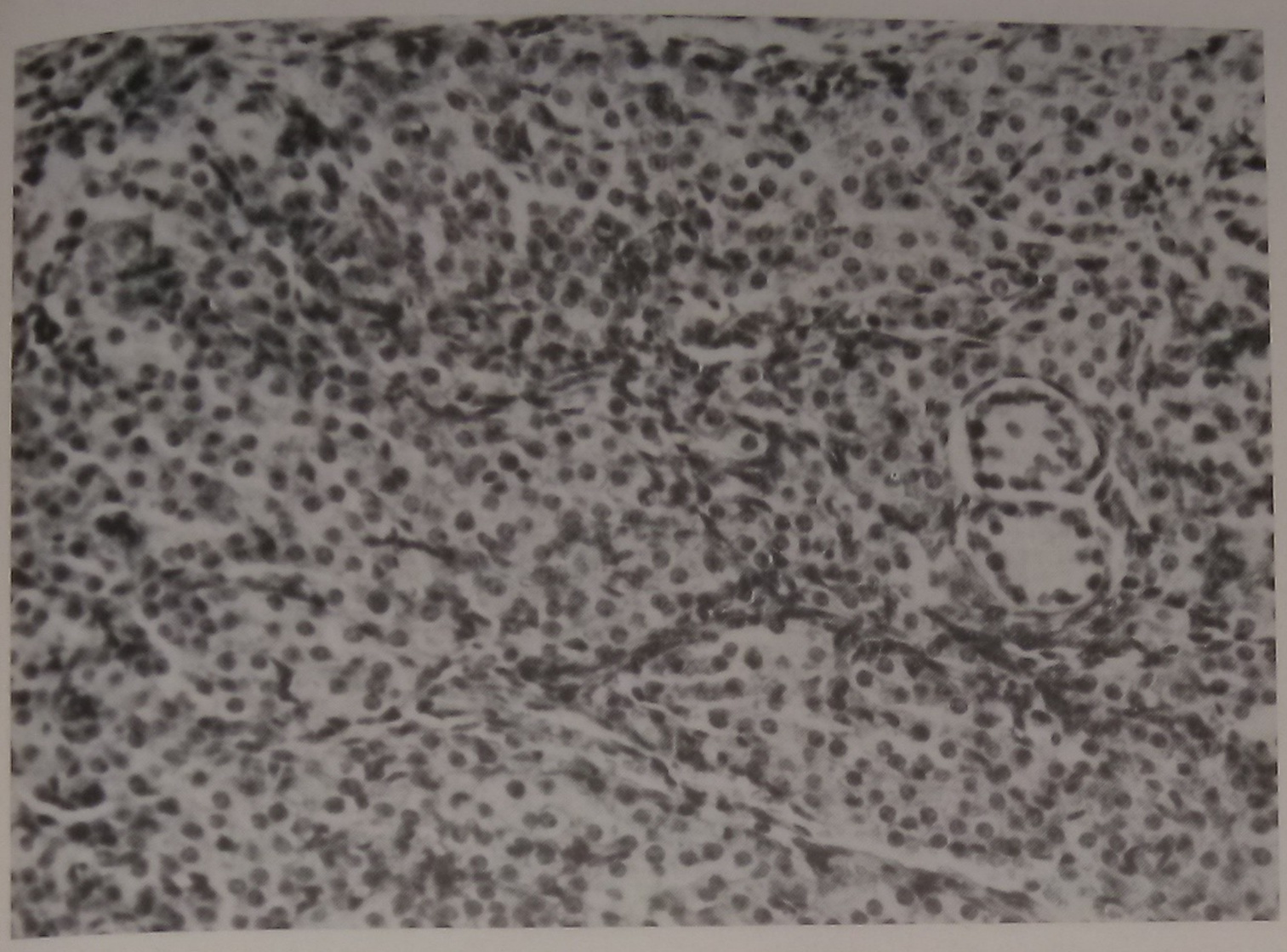


Fig. 5. Typical large aggregate of Leydig cells (Case 2). (×300.)

