INTERSEX DISORDERS IN THE NEWBORN
A Brief Summary of Current Views*

by

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“When a woman gives birth to an infant
that has no well marked sex,
calamity and affliction will seize upon the land,
the master of the house will have no happiness”.

Babylonian tablet. 1,700 B.C. (Ballantyne, 1894)

FEW congenital abnormalities can be so distressing for parents than the discovery
of ambiguous genitalia in their newborn infant. Intersex is the term used to
describe such patients, of which there are 3 groups: —

1. **The Female Pseudohermaphrodite** who has normal ovaries, but masculinized
external genitalia;

2. **The Male Pseudohermaphrodite** who despite testicular tissue, has external
genitalia which are incompletely masculinized, or even completely feminized, and

3. **The True Hermaphrodite** in whom gonadal tissue of both sexes is associated
with varying degrees of masculinization of the external genitalia.

The term hermaphrodite comes from Greek mythology. Hermaphroditus was
the offspring of Hermes and Aphrodite. A water nymph became infatuated with
this youth and prayed to be united with him for ever. Immediately their two bodies
were joined and they became as one. “In their double form they are neither man
nor woman; they seem to have no sex yet to be of both sexes”. (Larousse, 1959).

An understanding of the genesis of these disorders requires a brief review of the
embryological events which control the formation of the genitalia (Fig. 1). Prior
to the seventh week the fetal gonads are bi-potential and each is associated with
both a Müllerian and a Wolffian duct. If the individual’s karyotype is 46XX
(female) the cortex of the primitive gonad become an ovary. The Wolffian ducts
then atrophy and the Müllerian ducts persist to form the fallopian tubes, uterus
and upper vagina. On the other hand, if the karyotype is 46XY (male) the medulla
of the gonad becomes a testis. Although much is not understood of the factors

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controlling gonadal differentiation, it seems certain that the presence of a Y chromosome, even an aberrant Y chromosome, in just a proportion of the somatic cells, will initiate testicular development at least on one side (Ferguson-Smith, 1966).

During the eighth week Leydig cells appear in the fetal testes. Testosterone secreted by these cells diffuses locally, inducing the development of an epididymis, vas deferens and seminal vesicle from the Wolffian duct; it may also induce testicular descent. In addition, the testis secretes another substance which actively suppresses Müllarian duct development. Each testis controls this induction and suppression on its own side. With the exception of testicular descent into the scrotum which is delayed until the thirty-sixth week, these events take place prior to the twelfth week of fetal life.

The external genitalia, in contrast to the internal organs, develop from a common primordium. In the female fetus the genital tubercle becomes the clitoris, the genital folds the labia minora and the genital swellings the labia majora. In the male, fetal testosterone causes further differentiation of these structures. The genital tubercle becomes the glans penis, while the genital folds form the shaft of the penis and by fusion from below upwards move the urethral opening out to its tip. Fusion of the genital swellings forms the scrotum. External genital development is complete by the sixteenth week of gestation.

Our knowledge of these events is largely the result of the brilliant animal experiments of Jost and co-workers in Paris (1958). They demonstrated conclusively the positive role played by the fetal testes in the differentiation of male internal and external genitalia.

The fetal ovary apparently plays a negative role in the genesis of these organs, since in the absence of normal fetal gonads of either sex the Wolffian ducts atrophy and the internal and external genitalia are female.

In this orderly sequence of events, anomalies may occur at any of the three points shown in Figure 1. Abnormalities in each of these three areas of development produce the three groups of intersex already defined. Patients illustrating each group are now described.

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\begin{align*}
(3) & \quad \text{SEX CHROMOSOME CONSTITUTION} \\
(2) & \quad \text{GONADAL DIFFERENTIATION} \\
& \quad \text{INTERNAL DUCTS} \quad \text{EXTERNAL GENITALIA} \quad (1)
\end{align*}
\]

**Fig. 1.** The developmental sequence by which normal gonads and internal and external genitalia are formed. Intersex may be the result of an abnormality at (1), (2) or (3).
CASE REPORTS

(1) The Female Pseudohermaphrodite

The female pseudohermaphrodite is a normal female, karyotype 46XX, whose external genitalia have been masculinized by androgens in utero. This is usually due to congenital adrenal hyperplasia (CAH), which is the result of an inborn error in cortisol biosynthesis. Hence cortisol secretion is deficient (Fukushima and Gallagher, 1959). Ninety per cent have a deficiency of the 21-hydroxylase enzyme system (Fig. 2). The resultant excess pituitary adrenocorticotrophin (ACTH) causes both cortical hyperplasia of the adrenal and stimulates the unaffected androgen pathway to produce excess androstenedione. This masculinizes the external genitalia in a female fetus. Accumulation of 17α-hydroxy-progesterone results in an increased excretion of its major urinary metabolite, pregnanetriol. Thirty per cent of infants with this enzyme defect also have inadequate production of mineralocorticoids, such as 11-deoxy-corticosterone and aldosterone. This causes excessive renal salt and water loss, which may lead to circulatory collapse and early death.

