WOMEN WITH TESTES—A VARIETY OF MALE PSEUDOHERMAPHRODITISM*

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The condition under discussion is a specific variety of male pseudohermaphroditism, variously known as 'oestrogen-producing testis'[1] or 'testicular feminization'.[2-4] Both these names are fundamentally misleading, for every testis produces oestrogen and no special feminizing substance is secreted by the testis in this condition.

Only recently categorized by Goldberg and Maxwell,[5] and not commonly reported, this is a distinct entity which can and should be confidently diagnosed on clinical grounds, for it is assuming increasing importance as a genetic cause of primary amenorrhoea. In recent years 4 such patients have been studied by the University of Cape Town Endocrine Group.

PATHOGENESIS

In normal embryos the primitive gonads develop from the gonadal ridge, which appears in the fourth week of development. At this stage the gonad consists of a cortex containing the germinal epithelium and a medulla containing the primary sex cords; it is bipotential, i.e. capable of differentiating into testis or ovary. Under the appropriate genetic stimulus, either the medulla dominates and testes develop, or the cellular cortex dominates, leading to ovarian maturation. The subsequent embryogenesis of male or female internal and external sex characters, i.e. Wolffian and Müllerian ducts, follows cephalo-caudally.

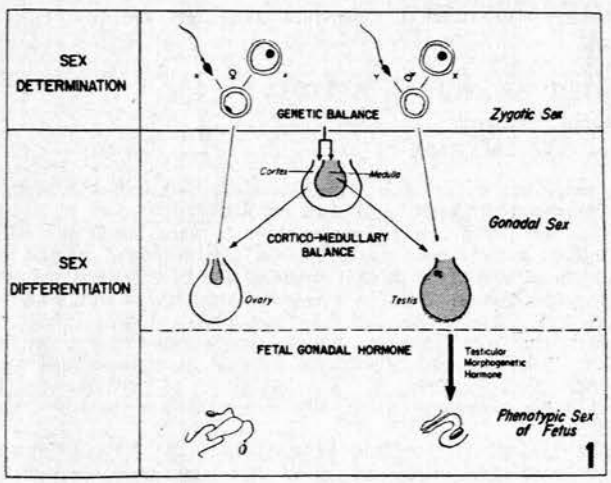

Fig. 1. A concept of sex determination and differentiation. [From Grumbach, M. M. *et al.* (1957): J. Clin. Endocr., **17,** 703.]

The critical period of this differentiation is the 7th - 9th weeks of gestation. This concept is summarized in Fig. 1.

Jost's experiments with intra-uterine castration of rabbit foetuses,[6] and subsequent *in vitro* cultures of rat sex primordia,[7,8] have shown that in the absence of male gonadal stimulus female sex differentiation always occurs.

The testis is thought to secrete a morphogenetic substance which causes male differentiation and, by inference, the ovary probably secretes nothing and sex differentiation is therefore female. Thus women are essentially 'neuter'. The nature of the male morphogenetic substance is unknown, but function may be correlated with the early and remarkable growth of the Leydig cells at this stage of gestation.[9] Its effects, which are on the side of secretion only, are not identical with testosterone which, though causing male development, does not completely suppress the Müllerian duct. Organization of the duct system is completed during the first half of pregnancy, but external genitalia continue to develop after mid-term.

'Testicular feminization', an intersex state, falls into the group of male pseudohermaphrodites (Table I). These patients are thus genetically and chromosomally male (XY),[2,10] and therefore testes develop from the primitive

TABLE I. CLASSIFICATION OF CONGENITAL INTERSEX

1. True hermaphrodites (XX usually)
2. Male pseudohermaphrodites (XY) — genetic males, testes
   (*a*) Simulant female — 'testicular feminization' (Wolffian vestiges)
   (*b*) Ambiguous or male genitalia, with either prominent Wolffian or Müllerian derivatives
3. Female pseudohermaphrodites (XX) — genetic females, ovaries
   (*a*) Adrenal hyperplasia
   (*b*) Maternal causes (progesterone treatment, arrhenoblastoma)
   (*c*) 'Idiopathic'

gonad under the influence of the Y chromosome. It is currently speculated that after testicular development in these patients secretion of morphogenetic substance alters, either qualitatively or quantitatively and subsequent morphogenesis occurs without the specific stimulus. The neuter, i.e. female, form develops.