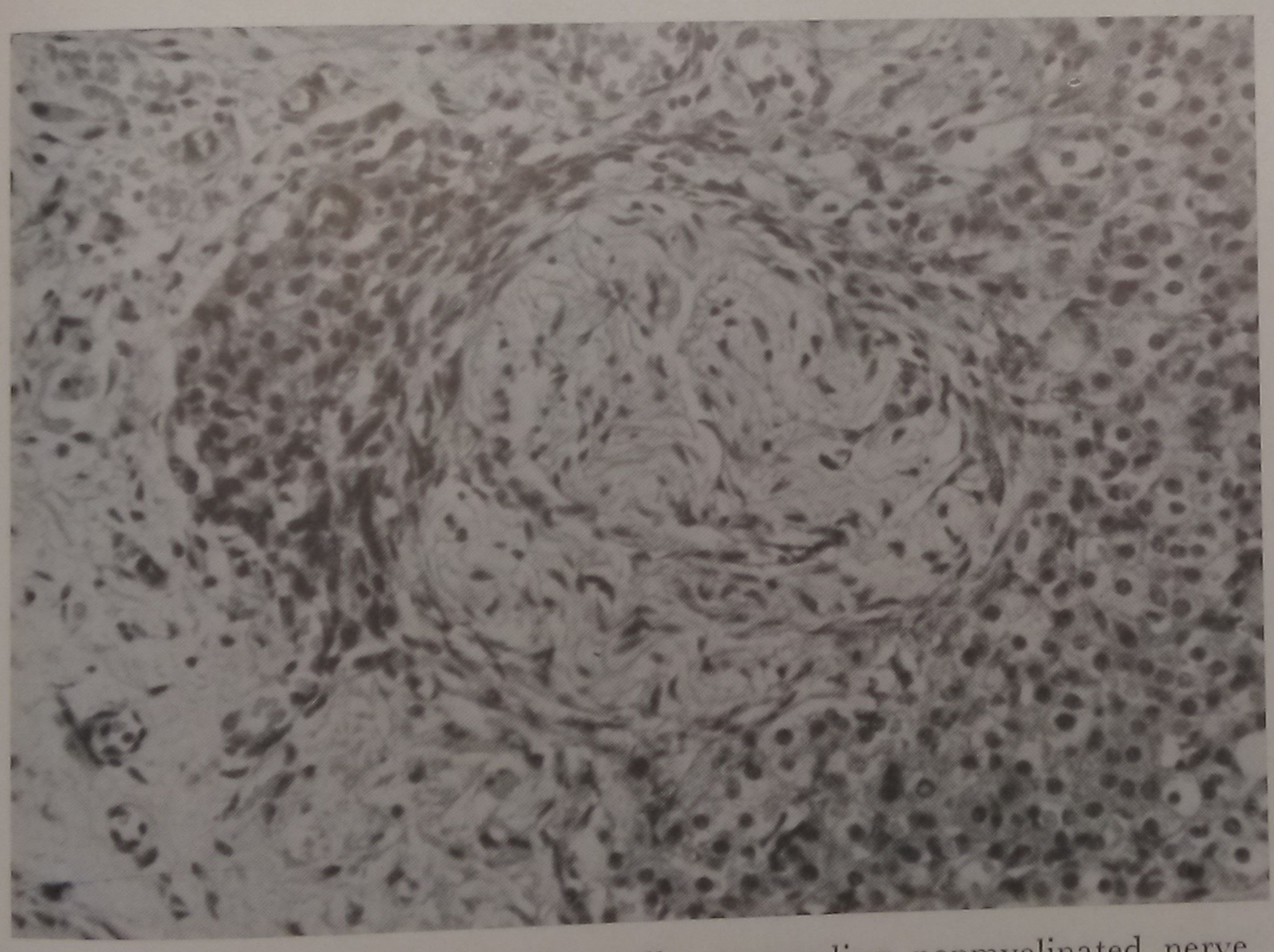


Fig. 6. Extragonadal hilar Leydig cells surrounding nonmyelinated nerve (Case 3). (×300.)

tution therapy after secondary sex characteristics have developed.

The nodular appearance the gonad may take is illustrated in Fig. 8. This is not always present, but it may be difficult to decide whether some nodules represent adenomas or not.

Genetic aspects

The syndrome is hereditary with transmission through the maternal line. The carriers are usually normal females, but decreased axillary or pubic hair has been noted in otherwise apparently normal mothers, grandmothers, aunts, or sisters by a

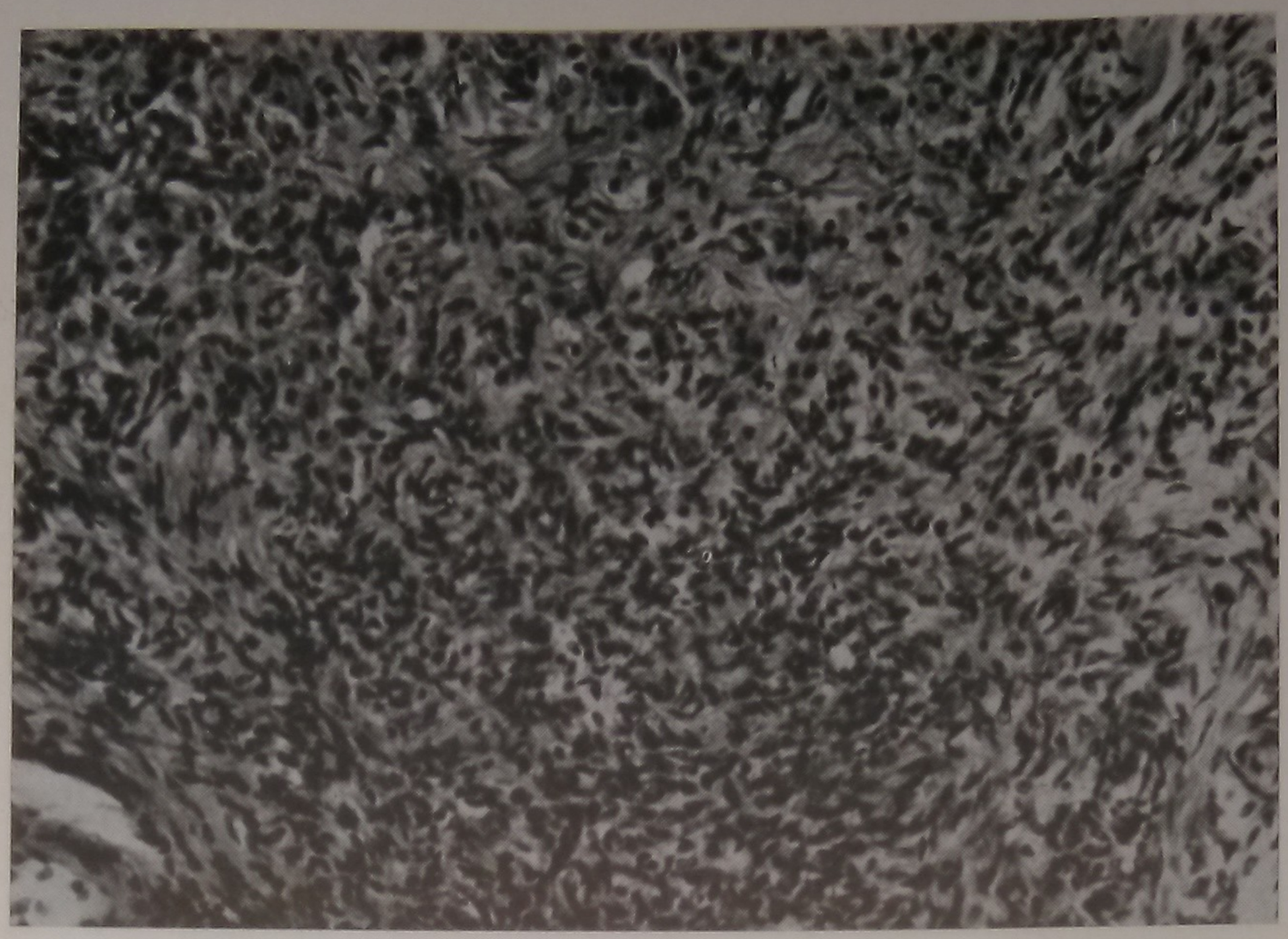


Fig. 7. Area of nonspecific fibrous stroma (Case 1). (×300.)