Patient MM was a 3Kg female infant born, following a normal pregnancy, in 1954. At the end of the first week of life she began refusing her feeds, vomiting and having diarrhoea. Two older sibs had died—a male of apparent "gastroenteritis" at 3 weeks of age, and a sister at 5½ months from an undetermined cause.

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**Fig. 2.** A simplified version of cortisol biosynthesis. The 21-hydroxylase deficiency blocks the pathways as shown. Androgens are produced in excess. The accumulation of 17α-hydroxy-progesterone results in increased pregnanetriol.
On examination she was mildly dehydrated. The systolic blood pressure was 65mmHg. The external genitalia showed a large phallus with a single small opening at its base. No gonad was palpable.

Investigations: plasma sodium was 133, chloride 91, and potassium 5.7 mEq/L and blood urea 95mg/100 ml. The urinary chloride concentration was 83mEq/L, indicating a salt-losing state. The urinary 17-ketosteroid (17-oxosteroid) excretion was 2 mg per 24 hours. This is greater than the upper limit of normal at this age (Forsyth, 1974) and signifies androgen over-production. On these clinical and biochemical findings the infant was diagnosed as having CAH.

She was immediately treated with cortisone acetate, added salt and DOCA (fluorocortisone acetate has replaced DOCA and salt supplements may not be required). Vomiting and diarrhoea ceased and she began to thrive. The clitoris was made smaller at 4 years of age. Before the onset of menstruation at 12 years of age the common urethro-vaginal orifice was corrected. This patient is therefore an example of abnormality 1 (Fig. 1).

(2) The Male Pseudohermaphrodite

The male pseudohermaphrodite, karyotype 46XY, is an individual who has testicular tissue but the genitalia are poorly masculinized and there is incomplete descent of the testes. Within this group various distinct entities are recognised. One such, probably the result of fetal testicular abnormality, is now described.

Patient EK was the youngest child in a family of 5 sibs. Three were normal females. The eldest child in the family, born in 1954, had a small phallus with a single opening at the base and bilateral undescended testes. He was reared as a boy and had repeated operations in a vain attempt to construct a penile urethra. During teenage he developed a personality disorder and became an alcoholic.

EK was born in 1964 with the same type of ambiguous genitalia. On discharge from the maternity unit no definite medical advice was given to the parents as to the sex in which the child should be reared. The parents themselves wisely decided to rear the infant as a girl.

Whenever the child was admitted with a respiratory infection at 2½ years of age, ambiguous external genitalia were noted. The phallus was 1.5cm long with a single small orifice 1 cm below its base. A gonad was palpable at the left external inguinal ring. The karyotype was 46XY.

Because the external genitalia were so poorly masculinized that the phallus would be unlikely to function as a normal penis and plastic surgery had manifestly failed to achieve this result in an older sib, it was decided to continue rearing the child as a girl.

The phallus was therefore reduced in size surgically and exploration of the gonads and pelvic organs carried out. The left gonad, which on frozen section showed testicular tissue, and its associated inguinal hernia were removed. At laparotomy the right gonad with a vas deferens was present in the pelvis. Frozen section biopsy of this gonad showed it was a testis and it was also removed. No uterus, tubes or vagina were present.

At the age of about 14 years the child will require oestrogen therapy to induce breast development. Masculinization will have been prevented by orchidectomy. In adult life a vagina should be fashioned surgically.

This patient had incomplete masculinization; by contrast, the child who will now be discussed, has normal testes but female external genitalia. This curious syndrome of testicular feminization, originally described by Morris (1953), is the most clearly defined disorder within the group of male pseudohermaphrodites. Although normal testes are present, masculinization of both internal and external
genitalia was prevented by end organ resistance to testosterone. However, normal activity of testicular Müllerian suppressor substance is suggested by the absence of a uterus and a short vagina (Federman, 1967).

*Patient RL*—born in 1974, was the first child of healthy, unrelated parents. The pregnancy was normal. There was an interesting family history. A maternal aunt of the patient had previously been investigated for primary amenorrhoea. The uterus and tubes were absent and the vagina was short. Gonads were normal testes. The karyotype was 46XY. