The incomplete male

During the last 20 years a great deal has been learned about the aetiology and management of intersex states. In particular, the importance of congenital adrenal hyperplasia as a cause of female pseudohermaphroditism has become widely recognised. Cytogenetic methods have clarified the cause of the genital anomalies associated with sex chromosome abnormalities and while techniques such as banding and Y-fluorescence have failed to define the aetiology of true hermaphroditism, this has not generally interfered with correct clinical management. However, the investigation and management of patients with a male chromosomal complement but incomplete masculinisation of the external genitalia (male pseudohermaphroditism) remain among the most intriguing and difficult aspects of paediatric endocrinology.

Male intersexuality represents a disturbance of the normal process of fetal sexual differentiation and is characterised by genital ambiguity and deficient masculinisation at puberty. In his classical experiments with gonadectomy in fetal rabbits, Jost¹ showed that the mammalian embryo has an inherent tendency to develop as a female. The development of the male phenotype is more complex than that of the female and depends on the differentiation and action of the fetal testis. Human testicular differentiation appears to be controlled by the Y chromosome. At a critical period in fetal life (10-18 weeks after fertilisation) the testicular Leydig cells secrete testosterone which directly stimulates the formation of the internal genitalia (the vas deferens, epididymis, and seminal vesicles) from the Wolffian ducts. The external genitalia are masculinised by dihydrotestosterone which is derived from testosterone by the action of the enzyme 5- α -reductase. A second testicular hormone known as muellerian inhibiting factor, a polypeptide, is secreted during the same period by the Sertoli cells and causes suppression of the female muellerian ducts.²

The aetiology of male intersexuality may be divided into three basic categories³ (Table). These are abnormal testicular differentiation, abnormal testicular function, and target organ unresponsiveness to androgen.

Abnormal testicular differentiation

This may result from a defect of the testis-determining genes on the short arm of the Y chromosome, or from

Table *Aetiological categories of male intersexuality*

Abnormal testicular differentiation
Defect of the Y chromosome
Leydig cell hypoplasia
Abnormal testicular function
Gonadotrophin deficiency
Dysmorphic syndromes (Smith-Lemli-Opitz)
Disorders of testosterone biosynthesis
Target organ unresponsiveness to androgen
Androgen receptor defects
5 α -reductase deficiency

a reduction in the XY cell line in the fetal gonad. The testes are dysgenetic and both Leydig and Sertoli cell functions are affected causing incomplete masculinisation and persistence of the muellerian structures. Inadequate masculinisation may also result from primary Leydig cell hypoplasia.⁴

Abnormal testicular function

This is most commonly due to the congenital deficiency of one of the enzymes involved in the different steps of testosterone biosynthesis. The enzymes normally participating in this pathway are, 20-22 desmolase,⁵ 3- β -hydroxydehydrogenase,⁶ 17 α -hydroxylase,⁷ 17-20 desmolase,⁸ and 17-ketosteroid reductase.⁹ These enzyme deficiencies which usually occur both in gonads and adrenals, are becoming increasingly recognised as causes of male intersexuality. Muellerian suppression is unaffected and the degree of genital ambiguity usually reflects the severity of the enzyme defect. The presence of salt-loss (in 20-22 desmolase and 3- β -hydroxydehydrogenase deficiencies) or hypertension (in 17 α -hydroxylase deficiency) may provide a clinical clue to one of these disorders. In general, however, fairly sophisticated biochemical techniques, coupled with the measurement of testosterone and its precursor hormones before and after HCG stimulation of the prepubertal testis, are necessary to characterise fully the enzyme deficiency.

Another potential cause of abnormal testicular function is impaired fetal gonadotrophin production. Prader¹⁰ reported a child with a male karyotype and female genitalia who was found to have LH deficiency. This mechanism may also contribute to the poor virilisation in some dysmorphic states such as the Smith-Lemli-Opitz syndrome.