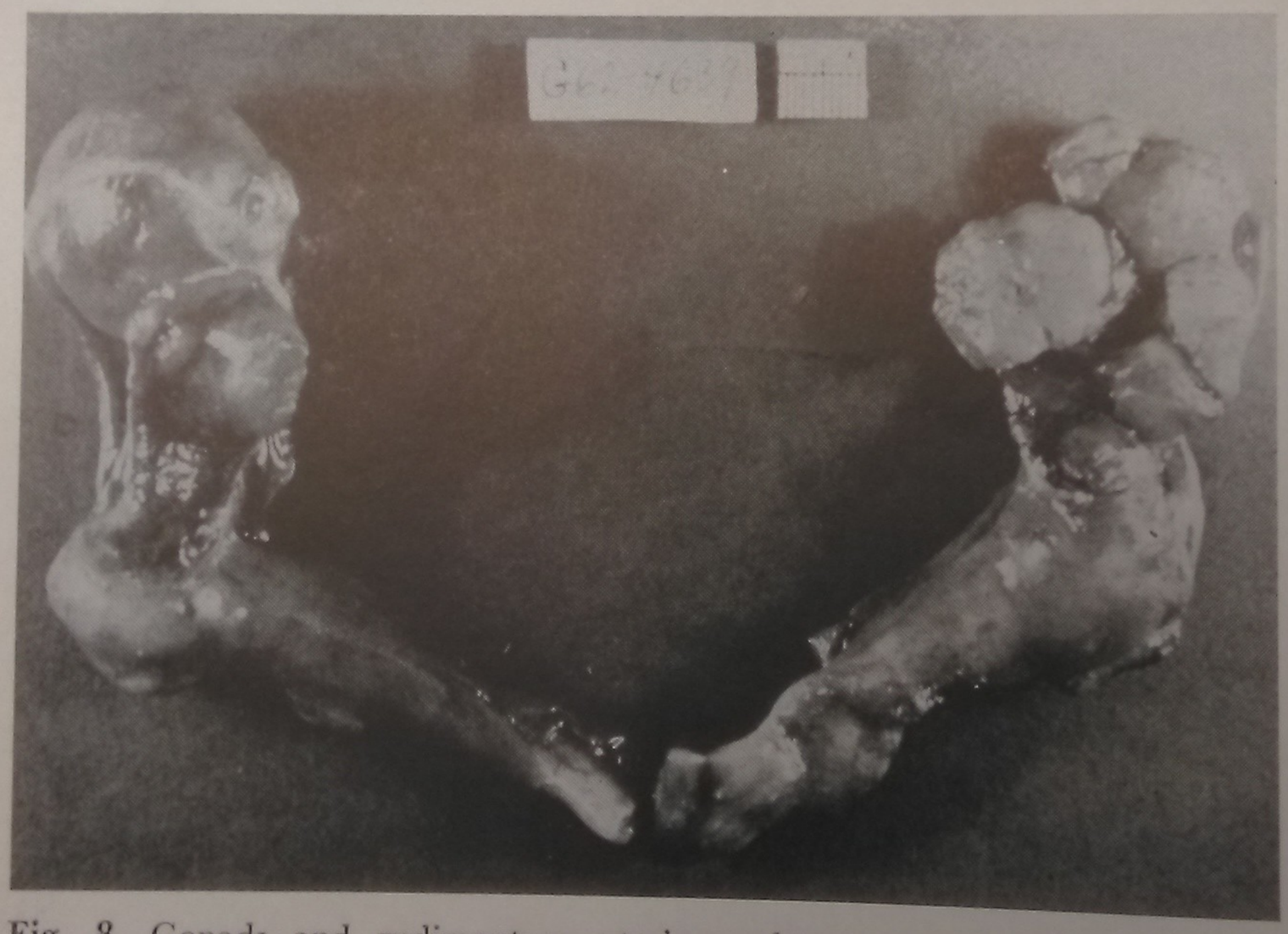


Fig. 8. Gonads and rudimentary uterine enlage removed from Case 3. Note nodular appearance of gonad.

number of authors.[17, 34, 43, 56, 64, 97, 102] Late menarche has also been mentioned as a familial trait.[5, 54]

Jacobs and associates,[28] Lennox,[89] Puck, Robinson, and Tjio[54] and subsequently others have found the chromosome complement in cases of this syndrome to be XY. While the karyotypes of the four cases in this report are all XY, Miller[96] has encountered a typical case which is apparently an XO/XY/XX mosaic. Dr. Morton Vesell has kindly sent slides from a pair of identical 9-year-old twins who apparently have typical features of the syndrome in which both the buccal smear and the testis are chromatin positive, suggesting mosaicism or,

possibly, an XXY constitution. If chromosome complements other than XY are associated with the same clinical picture, it would suggest that this syndrome may be basically a hereditary endocrine defect rather than just a form of male pseudohermaphroditism. Furthermore, the absence of sexual hair noted in female carriers above, suggests that the female may be affected by the same defect to some extent.

Reviews of the hereditary features of this syndrome, notably those by Lenz[37] and Grumbach and Barr[82] have pointed out the fallacy of including only those pedigrees that have more than one case of the syndrome. This leads to the false presumption that these are more affected than unaffected males. For example, in available reports there are a total of 351 siblings, of which 159 are female, 70 are male, and 122 are this syndrome (excluding 27 children who died in infancy). In families with only a single case reported there are 146 siblings, 65 females, 39 normal males, and 33 affected males. Using such statistical methods as those of Weinberg[104] or of Levit[90] the ratio of female to male to affected male approximates 2:1:1 leading to the conclusion that this syndrome is either an X-linked recessive trait or a male-limited autosomal dominant inheritance.

In differentiating between these two possibilities, hereditary studies in relation to such sex-linked defects as color blindness or hemophilia gives some suggestive evidence. Nilsson and associates[99] reported observations of a sexually normal male and an apparent case of testicular feminization in the same set of siblings, both exhibiting hemophilia A, and Stewart[66] made similar observations of independent segregation in pedigrees with color blindness. Case 3 had partial red-green color blindness. Her two normal brothers exhibited the same defect, while her sister had normal color vision. However, the fact that the mother, herself, was color-blind would indicate that all XY offspring should be color-blind.

In his magnificent review of the X-chromosome in man, McKusick[95] studied the blood group antigen X_g^a, which is X-linked, in relation to testicular feminization. In a family with three affected and one unaffected male there was one crossover.

These observations suggest that the defect causing testicular feminization is either sufficiently far removed from the genes of color blindness, X_g blood groups, and hemophilia to permit frequent crossing over, or that the condition is autosomal.

Endocrine aspects

Endocrine studies performed on patients with this syndrome have in general shown normal or elevated levels of urinary ketosteroids, normal male or female levels of urinary estrogens, cornification of the vagina, and normal or slightly elevated gonadotropins. With castration there has been a fall in ketosteroids and estrogens, a decrease in vaginal cornification, and a rise in gonadotropins indicating at least in part a gonadal hormone source. Similar findings were encountered in the cases reported in this paper.

Clinical evidence of androgen secretion is usually present when urinary 17-ketosteroid values reach 15 to 30 mg. per 24 hours or more, but in the complete form of this syndrome in spite of such levels there is a lack of androgen effect. Among the possible explanations that might account for this discrepancy are:

1. An inability of the gonad to produce androgens of high biologic activity, such as testosterone. This might be caused by deficiency of enzymes such as 3β-ol dehydrogenase or 17β-hydroxysteroid dehydrogenase.

2. An accelerated metabolism of androgens to inactive metabolites, or a rapid conversion of androgens to estrogens at peripheral sites such as the liver and kidney.

3. End organ failure to respond to androgens or "androgen insensitivity." This concept has been suggested by Wilkins.[71] However, it provides no explanation for the breast development or female habitus.

With a view to gaining more exact information regarding the steroid synthesis and

Table I. Steroid content of gonadal venous plasma

Gonadal venous plasma (μg per 100 ml.)	*Case 1**	*Case 2**	*Case 3*	*Case 4**
Dehydroepiandrosterone	3.6	2.7	3.9	Not detectable all values < 0.6
Androstenedione	0.9	3.8	2.7	
Testosterone	< 0.4	2.5	0.2	
Estradiol	0.4	1.9	2.0	
Estrone	< 0.2	0.15	0.25	

*On dexamethasone and chorionic gonadotropin.

secretion of the gonads in this syndrome, a detailed study was carried out in the 4 cases presented in this paper. This included determination of gonadal steroid content (Case 1), gonadal venous plasma steroids, in vitro incubation of gonadal tissue with radioactive precursors, steroid secretion rates, and estimation of some peripheral plasma steroids.