The stage at which this dysfunction occurs presumably determines the exact admixture of male and female sex characters. Early failure of masculinizing secretion gives rise to complete female development and habitus apart from the presence of a few Wolffian structures such as the epididymis and vas deferens, i.e. women with testes. The testes secrete normal male amounts of oestrogen, which seem to be sufficient to stimulate breast development, at least in the absence of any masculinizing hormone *(vide infra).* It is interesting to compare this concept with that probably operating in gonadal dysgenesis, the most complete form of gonadal failure. Based on the theories of Jost, it is assumed that very early gonadal failure leads to a lack of morphogenetic secretion, followed by complete feminization. In contrast, however, a negligible amount of oestrogen is produced (since no gonadal tissue of any type is present) and this accounts for the poor or absent breast tissue and poor vaginal development.

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PATHOLOGY

Fig. 2 shows the spectrum of genital differentiation in male pseudohermaphrodites, ranging from strikingly female to remarkably male. The group under discussion is depicted by B2 and very occasionally by B1.

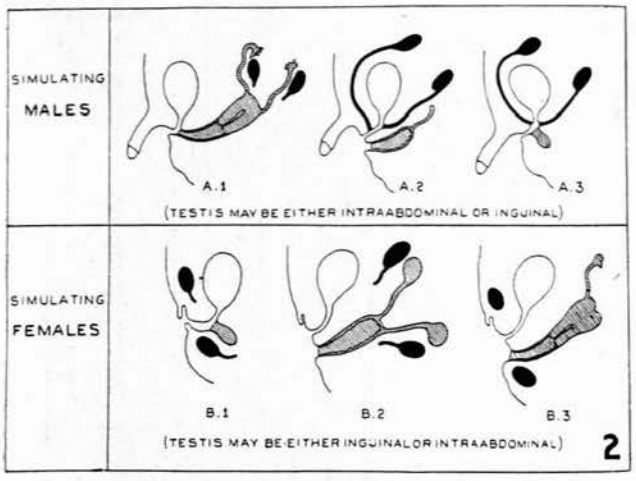

Fig. 2. Range of genital differentiation in male pseudohermaphroditism.
[From Wilkins, L. *et al.* (1955): Pediatrics, **16,** 287.]

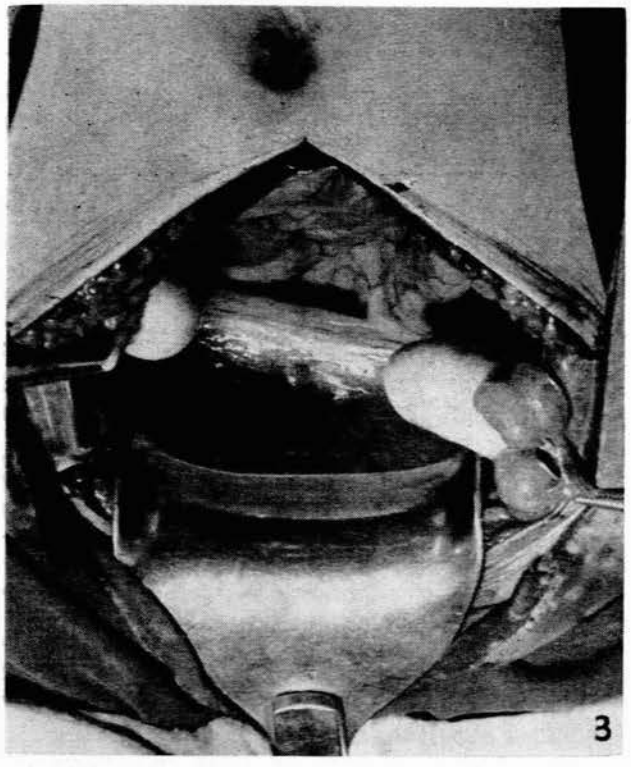

Fig. 3. Laparotomy in a 29-year-old patient with primary amenorrhoea. The gonads, shown to be testes histologically, were linked by a transverse fold of peritoneum. The uterus was absent. Epididymal cysts are present on the left gonad.

