The XY female

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OVER 150 years ago Steglehner (1817) described the first case of an apparently normal woman with undescended testes. Since that time numerous reports and reviews of genetic males with a female phenotype have appeared in the literature. Various names and classifications have been applied to these individuals — male pseudohermaphroditism, testicular feminization (Morris, 1953), Lubs' syndrome (Lubs et al, 1959), Reifenstein's syndrome (Reifenstein, 1947), incomplete androgen insensitivity (Morris and Mahesh, 1963), and most recently familial incomplete male pseudohermaphroditism types 1 and 2 (Wilson et al, 1974). These terms have been useful in their time but as they have multiplied they have only served to confuse the situation.

There is no single criterion of an individual's sex. In the normal female the chromosomal sex is 46XX, the gonadal sex is ovarian, and the genital sex is characterized by the presence of a vulva, a vagina, a uterus, and fallopian tubes. Our concern here, however, is with those patients whose chromosomal sex is not XX but XY although their genital organs and habitus are wholly or predominantly female. This group embraces all the syndromes mentioned above and we have designated it simply "the XY female" because in our view this is the most satisfactory term for general use. Our purpose in this paper is to indicate clearly the different conditions that give rise to the XY female, to discuss their aetiology, and to outline their management.

Normal sexual differentiation

Without some knowledge of the normal sexual differentiation of the embryo it is impossible to understand the various abnormalities that occur in the XY female. Biologically there are two important interrelationships: the first concerns the connection between the sex-chromosome constitution of the zygote and the nature of the gonad, and the second the influence of that gonad on the development of the other genital organs.

Following fertilization, if an X and one or more Y chromosomes are present the primitive gonads differentiate into testes. In a normal male there is only a single X and a single Y chromosome, but even if there is more than one X or Y chromosome the presence of a Y component results in testicular development. If there is no Y chromosome but two X chromosomes, the primitive gonads develop into ovaries. A single X chromosome in the karyotype allows the gonadal analogues to begin to differentiate as ovaries (Singh and Carr, 1966), but these soon atrophy and become streaks of fibrous tissue. Cells that have only a single Y chromosome are not viable. Thus sex chromosomes are important in so far as they determine gonadal sex, but once this has been ascertained they have no further function.

Normal testicular formation results in the production of two critical substances — androgens and müllerian inhibitor (Jost, 1971). Androgens cause the development of primitive wolffian structures into epididymides, vasa deferentia, seminal vesicles, and so on, and they also masculinize the indifferent external genitalia. Müllerian inhibitor (although it has not yet been isolated its existence is supported both clinically and experimentally) prevents the growth of primitive müllerian structures which if uninhibited develop into the vagina, uterus, and fallopian tubes.

Thus the normal development of male genital organs is brought about by normally functioning testes. If during the first 12 weeks of embryonic life there are no testes, the testes do not function properly, or the metabolic products are not utilized, the genital organs develop as the female phenotype. The presence or absence of ovaries is, however, immaterial to the development of genital organs and the female can be considered biologically as a non-masculinized individual.

Androgen synthesis and utilization

The synthesis and utilization of androgens are critical to the development of the male external and internal genitalia. Testosterone is formed from cholesterol through two basic pathways (**Fig. 1**), one via 17-hydroxypregnenolone and the other via progesterone. Both of these metabolic chains require enzyme action in order to produce the required androgens, especially testosterone, for complete masculinization. Testosterone is then converted to dihydrotestosterone by the action of the enzyme 5-alpha reductase in the target cells of the responsive tissues (Bruchovsky and Wilson, 1968).

Recently intracellular events have been studied more intensively and it has been shown that steroid target organs contain receptor sites for a specific steroid to which they respond (Liao and Fang, 1969). The receptor for testosterone is a protein located in the cytosol, that is the extranuclear fluid compartment of the cell. The combination of dihydrotestosterone and the receptor is stable and this complex is transferred to the cell nucleus which then allows gene activation with resultant synthesis of RNA (Fang et al, 1969). Although simplified greatly, testosterone utilization can be thought of as occurring in three steps: formation, conversion to active dihydrotestosterone, and finally cytosol binding and nuclear activation.

Classification of the XY female

An XY individual may develop a female phenotype for two reasons:

1. Failure of androgen production
2. Failure of androgen utilization.

The first may result from an anatomical failure of testicular development producing gonads that are rudimentary or useless streaks of tissue (anatomical testicular failure). Alternatively there may be an enzymatic failure of androgen production by normally formed testes (ineffectual androgen biosynthesis).