After certain baseline values were obtained, Cases 1, 2, and 4 were placed on dexamethasone (0.75 mg. three times a day) for adrenal suppression and 14 days later chorionic gonadotropin stimulation (10,000 intravenously at bedtime) was carried out for 6 days. Studies were then carried out 1 week postoperatively with the patient still on dexamethasone.

Study of the steroid content of the gonad and in vitro incubation studies with gonadal tissue and radioactive precursors in Case 1, as well as determination of the steroids in the gonadal vein plasma in all four cases was carried out by one of us (V. B. M.), employing procedures similar to those used with polycystic ovaries.[92-94]

The gonads in Case 1 contained 2.9 μg of dehydroepiandrosterone and 1.2 μg of Δ^4-androstenedione per gram of tissue. Detectable amounts of testosterone and estrogens were not present in the gonad. The dehydroepiandrosterone levels are higher than that found in normal ovaries. Normal values for the human testis are unknown.

Results of the study of the gonadal vein plasma are presented in Table I. It should be mentioned that the collection of the specimen was in some instances complicated by the presence of very small veins and possible contamination with peripheral blood. The results, nevertheless, show the presence of significant levels of free dehydroepiandrosterone and androstenedione. It is also of interest to find a high level of testosterone in Case 2 and significant amounts in Case 3. The level of estradiol in Cases 2 and 3 is comparable to that found in normal females around the ovulation peak.[9] Small quantities of estradiol were also found in Case 1 and estrone in Cases 2 and 3. In Case 4, the variant of the syndrome, the venous plasma did not contain measurable amounts of free steroids although the minimal detectable amount (because of available plasma volume) was 0.6 μg per 100 ml.

The in vitro incubation studies in Case 1 show a good conversion of various precursors to testosterone, which goes beyond the range found in the normal ovary and may be within testicular range (Table II). This is in agreement with the findings of Griffiths and Grant,[20] who, however, only incubated with Δ-4 precursors. Furthermore evidence of aromatization of ring A of androgens to form estrogens by the gonads is also present.

Secretion rates being performed by Dr. Raymond Vande Wiele on Cases 1, 2, and 4 and gonadal incubation studies on Cases 2, 3, and 4 by Dr. Nathan Kase, which will be published separately, suggest that in Cases 2 and 3 there is very significant testosterone production in the male range, while in Case 4 the gonads appeared relatively inactive.

Determinations of the conjugated 17-ketosteroids in peripheral plasma were carried out by the method of Conrad, Mahesh, and Herrmann[74] and results are presented in Table III. Except in Case 4 levels of dehydroepiandrosterone sulfate were high. Dexamethasone suppression lowered these values, and further significant decrease was brought about by castration indicating both adrenal and gonadal origin. In Case 3 the relatively slight lowering of these levels after castration suggests a significant extragonadal source. In Case 2 there was an elevated

Table II. Incubation of tissue slices from the gonads of Case 1 with 50 μg quantities of various radioactive precursors

	Δ⁵-Pregnenolone 7-H³	*Dehydroepi-androsterone 7-H³*	*Progesterone 4-C¹⁴*	*Δ⁴-Androste-nedione 4-C¹⁴*
Metabolite (per cent conversion per gram of tissue)				
17α-Hydroxypregnenolone	18.8			
Dehydroepiandrosterone	7.6			
Progesterone			23.6	
17α-Hydroxyprogesterone	2.8	9.6	6.8	
Δ⁴-Androstenedione	0.4	0.8	0.4	1.2
Testosterone	0.05	0.25	0.08	0.6
Estrone	0.06	0.3	0.08	0.8
Estradiol				

Table III. Peripheral plasma steroid levels

Peripheral plasma (μg per 100 ml.)	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Baseline period				
Dehydroepiandrosterone-SO_4	351	211	455	19
Androsterone-SO_4	85	154	47	0
Cortisol	15	16.5		
Dexamethasone suppression				
Dehydroepiandrosterone-SO_4	88	147		
Androsterone-SO_4	77	73		
Cortisol	2.5	4.4		
Dexamethasone and A.P.L.				
Dehydroepiandrosterone-SO_4	82	109		
Androsterone-SO_4	42	91		
Testosterone	0.085			
Castration (on dexamethasone)				
Dehydroepiandrosterone-SO_4	34	35		
Androsterone-SO_4	< 25	41		
Castration (no dexamethasone)				
Dehydroepiandrosterone-SO_4			432	
Androsterone-SO_4			15	

level of androsterone sulfate, but in the others values were normal and etiocholanolone sulfate was not detectable in any patient. Thus, there did not appear to be a significant increase in inactive androgen metabolites. Furthermore, Dr. Ralph Dorfman was kind enough to carry out a testosterone determination on the peripheral plasma in Case 1, which was found to be in the normal female range.[77]

Certain inferences can be drawn from these results:

1. The gonads may not all behave in an identical fashion, as is shown by the relatively inactive hormone production in the incomplete syndrome (Case 4) as compared with the others.

2. In the complete syndrome there is an exceptionally high production of dehydroepiandrosterone sulfate and dehydroepiandrosterone in which both gonad and adrenal appear involved. These values are in the upper male range and may in part account for the high urinary ketosteroids sometimes encountered.

3. There is possibly a quantitative but

certainly no qualitative defect in hormone output. The Δ-4 compounds occur in sufficient quantity to rule out a 3β-ol dehydrogenase deficiency. The findings of testosterone in the gonadal vein plasma indicates the presence of the 17β-hydroxysteroid dehydrogenase. The aromatization of the A-ring to form estrogens appears normal.

In view of the limited number of studies of this nature carried out on normal ovaries and normal testes, as well as undescended testes, it is very difficult at this stage to compare these gonads either with the testis or the ovary. The studies presented in this paper show that the gonads in this syndrome are capable of producing significant levels of both androgens and estrogens of high biological activity which compare favorably with both the testis and the ovary. There may, however, be variants of this function as shown in the incomplete form of the syndrome (Case 4) which was widely different by the above mentioned criteria as compared with Cases 1 through 3.

Comment on etiology

There is strong evidence that this syndrome is a hereditary endocrine abnormality, essentially related to a lack of androgen effect. This is borne out both in the abnormal embryonic development and in the abnormal secondary sex characteristics.

In fetal life deficient androgen effect is indicated by the fact that the urogenital sinus development is female, and the Wolffian duct system fails to develop. The male development of these structures is androgen dependent, and they will be female in the absence of androgen, as has been shown by the studies of Jost and others[86] on the effect of castration of the male fetus in utero.