Androgen target organ unresponsiveness

The third aetiological category accounts for most cases of male intersexuality. Included in this category are complete and incomplete testicular feminisation, and deficiency of the enzyme 5- α -reductase. The androgenic action of testosterone and dihydrotestosterone is normally initiated by the binding of the steroid to a specific cytoplasmic receptor protein. The androgen receptor is under the control of a gene or set of genes on the X chromosome.¹¹ In testicular feminisation there is thought to be a mutation of one such gene leading to a lack of androgen binding. *In vitro* receptor studies¹² have demonstrated impaired dihydrotestosterone binding in fibroblasts cultured from the perineal skin of patients with this form of androgen unresponsiveness. In complete testicular feminisation the phenotype is totally female and the affected subjects are brought up as girls. Incomplete testicular feminisation¹³ is presumably due to a partial defect¹⁴ at the receptor level, the genetics of which are not clear. These subjects have a varying degree of fetal masculinisation and some virilisation at puberty, usually with breast development. The clinical syndromes of Reifenstein, Lubs, and Gilbert-Dryfus are now also thought to be examples of a partial receptor defect.¹⁵ They emphasise the clinical heterogeneity of this aetiological category.

Adult patients with androgen insensitivity have a characteristic hormonal profile. There is simultaneous increase in plasma androgen and LH concentrations, indicating a disturbance of the negative feedback control of pituitary gonadotrophin secretion. This profile normally manifests itself only at puberty¹⁶ and is therefore of limited diagnostic value. However there is some evidence that markedly raised levels of both androgens and LH during the first 6 months of life—when the pituitary axis is particularly active—may indicate a receptor defect and hence predict a future defect in pubertal masculinisation.

Deficiency of the enzyme 5- α -reductase is a recently established disorder and was first described in 1974 by Imperato-McGinley *et al.*^{17,18} who reported 24 cases of male intersexuality in an isolated community in the Dominican Republic. These patients were shown to have impaired conversion of circulating testosterone to dihydrotestosterone and an inherited deficiency of 5- α -reductase was suggested as the primary abnormality. The external genitalia in the prepubertal subjects were essentially female but normal male internal genitalia were present. At puberty there was marked penile growth with male gender identity and normal spermatogenesis. Walsh *et al.*¹⁹ described a similar patient

in whom they demonstrated an absence of dihydrotestosterone formation in genital skin, although the concentration of circulating dihydrotestosterone was normal. In the short report on page 751, Greene *et al.* report a further case of 5- α -reductase deficiency. It therefore appears that decreased conversion of testosterone to dihydrotestosterone, or deficiency of 5- α -reductase in external genital tissues, causes a form of male intersexuality which is characterised by the lack of fetal masculinisation of the external genitalia which are dihydrotestosterone dependent. This contrasts with the normal formation of the internal genitalia and normal pubertal virilisation which are brought about by testosterone itself.

The wide variety of causes of male intersexuality may make it difficult to decide on the most appropriate gender for some males born with genital ambiguity. The choice of sex may be made more difficult by the impossibility of predicting the degree of masculinisation and penile growth at puberty. Yet, for successful gender identification it is important that the decision whether the child should be reared as a boy or a girl is made as soon after birth as possible.

Generally, there is normal tissue responsiveness to androgens in those cases which are due to defective testicular function in fetal life, and masculinisation may be anticipated as a result of androgen therapy in adolescence. In contrast, normal testosterone and dihydrotestosterone secretion after HCG²⁰ suggests that the genital defect is due to tissue unresponsiveness. Pubertal masculinisation in this group is much less certain and the presence of a small phallus may make the choice of female gender preferable. There is an urgent need for an *in vitro* test to quantitate androgen responsiveness in the prepubertal child. Evain *et al.*²¹ recently showed that the dihydrotestosterone cytoplasmic receptor may be measured directly from the analysis of a fragment of perineal skin. This technique however is still being developed and is not generally available for clinical use.

In doubtful cases there is a place for an early trial of testosterone therapy before the final decision on the most appropriate gender for the child is made. Appreciable growth of the phallus after 3 injections of depot testosterone (25–50 mg), at monthly intervals, suggests that further virilisation will occur at the time of puberty, either as a result of endogenous androgen secretion or further testosterone therapy. This penile growth also has the advantage of simplifying any subsequent operation for correction of chordee and repair of hypospadias. Cases which show a very poor response to testosterone, or which have no appreciable erectile tissue in the phallus, may fare better as girls.

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