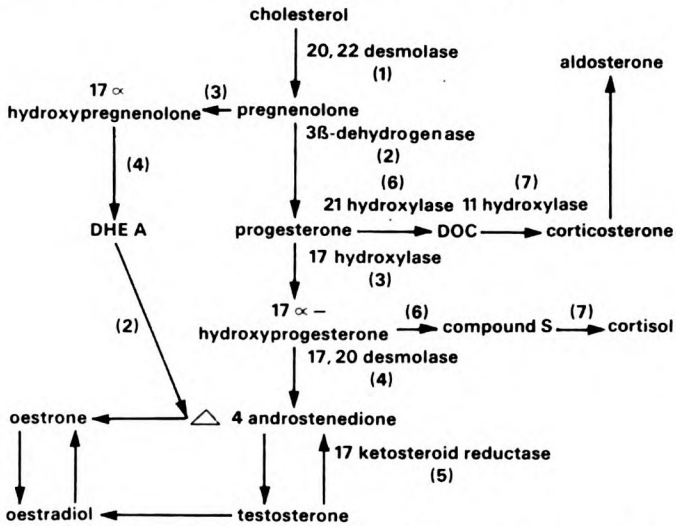


Fig. 1. *Two pathways for the biosynthesis of testosterone. The numbers in brackets indicate special enzyme action.*

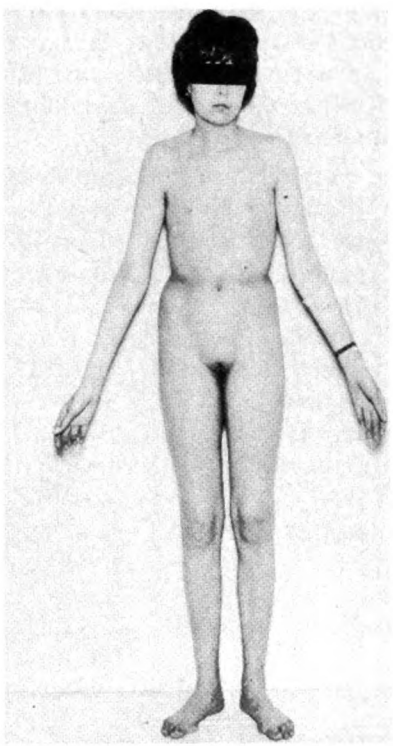
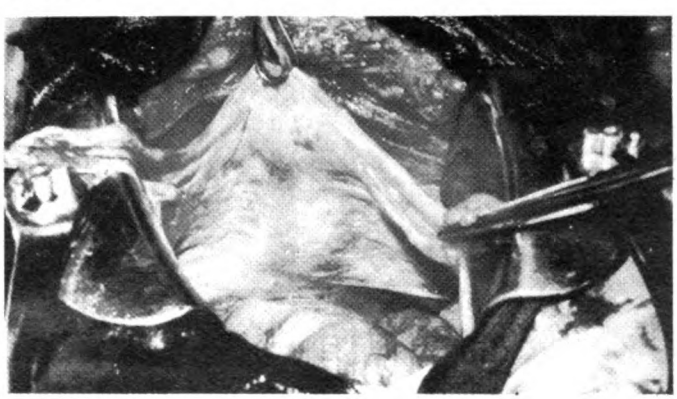


Fig. 2. a (right) *The external appearance of an XY female due to complete anatomical testicular failure.*
b (below) *The internal genitalia showing the uterus and two fallopian tubes; the gonads are represented by two useless streaks of tissue.*



The second is as yet of uncertain aetiology although, as will be seen presently, evidence of a possible mode of action is emerging. Clinically the condition is best recognized as the syndrome of androgen insensitivity formerly known as testicular feminization.

It is most important to appreciate that each of these conditions can occur in a complete or an incomplete form. It is the incomplete forms that have hitherto caused such confusion and have been referred to by the general but inaccurate term of "incomplete testicular feminization". For clarity we shall describe the complete forms before dealing with the incomplete ones.