As androgenic steroids do not appear to inhibit the development of the Müllerian system, the absence of Müllerian derivatives in this syndrome must be explained by the presence of the testis and of the Müllerian inhibiting factor which prevents the development of uterus in the normal male.[85]

At puberty the complete failure of development of any male secondary sex characteristics in the complete syndrome again point to an androgen defect. One could then conclude that these represented relatively inactive gonads from the endocrine point of view if it were not for the appearance of certain female characteristics reflecting estrogen production. That the testis rather than some extragonadal source is responsible is borne out by the fact that such secondary sex development does not take place after prepubertal castration.[80]

While it is obvious that such female secondary sex characteristics cannot develop without estrogen, they are not necessarily those of an excessive estrogen output. For example, the labia minor are invariably small. The nipples are frequently underdeveloped, and the breasts contain relatively little glandular tissue. In some instances the build is eunuchoid and the pituitary gonadotropin somewhat elevated.

Instead of postulating excessive estrogen secretion then it seems quite possible that in the presence of normal or only slightly elevated amounts of testicular estrogen it is chiefly the "nonaction of androgen" that results in these sometimes rather impressive secondary sex changes. The mild androgen defect seen in such conditions as Klinefelter's syndrome may result in some breast development and suggests that this may be possible. Better evidence that androgen does, in fact, suppress estrogen effect is seen in congenital adrenal hyperplasia. In untreated cases the androgen formed by the adrenal may prevent breast development and other female secondary sex characteristics in spite of the presence of ovaries and of estrogens.

While Lawson Wilkins might not accept any responsibility for the thought that men might be wearing brassieres if it were not for the suppressive effect of their testosterone, he should receive the credit for the hypothesis that there is an insensitivity to androgen present in this syndrome. He and others have administered large doses of androgen to patients with this syndrome without producing significant hair growth or other virilizing manifestations. This was true also of the first three patients in this re-

port, in all of whom androgen appeared to have little effect. However, in Case 4 the administration of androgen produced sexual hair growth and significant evidence of virilization, indicating in this instance a different etiology, undoubtedly related to deficient androgen production.

The mechanism of androgen action at an end organ is unknown. One can then only speculate as to the nature of any defect. An inherent end organ failure seems unlikely as the tissues of the various end organs are so different—hair follicles, laryngeal cartilage, Wolffian duct, phallus, bone, fat, muscle, etc. A defect in steroid metabolism such as peripheral inactivation of testosterone by conjugation or aromatization of the A-ring is possible but is not supported by any existing evidence. Some factor that mediates androgen effect may be missing or some unknown antagonist may be present. With present knowledge one can only revert to "nonaction of androgen."

Summary

1. The name "testicular feminization" is in part a misnomer as the basic defect appears to be some interference with the mechanism of androgen action.

2. It should be differentiated from incomplete forms of the syndrome, in which there is some degree of clitoral enlargement and the secondary sex characteristics are unpredictable. In one such case deficient androgen production and a normal response to exogenous androgen was noted.

3. Some element of gonadal dysgenesis may be present as the gonads of this syndrome differ morphologically from the undescended testis of the male.

4. With present evidence it is not possible to say whether the syndrome is a hereditary autosomal dominant trait, which is sex-limited, or an X-linked recessive. The karyotype is apparently not always XY. Decreased sexual hair may be found in maternal carriers suggesting a similar defect may occur in the female.

5. Peripheral and gonadal blood steroid determinations as well as incubation studies indicate that there may be a quantitative, but no qualitative defect in hormone production. Dehydroepiandrosterone, both free and as the sulfate, is exceptionally high, but androstenedione, testosterone, estradiol, and estrone appear to lie in ranges between that produced by the ovary and the testis.

6. The nonaction of androgen plus the presence of testicular Müllerian inhibiting factor would appear to account for the fetal development, while the nonaction of androgen plus testicular estrogens is offered as an explanation for the type of secondary sex characteristics encountered.

REFERENCES

Additional cases of testicular feminization

1. Arenas, N., Sammartino, R., and Traverso, J.: Bol. Soc. Obst. y Ginec. Buenos Aires **29:** 102, 1950.
2. Armstrong, C. N.: Brit. M. J. **1:** 1173, 1955.
3. Barber, H. W., Proper, R., and Chiffelle, T. L.: Obst. & Gynec. **19:** 269, 1962.
4. Barno, A.: Am. J. Obst. & Gynec. **84:** 710, 1962.
5. Beatty, D. C., Champ, C. J., and Swyer, D. M.: Brit. M. J. **1:** 1369, 1953.
6. Béclère, M. C.: Compt. rend. Soc. Franç. gynéc. **22:** 296, 1952.
7. Botella-Llusia, J., and Nogales, F.: Arch. Gynäk. **182:** 675, 1953.
8. Boute, J., Fanard, A., and Limage, J.: Ann. endocrinol. **13:** 516, 1952.
9. Bricaire, J., and Thyoer-Rozat, J.: Bull. Fed. soc. gynéc. et obst. **10:** 130, 1958.
10. Brocq, P., and Robert, H.: Gynéc. et Obst. **50:** 229, 1951.
11. Burgermeister, J. J.: J. Génét. Humaine **2:** 51, 1953.
12. Cavallaro, C., and Zanardi, F.: A. M. A. Arch. Path. **55:** 142, 1953.
13. de la Harpe, M. M.: South African M. J. **33:** 751, 1959.
14. DeLima, O. A., Rudolph, K. M., and Gastim, A.: Rev. ginec. e obst. **48:** 365, 1954.
15. Figueroa, C. P., and Fort, C. J.: Bol. Soc. Obst. y Ginec. Buenos Aires **29:** 176, 1950.
16. Flor, S. F., Schadt, D. C., and Benz, E. J.: J. A. M. A. **181:** 375, 1962.
17. Gayral, L., Barraud, M., Carrie, J., and Candebat, L.: Toulouse Med. **61:** 637, 1960.
18. Granjon, A., and Yannotti, S.: Presse med. **65:** 2180, 1957.