Note: (*i*) Sites of testes, which may be labial, inguinal or in the ovarian position.

(*ii*) The relatively normal-sized blind vagina with absence of uterus and tubes, their place being taken by the epididymis and vas deferens.

(*iii*) The normal-sized clitoris and normal urethral opening. However, a urogenital sinus with a very hypoplastic vagina may sometimes occur (B1), and very, very rarely, a hypoplastic uterus may be present (B3).

At laparotomy in a classical case (Fig. 3), a well-marked transverse fold of peritoneum is seen linking the two gonads. The uterus is absent, and epididymal cysts are present on the left gonad.

Characteristic histology (Fig. 4) consists essentially of immature seminiferous tubules, closely packed, and lined by a single layer of Sertoli cells and primitive spermatogonia. Spermatogenesis does not occur. Interstitial (Leydig) cells are usually well developed and interstitial fibrosis is common. Hyalinization of tubules, similar to that seen in

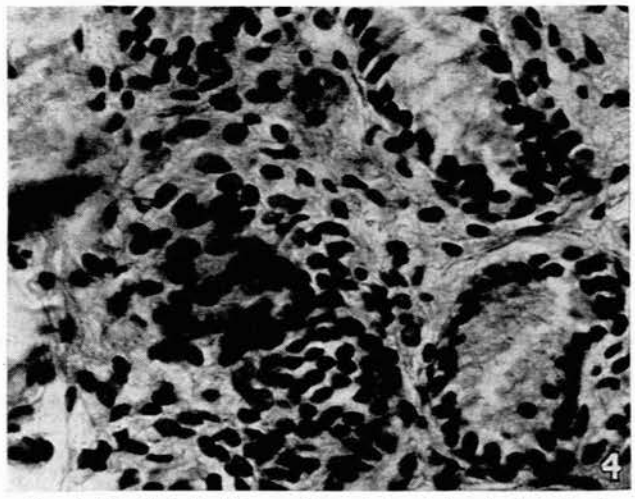

Fig. 4. Typical histology of an intra-abdominal testis in 'testicular feminization'. Seminiferous tubules show no spermatogenesis, and are lined by a single layer of Sertoli cells and spermatogonia only. A large clump of normally developed Leydig cells is present.

Klinefelter's syndrome, occasionally occurs. These are the features associated with immature, sterile cryptorchid testes, with which they share the same high incidence of malignancy. Morris[11] found 7 patients with neoplasia in 82 cases he reviewed.

CLINICAL FEATURES

The condition, although described in the medical literature during the last century, was only recognized and categorized by Goldberg and Maxwell in 1948.[5] Since then, only 130 - 140 cases have been reported, but the incidence is certainly considerably higher than the number of reported cases suggests. In this country, the literature has been reviewed recently by de la Harpe,[1] who added 2 cases of his own.