Anatomical testicular failure

Anatomical testicular failure gives rise to the simplest form of the XY female which is sometimes known as pure gonadal dysgenesis (**Fig. 2a**). After the formation of an XY zygote there is complete failure of testicular formation and development so that neither androgens *nor* Müllerian inhibitor are produced. These deficiencies result in non-masculinization of the external genitalia and non-supression of the müllerian system so that the genitalia consist of a vulva, a vagina, a uterus, and fallopian tubes (**Fig. 2b**). All that remains of the gonad is a fibrous streak of connective tissue.

The cause of this abnormality is difficult to determine. It may occasionally be chromosomal, such as in a 45 X/46 XY mosaic, or due to a structural defect, for example loss of part of the Y chromosome. Usually, however, there is no recognizable chromosomal fault and the possible aetiologies to consider are loss of testicular differentiating genes from the fertilizing Y chromosome (Dewhurst, 1971), a vascular lesion of the genital ridge, and even infection.

An affected girl usually grows quite normally and the condition is unrecognized until puberty when secondary sexual characteristics do not appear. Physical examination, buccal smear, and chromosome analysis usually confirm the diagnosis. The distinguishing clinical features are failure of secondary sexual development and the presence of a uterus.

Failure of androgen biosynthesis

As already indicated the biosynthesis of testosterone involves a number of enzymatic processes. Defects have been reported in all of the following: 20-22 desmolase (Camacho et al, 1968), 17α-hydroxylase (New, 1970), 3β-hydroxysteroid dehydrogenase (Zachmann et al, 1970), 17 keto-steroid reductase (Saez et al, 1972), and 17-20 desmolase (Zachmann et

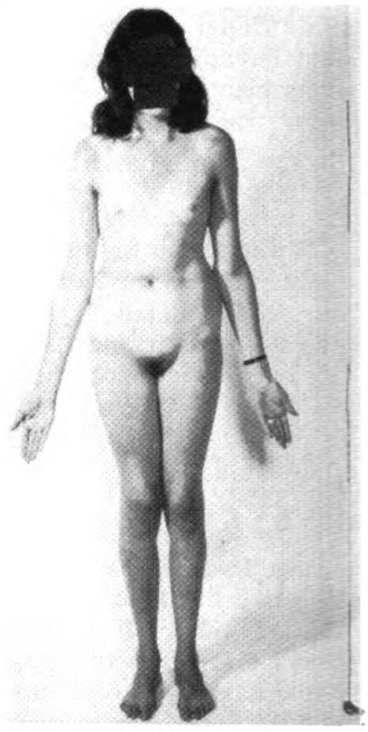


Fig. 3. *An XY female with enzymatic failure of testosterone biosynthesis. The testes are normally formed and lying in the groin. The degree of breast development seen is spontaneous. Plasma testosterone values were in the low normal female range and showed no increase following stimulation with human chorionic gonadotrophin.*