19. Greenblatt, R. B.: Am. J. Obst. & Gynec. **70:** 1165, 1955.
20. Griffiths, K., and Grant, J. K.: Biochem. J. **84:** 22, 1962.
21. Guggisberg, H.: Schweiz. med. Wchnschr. **64:** 181, 1934.
22. Guillemin, P., and Guillemin, A.: Bull. Fed. Soc. gynéc. et obst. **4:** 758, 1952.
23. Hauser, G. A.: *In* Overzier, C., editor: Die Intersexualität, Stuttgart, 1961, Georg Thieme Verlag, p. 261.
24. Hauser, G. A., Keller, M., Koller, T., Wenner, R., and Gloor, F.: Schweiz. med. Wchnschr. **87:** 1573, 1957.
25. Holmer, A. J. M.: Nederl. tijdschr. verlosk. en gynaec. **46:** 47, 1943.
26. Ikle, A., and Käser, O.: Gynaecologia **146:** 339, 1958.
27. Ikkos, D., Tillinger, K. G., and Westman, A.: Acta endocrinol. **32:** 222, 1959.
28. Jacobs, P. A., Baikie, A. G., Brown, W. M. C., Forrest, H., Roy, J. R., Stewart, J. S., and Lenox, R.: Lancet **2:** 591, 1959.
29. Jamain, B., and Legros, R.: Gynec. & Obst. **51:** 138, 1952.
30. Johansen, A.: Ugesk. laeger **122:** 1023, 1960.
31. Jones, H. W., and Scott, W. W.: Hermaphroditism, Genital Anomalies and Related Endocrine Disorders, Baltimore, 1958, Williams & Wilkins Company, p. 170.
32. Kendall, B., and Loewenberg, L. S.: Obst. & Gynec. **20:** 551, 1962.
33. Kessler, A.: Geburtsh. u. Frauenh. **1:** 31, 1959.
34. Kessler, A.: Geburtsh. u. Frauenh. **6:** 508, 1959.
35. Kirchhoff, H.: Med. Klin. **53:** 1636, 1958.
36. Koller, T.: Schweiz. med. Wchnschr. **73:** 83, 1943.
37. Lenz, W.: J. Génét. Humaine **8:** 199, 1959.
38. Loennecken, W.: Nord. med. Medicinsk revue **39:** 403, 1922.
39. Marshall, H. K., and Harder, H. I.: Obst. & Gynec. **12:** 284, 1958.
40. Martines Montes, E. A., and Bagnati, E. P.: Prensa méd. argent. **46:** 394, 1959.
41. Matthaei, H.: Zentralbl. Gynäk. **34:** 1355, 1954.
42. May, H.: Plastic & Reconstruct. Surg. **16:** 201, 1955.
43. Membrives, J. R., Rocca, D. Z., Pinto, R. M., and Luchetti, S. E.: Prensa med. argent. **45:** 561, 1958.
44. Molinoff, S. J., and Armstrong, M. V.: Am. J. Obst. & Gynec. **83:** 382, 1962.
45. Neimann, N., Pierson, M., Lesure, J., and Pierson, B.: Bull. Fed. Soc. gynec. et obst. **11:** 387, 1959.
46. Netter, A., Lumbrosa, P., Yaneva, H., and Bellaisch, J.: Ann. Endocrinol. **19:** 994, 1958.
47. Neubecker, R. D., and Theiss, E. A.: Am. J. Clin. Path. **38:** 52, 1962.
48. Nguyên-Ngoc-Duyên, Cao-Zuàn-an, and Dinh-Văn-Túng: Acta medica Vietnam **4:** 1435, 1960.
49. Oles, H.: Zentralbl. Gynäk. **80:** 1877, 1958.
50. Philipp, E.: Deutsche med. Wchnschr. **81:** 1298, 1956.
51. Philipp, E., Staemmler, H. J., and Stange, H. H.: Deutsche med. Wchnschr. **80:** 1721, 1955.
52. Salaber, J. A., Del Castillo, E. B., Contreras Ortiz, N., and Nogues, A.: Medicina Buenos Aires **9:** 399, 1949.
53. Plate, W. P.: Nederl. tijdschr. geneesk. **105:** 1666, 1961.
54. Puck, T. T., Robinson, A., and Tjio, J. H.: Proc. Soc. Exper. Biol. & Med. **103:** 192, 1960.
55. Salassa, R. M., Paris, J., Mattox, V. R., Mason, H. L., and Albert, A.: J. Clin. Endocrinol. **21:** 506, 1961.
56. Scharplatz, A.: Gynaecologia **146:** 335, 1958.
57. Schneider, R. W., Van Ommen, R. A., and Hoerr, S. O.: J. Clin. Endocrinol. **12:** 423, 1952.
58. Schönthaler, J.: Zentralbl. Gynäk. **77:** 1867, 1955.
59. Schreiner, W. E.: Geburtsh. u. Frauenh. **19:** 1110, 1959.
60. Snaid, M. V.: Bull. Fed. Soc. gynéc. et obst. **7:** 362, 1955.
61. Snoeck, J., Tagnon, R., and Cordies, N.: Bull. Fed. Soc. gynéc. et obst. **4:** 627, 1952.
62. Southren, A. L., and Saito, A.: Ann. Int. Med. **55:** 925, 1961.
63. Spielman, F., and Motyloff, L.: New York State J. Med. **55:** 653, 1955.
64. Spurny, J., and Ulm, R.: Wien. med. Wchnschr. **108:** 886, 1958.
65. Stern, O. N., and Vandervort, W. J.: New England J. Med. **254:** 787, 1956.
66. Stewart, J. S. S.: Lancet **2:** 592, 1959.
67. Stollmeyer, J. E. C., and Latour, J. P. A.: Canad. M. A. J. **63:** 494, 1950.
68. Teter, J., Bulska, M., and Ruszkowski, J.: Bull. Soc. roy. belge gynéc. et obst. **31:** 1, 1961.
69. Tranquada, R. E., Bender, B. S., and Beigelman, P. M.: New England J. Med. **266:** 1302, 1962.
70. Vaish, R.: Brit. M. J. **2:** 1386, 1958.
71. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, 1957, Charles C Thomas, Publisher, p. 276.
72. Zuspan, E. P.: Am. J. Obst. & Gynec. **80:** 454, 1960.

Other references

73. Burns, R. K.: J. Exper. Zool. **142:** 353, 1959.
74. Conrad, S., Mahesh, V. B., and Herrmann, W. J.: Clin. Invest. **40:** 947, 1961.
75. Diefenbach, H.: Inaug. Dissertation (Berlin), Stuttgart, 1912, A. & W. Maurer.
76. Dieke, W.: Zentralbl. Gynäk. **78:** 889, 1956.
77. Dorfman, R. I.: Obst. & Gynec. Surv. **18:** 65, 1963.
78. Ernould, H. J., and Steenebruggen, A.: Ann. endocrinol. **17:** 490, 1956.