Patients present classically in 2 ways:

1. In the adult with primary amenorrhoea. Only one of our 4 patients presented with this as a major complaint.

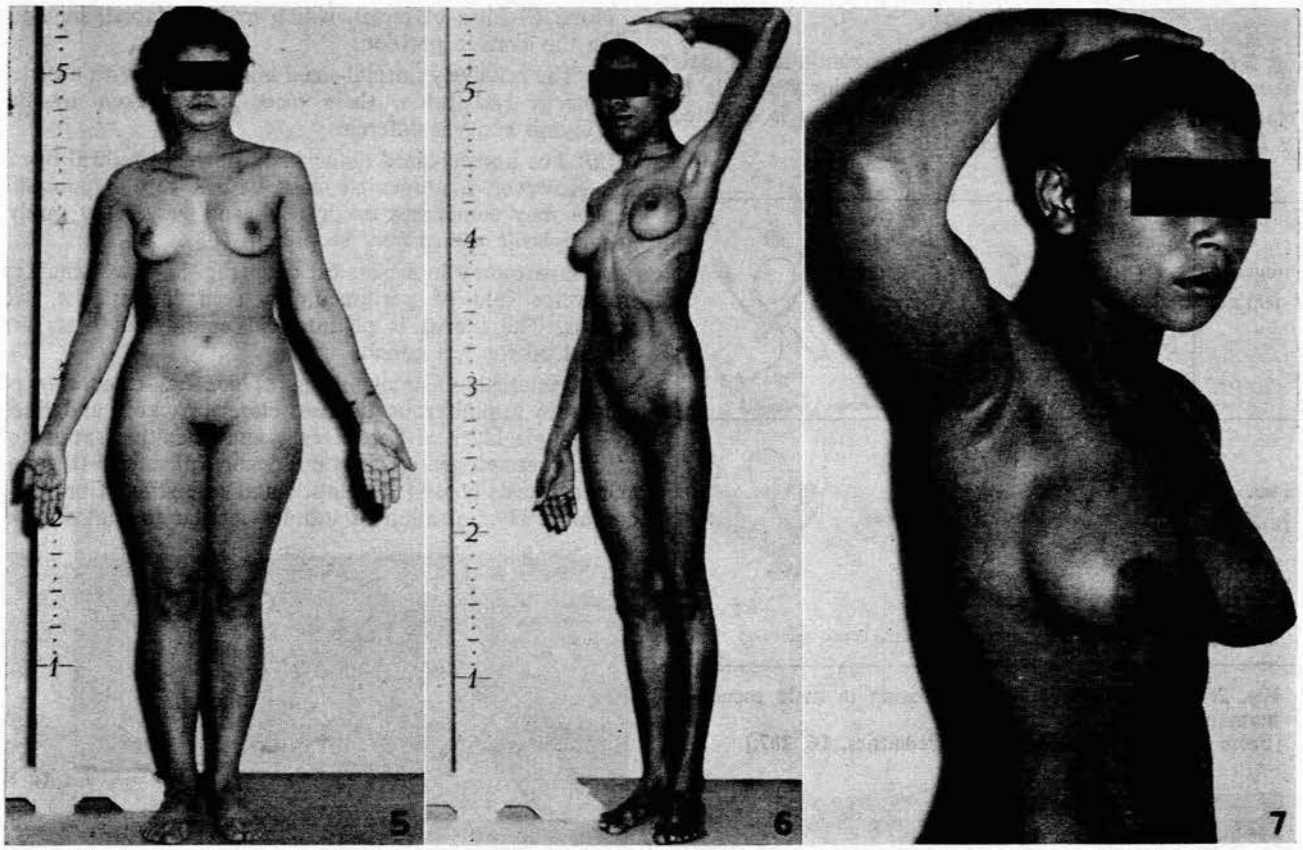

Fig. 5. Male pseudohermaphrodite. The habitus is entirely feminine, and good breast development is present. Pubic hair is absent.
Fig. 6. Male pseudohermaphrodite. Habitus is eunuchoid and breast development is good. Pubic and axillary hair is absent.
Fig. 7. Male pseudohermaphrodite. Axillary hair is absent and breast development is good.

2. With gonads found incidentally in inguinal hernial sacs, or as lumps in the labial area. The remaining 3 of our patients fall into this category.

It should be emphasized at this stage that ovaries never herniate into the lower inguinal canal. The presence of a low inguinal or labial gonad suggests that it is either a testis or ovo-testis.