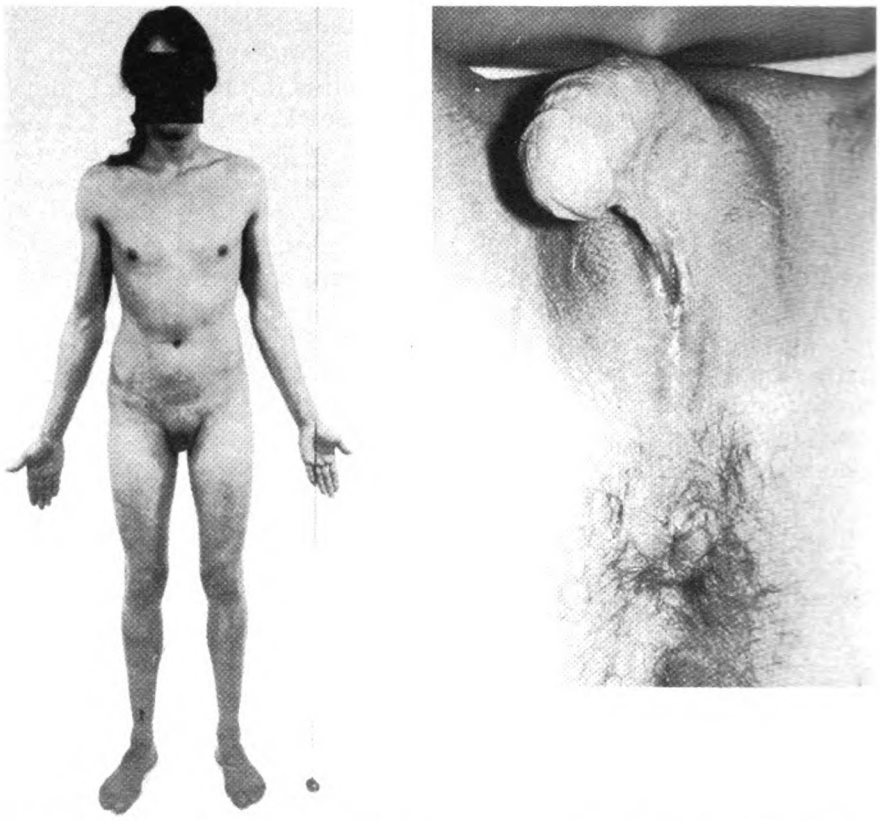


Fig. 4. left *Body configuration and* **right** *external genital appearance in an XY female with partial enzymatic failure of testosterone biosynthesis. The testes are well formed but plasma testosterone is in the normal female range.*

al, 1972; Wilson et al, 1974; **Fig. 1**). These result in absent or more often incomplete masculinization in an XY individual (**Figs 3** and **4**).

This is not a clearly defined group of conditions. The clinical features may vary with the precise defect and whether it is a complete or partial one, but the uterus is always absent since there is no failure of müllerian inhibitor formation. In general the degree of non-masculinization depends mainly on the partial or complete nature of whatever defect is present, while the extent of female secondary development depends upon the possibility of conversion of testosterone precursors to oestrogen. Complete feminization due to total failure of androgen biosynthesis is less common than incomplete forms which are discussed later.

Diagnosis is not easy. The male genetic sex is easily established by buccal smear and chromosome analysis. The demonstration of an enzyme fault and its precise nature is more difficult and is carried out by stimulating the gonads with human chorionic gonadotrophin (HCG) and determining the response in terms of testosterone or its individual precursors.

Androgen insensitivity

This condition was initially described by Morris (1953). Classically the patients have a female phenotype, feminine habitus, and good breast development (**Fig. 5**). The external genitalia have a tendency to underdevelopment of the labia and there is a short blind vagina. Pubic and axillary hair is absent or scanty. No female internal genitalia are present and the gonads which are histologically similar to undescended testes may be located within the abdomen, in the inguinal region, or in the labia. Other features are that the breasts, although often large, have small juvenile nipples and lack abundant glandular tissue; the stature may be eunuchoid with long extremities; the hands and feet may be large; and the height may be above average.

These patients have an XY karotype. The condition is transmitted through the maternal line and it is believed to be either a sex-limited autosomal dominant abnormality or an X-linked recessive abnormality. For this reason there is a strong familial tendency and seeming sisters of an affected individual have a one in four chance of also being examples of this condition. The prevalence of the disorder has been estimated to be between one in 62 400 (Jagiello and Atwell, 1962) and one in 2000 (Hauser, 1961). The mothers of these patients are usually normal but some authors suggest that they have decreased axillary and pubic hair (Mishell, 1938) or had a late menarche (Beatty et al, 1953).

Because of the strong familial trait the diagnosis may be made early in life if there is an elder affected sister. Sometimes the repair of an inguinal hernia in a young girl reveals unexpectedly a testis in the hernial sac. However, the condition is usually diagnosed after puberty when failure to menstruate is investigated.

The aetiology of this condition has interested many workers but credit for the hypothesis of insensitivity to androgens must be given to Wilkins (1957). Plasma testosterone levels in peripheral blood are within (French et al, 1965) or above (Judd et al, 1972) the normal male range. Castration causes a significant decrease in circulating testosterone (Southern, 1965) and oestrogen excretion also falls (Perez-Palacios and Jaffe, 1972). Oestrogen levels in spermatic vein samples have been shown to be higher than those in normal men and higher than those in peripheral venous samples (Saez et al, 1972). Exogenous testosterone fails to stimulate protein anabolism or cause masculinization (Volpé et al, 1968). Dihydrotestosterone is also inactive (Strickland and French, 1969) although plasma levels are reported as falling within the normal male range.