79. Ferin, M. J.: Bull. Fed. soc. gynéc. et obst. 7: 336, 1955.
80. Giusti, A.: Ann. ital. chir. 25: 23, 1948.
81. Gordon, G. B., and Bensch, K. G.: Unpublished data.
82. Grumbach, M. M., and Barr, M. L.: Recent Prog. in Hormone Res. 14: 255, 1958.
83. Hellinga, G.: Acta endocrinol. 41: 148, 1957. (Suppl.)
84. Jagiello, G., and Atwell, J. D.: Lancet 1: 329, 1962.
85. Jones, H. W., Jr., and Wilkins, L.: Am. J. Obst. & Gynec. 82: 1142, 1961.
86. Jost, A.: *In* Jones, H. W., Jr., and Wilkins, W.: Hermaphroditism, Genital Anomalies and Related Disorders, Baltimore, 1958, Williams & Wilkins Company, p. 15.
87. Kika, K., Suzuki, M., and Kandatsu, Y.: Gynaecologia 143: 33, 1957.
88. König, P. A.: Geburtsh. u. Frauenh. 20: 166, 1960.
89. Lennox, B.: Lancet 2: 591, 1959.
90. Levit, S. G.: J. Genetics 35: 151, 1938.
91. Lubs, H. A., Jr., Vilar, O., and Bugenstal, D. M.: J. Clin. Endocrinol. 19: 1110, 1959.
92. Mahesh, V. B.: Unpublished data.
93. Mahesh, V. B., and Greenblatt, R. B.: J. Clin. Endocrinol. 22: 441, 1962.
94. Mahesh, V. B., Greenblatt, R. B., Aydar, C. K., and Roy, S.: Fertil. & Steril. 13: 513, 1962.
95. McKusick, V. A.: Quart. Rev. Biol. 37: 69, 1962.
96. Miller, O. J.: Personal communication.
97. Mishell, D. R.: Am. J. Obst. & Gynec. 35: 960, 1938.
98. Morris, J. McL.: Am. J. Obst. & Gynec. 65: 1192, 1953.
99. Nilsson, I. M., Bergman, S., Reitalu, J., and Waldenstrom, J.: Lancet 2: 264, 1959.
100. Núñez, A. O., Fernández, M. F., and Casabón, A.: Rev. clín. espãn. 77: 386, 1960.
101. Präder, A.: Schweiz. med. Wchnschr. 87: 278, 1957.
102. Schultze, G. K. F.: Zentralbl. Gynäk. 54: 1173, 1930.
103. Sniffen, R. C.: Arch. Path. 50: 259, 1950.
104. Weinberg, W.: Z. indukt. Abstamm. u. Vererblehre 48: 179, 1927.
105. Weiser, P.: Med. Klin. 56: 137, 1961.

333 Cedar Street
New Haven 11, Connecticut

Discussion

Dr. Willard M. Allen, St. Louis, Missouri. Dr. Morris seems to have some apprehension about the term "testicular feminization" for the syndrome which he has been discussing this morning. I think we should applaud the term and that he should stick to it. These people do have testes and they are feminized. When the clinical syndrome is so definite a simple name, descriptive in this case, serves a very useful purpose. Earlier in the program we saw the advantage of restricting the name "Turner's syndrome" to a specific syndrome for now we find 25 years later that a specific chromosomal defect is found in virtually all cases clinically diagnosed as Turner's syndrome. On the other hand, ovarian agenesis encompasses other syndromes which have different chromosomal defects.

Another syndrome equally bizarre is the masculine "woman" with undescended testes, a short phallus, a rudimentary vagina, absence of the uterus, and male breasts. No one would refer to this syndrome as testicular feminization, but who would dare call it testicular virilism? It is known as male pseudohermaphroditism.

I mention these things only to emphasize the fact that the location of the testes—intra-abdominal or inguinal—does not lead necessarily to feminization. In the one case feminization is the rule, and in the other excellent masculinization. We wonder, therefore, why XY pseudohermaphrodites with testes can be masculine in one case and truly feminized in the other.

Dr. Morris and his "steroid" helpers have tried to evaluate the phenomenon which may explain the feminization in the syndrome of testicular feminization and I suspect that they find themselves somewhat frustrated already. I surely am. Their incubations of the gonadal tissues from these cases certainly show that the gonads are able to perform the synthesis of new steroids from labeled steroid precursors. For example, labeled Δ^5 pregnenoline was converted to dehydroepiandrosterone. This means that the tissue was able to reduce the steroid molecule for 21 carbon atoms to 19 carbon atoms. Likewise, testosterone was synthesized, indicating that the 3-hydroxy-Δ^5 configuration was converted to the 3-keto-Δ^4 configuration present in the biologically active, naturally occurring neutral steroids, such as progesterone, cortisol, and testosterone. This biosynthetic pathway is known to occur in the adrenal and ovary. The authors also have evidence that labeled estrogen is pro-

duced in these gonads. I am sure that the true significance of these studies will have to await more investigation of the normal biosynthetic pathways in both the ovary and testis, but I congratulate Dr. Morris and his associates in their study of these cases.

Their simpler studies do emphasize, however, that these gonads do produce hormones which enter into the pituitary gonadal balance. When the gonads were removed, the FSH levels increased in each of the 3 typical cases. This observation does not identify the steroid produced by the gonad for either estrogen or testosterone suppresses the output of FSH and castration in either sex results in an increase in the secretion of FSH. This observation seems to eliminate the adrenal gland as a potent source of either estrogen or androgen in this syndrome.

The most intriguing aspect of these cases, aside from the pseudohermaphroditic, is the failure of these patients to show any signs of virilism after fairly protracted treatment with methyltestosterone and estrogen. Normal women do show considerable virilism in their response to androgen to be sure, but I believe it is fair to state that most women will be virilized within 2 months by 20 mg. of methyltestosterone daily. Perhaps the skin of these people is really different, and this prompts my first question.

Does the skin of the mons have the normal quota of hair follicles in it? Biopsy in this area could be a part of the operation in these cases, and controls are surely readily available.

Have you tried 500 mg. of testosterone propionate per week intramuscularly? Doses of this magnitude have been given to patients with cancer of the breast.

Does the vaginal mucosa show prompt atrophy after gonadectomy?

Dr. Ronald R. Greene, Chicago, Illinois. One is always at a disadvantage in being the second "official" discussant of a paper in that one never knows exactly what the first discussant is going to say. At the risk of repeating what Dr. Allen might say, I would like to stress the fact that, in 1953, Dr. Morris brought order out of a minor chaos by tabulating and summarizing the findings in all reported cases of a condition that he named "the testicular feminization syndrome." In his present manuscript he semiapologizes for coining this term. I, however, think it is a good term, since these individuals with testicles have been feminized in respect to embryonic development (albeit imperfectly) as well as to appearance and function as an adult (again albeit imperfectly).

I am most interested in Dr. Morris's discussion of the etiology of this condition. Some years ago I had much interest and some experience in studying the effects of sex hormones on the embryogenesis of sexual structures. My coworkers and I were vigorous proponents of the dualistic theory that in mammals, androgen produced in the fetal testes caused male type development of the rest of the sexual structures and that fetal ovarian estrogens caused female type development. The last part of this concept has subsequently been proven to be incorrect, principally by Jost abetted by Raynaud, both in France, and by elegant in vivo and in vitro studies by Dorothy Price of the University of Chicago. It seems clear that testicular androgens probably cause development of sexual structures in the male, but development in the female (more or less perfect) takes place in the absence of androgens and not due to estrogens.

In the first three individuals presented by Dr. Morris, either the embryonic testes did not produce androgens or, more probably, the embryonic structures were unable to respond to the testicular androgens. Female type development resulted instead. The blighting of the paramesonephric or Müllerian structures must have been caused by whatever the embryonic testicular substance is that normally has this effect in the male. This substance is not any of the known adult type androgenic steroids.