The habitus is typically feminine (Fig. 5). Occasionally, the proportions are eunuchoid, possibly because of failure of oestrogen secretion (Fig. 6). Good breast development, often with glandular tissue, occurs and puberty is always female. Nipples, however, are usually juvenile. Genitalia are as described earlier, often with hypoplastic labia minora. The clitoris is rarely enlarged. The libido is normal, and psychosexual orientation is entirely feminine. Coitus is generally satisfactory. Pubic hair is usually, and axillary hair always, absent (Figs. 5, 6 and 7); the exact cause of this is not known. Hair follicles are present histologically on the mons veneris,[12,13] yet attempts to stimulate hair growth by local or systemic testosterone have failed — suggesting that the hair follicles show a non-responsiveness to hormonal stimulus, possibly as an associated congenital abnormality. The hairlessness cannot be explained either by pituitary or adrenal underaction.

Grumbach and Barr[3] have described a variant with more masculine differentiation; a hypoplastic phallus with either a urogenital sinus or a male-type urethra. Breasts develop at puberty. Testes are histologically more mature, and even active spermatogenesis sometimes occurs. This variant may occur in families showing the more classical form, but in most families the phenotype is constant.

GENETIC TRANSMISSION

A familial incidence has long been noted,[11] although many cases appear to be isolated. Family histories in the 4 patients studied were negative. In earlier studies of affected families it had been noted that the ratio of the number of females to the sum of the males and affected persons was 1 : 1,[3] so that it was postulated before nuclear sexing that these were genetic males. Patients also show a male incidence of colour blindness, a sex-linked recessive trait.[14] Two of our patients were tested for colour blindness, but were normal.

Published pedigrees[12] show that the disorder is transmitted by healthy mothers, and that only males are affected. This is consistent with either a sex-linked recessive gene or a sex-limited autosomal, dominant gene, but, since the patients are sterile, it is impossible to distinguish between these two modes of inheritance.

LABORATORY ASPECTS

1. *Urinary Pituitary Gonadotrophin Excretion*

This is raised in the vast majority of cases (generally to levels of about 96 mouse-units), but may be normal. Castration causes a further marked rise. All 4 of our patients excreted increased amounts of gonadotrophin. The reason for this is not clear, since normal amounts of circulating oestrogens are present and one would have expected the usual feed-back mechanism to operate.

As in Klinefelter's syndrome (where testicular histology is very similar), absence of spermatogenesis in the presence of Sertoli cells and mature Leydig cells is a striking feature. This would suggest that absence of spermatogenic elements permits a moderate rise in gonadotrophin. The question of whether the spermatogenic cells in health secrete a substance inhibitory to gonadotrophin secretion is an open one. Howard *et al.*[15] postulated the presence of an 'X' hormone produced by the Sertoli cells, which inhibits FSH secretion and possibly the development of gynaecomastia. But this theory seems untenable in view of the findings in the syndrome under discussion.

2. *17-Ketosteroid Excretion*

In only one case in the literature[16] has this been raised. Three of our patients excreted low normal values, which is what is usually described. In one patient, however, excretion was markedly raised to 54 mg. per 24 hours. No explanation can readily be offered since adrenal function was otherwise normal, and there was certainly no clinical evidence of virilization.

3. *Oestrogen Excretion*

Both vaginal cytological studies and the excellent pubertal breast development suggest the presence of oestrogen in adequate amounts. This has been confirmed by biological and chemical assays.[4,17] It is not generally known that the testes are major sources of oestrogens in normal men. Castration causes a drop in urinary oestrogens in normal men[18] and in male pseudohermaphrodites,[4] who in addition rapidly develop menopausal symptoms. Oestrogen has actually been recovered from human testes.[19] In 'women with testes', no increase in oestrogen output has been noted, so the term 'oestrogen-producing testes' conveys nothing very startling, and 'testicular feminization' is actually a misnomer.