These observations suggest that the gonads of such patients are normally functioning testes but the end organs are incapable of response. However, since the

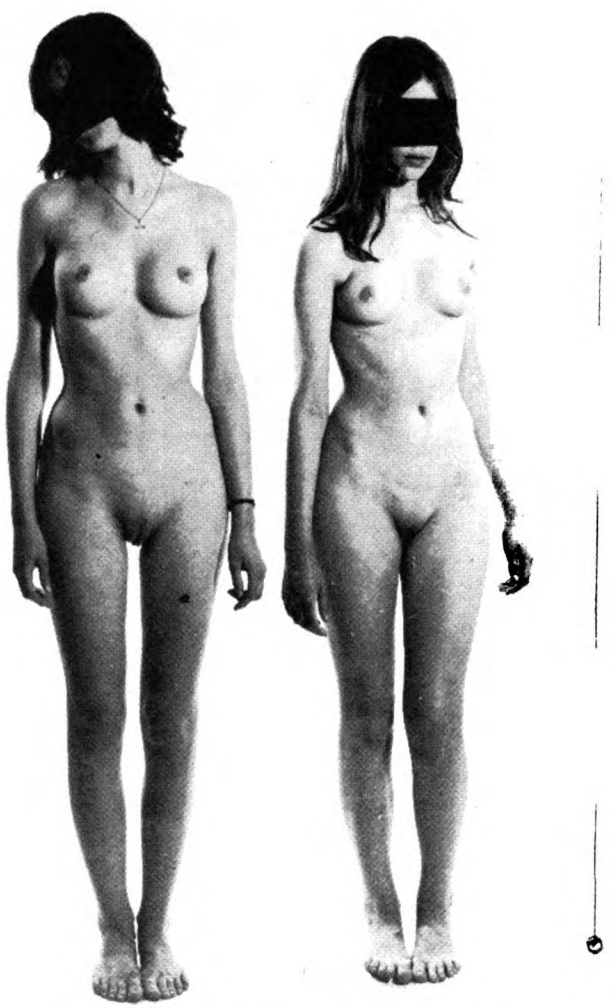
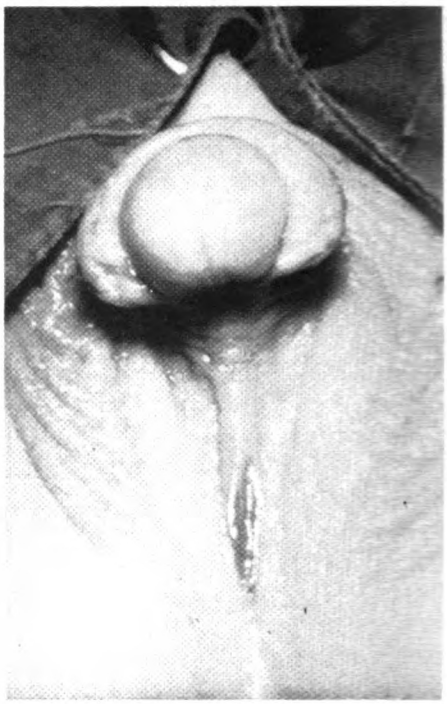


Fig. 5. *Sisters with complete androgen insensitivity. The clinical features are typical of this condition and plasma testosterone values are within the normal male range.*

Fig. 6a. *The external genitalia of an XY-phenotypic female with partial anatomical testicular failure.*



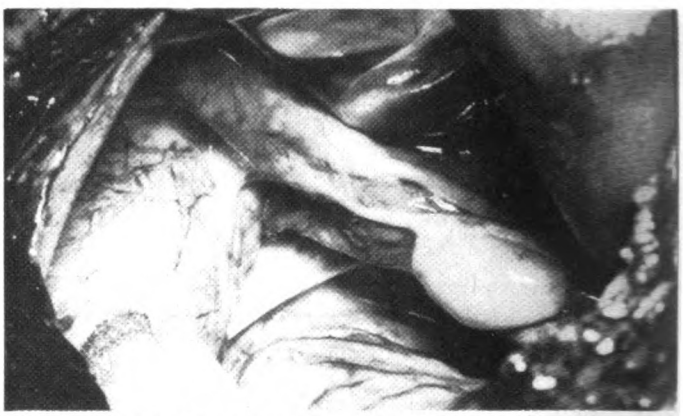


Fig. 6b. *The right lateral pelvic wall showing an abdominal testis above which is a fallopian tube that leads to a tiny uterus. No second gonad was present.*

upper vagina, uterus, and fallopian tubes are absent müllerian inhibitor formation must be normal.