To me, it seems likely that much of the tissues of these individuals, both as embryos and adults, is unable to respond in a normal manner to androgens. However, this is not the complete answer. These individuals have absent or sparse pubic hair. Pubic hair growth is a response to estrogens as well as to androgens. Dr. Morris has demonstrated that the gonads of these individuals produce an adequate amount of estrogens, and many of them are reported to have very little development of nipples and areoli. These are also supposedly estrogen sensitive. These facts would indicate to me that some of the tissues of these individuals respond poorly to estrogens as well as androgens.

I am purposefully avoiding the subject of little or no axillary hair, since it is a very complex subject involving gonad as well as adrenal function. I am also avoiding inadequately developed labia minor, since I am not sure whether the growth of these structures is estrogen or androgen conditioned.

There is one minor point that I feel it is necessary to quibble about. This is the implication that there is a direct antagonism of androgen which prevents the effects of estrogen on the breast. In the experimental animal this is not true. In the castrate or immature male, one can cause mild stimulation of both nipple and breast tissue with high doses of androgens. The development of a "subareolar node" on the breasts of a small proportion of pubescent boys, as reported by Jung and others, has been explained as a direct stimulation of the nonconditioned duct tissue to rapidly increasing amounts of testicular androgens. It is true that this response may be due to testicular estrogens but, if so, the testicular androgens are not inhibiting this response. The citation by Dr. Morris of the suppressive effect on the breast of estrogens by androgens in congenital adrenal hyperplasia is not valid, since this is an indirect effect. Namely, the excessive adrenal androgens inhibit hypophyseal gonadotropins and the ovary is essentially nonfunctional. Apropos of this latter, I succeeded many years ago in producing "Texas-sized" breasts in such an individual with stilbestrol. Needless to say, there was no reduction in hirsutism or rapidly developing baldness or 17-ketosteroid excretion.

In actual fact, excluding the embryo, I think there are very few, if any, instances of direct antagonistic effects of sex hormones in the human. Most of those effects considered to be antagonistic are due to depression of the individual's gonadal function. The rest are competitive or, more commonly, synergistic.

To return to Dr. Morris's patients, I am very willing to make an uninformed guess that their defect is enzymatic in nature, such that some or all of their tissues, as an embryo and as an adult, are unable to respond in a normal manner to androgens and poorly to estrogens.

Dr. Howard W. Jones, Jr., Baltimore, Maryland. Dr. Morris inferred that it is possible to understand the testicular feminization syndrome if one assumes that the steroidal excretion of the embryonic testis is inadequate to virilize the genitals. The problem of applying this is that Dr. Morris has not been able to demonstrate, in the cases he examined, that there is indeed a deficiency of the androgen produced. Actually, in 1958 and 1959, we had the opportunity to study the 17-ketosteroid excretion of four patients with this difficulty, but we did not have the courage of our biochemical convictions and it is, indeed, with a sense of relief that we hear that Dr. Morris found no abnormal secretion because in our four patients, studied by fractionation of the 17-ketosteroids, we could not distinguish between the four testicular feminization patients and the normal male controls. Also, following injection of human pituitary extract (HCG), the response was as in a normal male. Furthermore, they received large doses of androgen and we could not demonstrate aberration in the excretion in the urine from the normal male.

This makes it necessary to think of something other than lack of androgen as an explanation for the syndrome, and Dr. Morris has suggested that end organ failure is perhaps the explanation we seek. He referred to the fact that these testes histologically do differ from retained abdominal testes. This is true, but there is no characteristic histologic picture of testicular feminization as I once thought and wrote.

Dr. Morris originally pursued the idea that deficient androgen production because of 3β-ol dehydrogenase lack could explain this difficulty. Using a histochemical technique which demonstrates 3β-ol dehydrogenase, we have obtained a positive reaction on one testis from a patient with this syndrome. We, therefore, have confirmed by histochemical means the fact that in at least this one testis there was no 3β-ol dehydrogenase deficiency. Therefore, I think we must accept at the present time an end organ failure, since we cannot demonstrate any deficiency in androgen production. This brings up certain problems but it is a better working hypothesis than the complete absence of androgens in these testes.

I salute Dr. Morris for his presentation and for having the courage of his biochemical convictions in suggesting this pathogenesis for this condition.

Dr. Arthur T. Hertig, Boston, Massachusetts. My question obviously is not going to be on the sophisticated endocrinology of this condition but on the more pedestrian nature of malignant tumors so common in this group of patients. Are they of seminoma type or is there the usual spectrum of malignant tumors that arise in the testis?

Dr. S. Leon Israel, Philadelphia, Pennsylvania. I rise to say three things: I want to thank Dr. Morris most sincerely for this further extension of his fascinating study. We do know that there are examples of gene-linked disturbances in hair growth. If testicular feminization is a hereditary disorder, is it not possible that we have an expression of some chromosomal aber-

ration that links hair growth to disorder in the gene? To follow along in the same vein as one of Dr. Henriksen's ineffable Chinese aphorisms: "He who asks questions may seem momentarily stupid, but if he does not ask, he remains forever ignorant." The question is this: If the Müllerian inhibiting factor hypothesis has occupied Dr. Morris's thinking, has he extended this into the area of the woman who has perfect femininity but an absent uterus and vagina and who is XX?

DR. MORRIS (Closing). In reply to Dr. Allen's question, testosterone propionate and other androgenic preparations have been administered in doses up to 1 Gm. or more a month without significant effect. Biopsies of the skin in the pubic area do show the presence of hair follicles. The unilateral absence of vulvar hair in a female carrier reported by Gayral and co-workers suggests, however, that the site of nonaction of androgen is at the end organ.

Dr. Greene raised the question of whether estrogen causes sexual hair growth. I would rather doubt if it does, although Marshall and Harder reported some increase in hair after conjugated estrogen administration. It is possible that the ratio of androgen to estrogen in producing secondary sex effects may make a difference.

Dr. Hertig asked about the type of malignant tumors seen in this syndrome. There was 1 malignant arrhenoblastoma, 1 teratoma, 1 alveolar carcinoma, and 1 sarcoma. Most, however, were classified as seminomas or dysgerminomas. Such names as neuter cell tumor, gonocytoma, and dysgenetic gonadoma have also been suggested. I like the term germinoma because it is simpler than the others.

Dr. Israel's question regarding the relationship of Müllerian inhibiting factor to the absence of the uterus in the female I cannot answer because I have not done any work in this field. It may be a possibility, but this would not explain the frequent concomitant renal malformations.

I am happy to have Dr. Jones's corroborative findings. Unfortunately, we have very little in the way of values in the normal male to compare with the values obtained in this syndrome, especially gonadal vein blood, tissue content, and incubation studies. The male seems to be more reluctant to part with a slice of the gonad than the female.

In retrospect, there are defects in the plan of this study because we anticipated finding a defect in hormone synthesis due to 3β-ol dehydrogenase lack and we did not find it.