The actual site of oestrogen production has caused much controversy. Sertoli-cell tumours in dogs[20,21] and man,[22] have been reported with associated feminization. However, parenteral chorionic gonadotrophin, shown specifically to stimulate interstitial cells,[4,23] caused a great increase in urinary oestrogen output in a patient with 'testicular feminization' recently reported by Salassa *et al.*,[24] while the adrenals were being suppressed by dexamethasone. This fact, and the high oestrogen content of the testes of the foetal horse,[25] which are composed predominantly of massive aggregates of interstitial cells, suggest that the interstitial cells are the source of testicular oestrogen.

The cause of the feminization thus appears to be a lack of male gonadal morphogenetic substance rather than the positive presence of oestrogen. The fact that oestrogen causes breast development in these cases and that the same levels do not do so in the normal male, suggests that the level of circulating androgen may be a factor in the response of this end-organ to oestrogen.[3,26] Androgen output, though, as measured by the 17-ketosteroid excretion, is rarely deficient, so that a qualitative factor may be important.

4. *Other Investigations*

Other endocrine investigations were unremarkable in our 4 patients. All had male nuclear sex, 3 had normal 17-hydroxycorticoid output. One patient showed insulin sensitivity, and a poor eosinophil drop after 40 units of ACTH intravenously, suggesting a hypoadrenal state. Water load was normal. This is of interest in view of the 3 patients with 'testicular feminization' associated with adrenal hyperplasia and hypofunction reported by Prader and Gurtner,[27] but these all occurred in infants and had a fatal outcome.

DIAGNOSIS

Gonads which have prolapsed into a hernial sac in a female child should suggest the condition, and an associated blind vagina with absent uterus is almost diagnostic. In adults, the last two features together with primary amenorrhoea, absence of sex hair, and good breast development, are conclusive. Confirmation is provided by male nuclear sexing, increased urinary gonadotrophin excretion and, finally, gonadal biopsy.

The only condition likely to give rise to diagnostic confusion in the adult is gonadal dysgenesis, which can occur without associated congenital abnormalities, without shortness, and with good breast development and even evidence of oestrogenization.[28,29] Both may have complete lack of body hair and 'male' nuclear sex. An important clue is the inevitable presence of cervix and uterus in gonadal dysgenesis, while laparotomy and chromosomal analysis give the final answer.

In children, atypical forms of this condition, associated with clitoral enlargement, may be confused with other varieties of male pseudohermaphroditism, the adrenogenital syndrome, and true hermaphroditism. Other types of male pseudohermaphroditism will have greater anatomical evidence of 'maleness' on examination. The adrenogenital syndrome is suggested by active virilization, the presence of a uterus, a raised 17-ketosteroid excretion, and female nuclear sexing. The distinction between 'women with testes' and true hermaphroditism may be extremely difficult, though there is usually ample evidence of sexual ambiguity in true hermaphrodites. In certain cases laparotomy may be necessary to demonstrate this.

MANAGEMENT

These patients are physically (at least outwardly) and psychosexually females, and no hints as to possible ambivalence should be made. They should be warned to expect neither menstruation nor conception.

Because of the strong tendency to malignant change after puberty (8%), most authorities feel that gonadectomy should be proceeded with at that stage and adequate oestrogen replacement instituted.[5,11] Some authors[12,30] prefer to leave an organ that is actively secreting an essential hormone and have argued against this procedure.

SUMMARY

A distinct variety of male pseudohermaphroditism, erroneously known as testicular feminization, is reviewed. Embryogenesis is discussed and the aetiological concept of lack of appropriate androgenic stimulus rather than oestrogen excess is elaborated. Clinical, pathological and laboratory features are mentioned, with some reference to 4 personal cases. The importance of this condition as a genetic cause of primary amenorrhoea is stressed. The paucity of sex hair is thought to be an associated anomaly.

The site of testicular oestrogen production is discussed. Finally, a therapeutic bias of most authorities in favour of gonadectomy at puberty with oestrogen replacement is reported.

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