The exact nature of the defect has not been established with certainty. It was thought that the fault was a failure to convert testosterone to dihydrotestosterone but recent work appears to disprove this (Wilson, 1972; Dewhurst, 1974). Animal experiments in the rat and mouse (Bullock and Bardin, 1972) suggest that the end-organ defect is due to an absence or deficiency of the cytosol receptor mechanism. The lack of an effective receptor for dihydrotestosterone would then result in failure of gene transcription and thus androgen inaction. Support for this theory was provided by Keenan et al (1974) who found no appreciable dihydrotestosterone binding in cultured skin fibroblasts from patients with androgen insensitivity. Further work is awaited before this aetiological explanation can be fully accepted.

Diagnosis in these patients is usually easy. The important features are good breast development, lack of sexual hair, and a short blind vagina; the gonads are often palpable in the inguinal canals. The chromatin-negative buccal smear and XY karyotype on chromosome analysis of peripheral blood complete the diagnostic picture.

Incomplete forms

The broad term "incomplete testicular feminization" has been used to describe individuals with some features of the classic syndrome of androgen insensitivity (Morris and Mahesh, 1963) and others which are atypical. As already indicated, these forms constitute a spectrum of varying degrees of different conditions (**Figs 4, 6, and 7**). Most patients, however, have some evidence of virilization. This may be minimal, as in the patients reported by Lubs et al (1959), or more pronounced, as in those described by Gilbert-Dreyfus et al (1957) and Reifenstein (1947). The phenotypes of these genetic males and the natures of the wolffian derivatives depend on the quality and quantity of the androgens produced and on the sensitivity of the end-organs. The nature of the müllerian system is due to the presence or absence of müllerian inhibitor.

Inheritance

All forms of XY female show some familial inheritance. Androgen synthesis defects are reported as resulting from an autosomal recessive trait (Wilson et al, 1974). In its complete form androgen insensitivity appears to be either X-linked and recessive or sex-limited and autosomal dominant: further clarification is not possible as these patients are infertile. Walsh et al (1974) reported that two incomplete forms of androgen insensitivity can be detected, each having a different pattern of inheritance. They describe type 1 as an apparently X-linked recessive trait and type 2 as an autosomal recessive trait. These workers conclude that the syndromes previously described by Reifenstein (1947), Lubs et al (1959), and Gilbert-Dreyfus et al (1957) among others are due to partial defects of androgen utilization.

The inheritance of anatomical testicular failure is not yet determined. Indeed, the majority of cases appear to be sporadic although Espiner et al (1970) reported five patients with the complete syndrome in three generations of the same family. This condition has also been reported in sisters by Cohen and Shaw (1965) and Brøgger and Strand (1965), and in twins by Frasier et al (1964). Of special interest is a report by Barr et al (1967) of two "sisters" with complete and incomplete anatomical testicular failure.

Management

The management of the XY female patient is influenced by four important considerations.

First, if the external genitalia are wholly or predominantly female, the mode of upbringing must be female also. Only in those incomplete forms in which there are significant degrees of masculinization, such as several reported by Reifenstein (1947), can the manner of upbringing be male.

Secondly, if the female role is chosen and a degree of external masculinization is present, removal of the gonads during childhood is indicated. The precise aetiology of the condition is unimportant; either there will be a partial tissue sensitivity to androgens produced in normal amounts or there will be normal tissue sensitivity to androgens produced in reduced

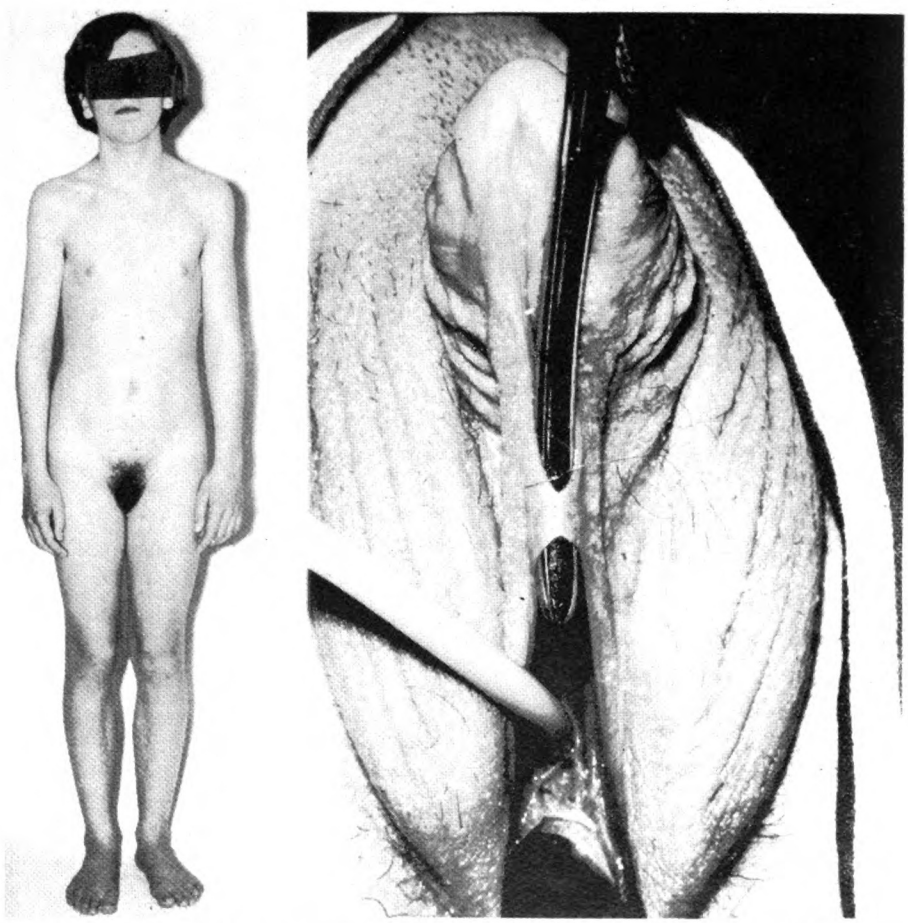


Fig. 7. left *Body configuration and* **right** *external genital appearance in an XY female with partial androgen insensitivity. The plasma testosterone level is well within the normal male range and the testes are well formed. The opening of a short blind vagina is seen in the lower part of the picture.*

amounts. In both cases the secondary changes at puberty are likely to be masculine and to allow such changes to occur in a child being reared in the female role can have disastrous psychological repercussions.

Thirdly, the liability of the gonads to malignant change must be borne in mind. This possibility is almost certainly different in the various conditions described here. When testes are rudimentary or streaks it may be 30 per cent (Barr et al, 1967; Dewhurst et al, 1971) or so. If testicular development is normal or near normal, as in androgen insensitivity or biosynthetic defects in testosterone production, the malignancy risk may be lower; Jones and Scott (1971) and Dewhurst et al (1971) suggest that an incidence of 5 per cent is probably realistic.

Fourthly, one must consider the need for oestrogen therapy whenever secondary feminization is inadequate, or after gonadal removal in patients whose secondary feminization has been satisfactory. It is best given on a monthly basis. An oestrogen such as ethinyloestradiol 0.02 mg or conjugated equine oestrogen (Premarin) 1.25 mg is given for the first 24 days of each calendar month. It is accompanied from day 20—24 by a progestogen such as norethisterone 5 mg daily which gives the satisfactory withdrawal period, promotes or maintains breast growth, and is a convenient aid to the memory.

Specifically, patients with anatomical testicular failure require replacement therapy when the diagnosis is made, usually around 11, 12, or 13 years of age. Gonadal streak removal can be performed whenever it is convenient but the earlier the better as a rule. Patients with complete androgen insensitivity can be allowed to complete their sexual development so long as one is certain that there will be no heterosexual component. Following the completion of breast development the testes can be removed as soon as is convenient. Replacement therapy avoids the menopausal symptoms which otherwise often occur and prevents atrophy of the secondary sexual characteristics. As already indicated, incomplete forms of whatever aetiology require immediate surgical removal of the testes to avoid further virilization; the patient usually requires reconstruction of the external genitalia (Dewhurst and Gordon, 1969; Jones and Scott, 1971) and replacement oestrogen therapy is again essential.

Psychological implications

As in all cases of uncertain sex, patients are best managed by a thorough investigation of their chromosomal, gonadal, and genital sex, and of their psychological orientation to the sex of rearing (Money et al, 1955). In the XY female patients discussed here, the psychological orientation and sex of rearing are almost invariably female and they should be thought of as females. They should at no time be told of the true nature of their chromosomes or gonads and the latter must be referred to as "poorly developed ovaries", never as testes. This is of cardinal impo tance. Unthinking needless disclosures can disastrous. Wherever possible everything must done to reinforce the female role.

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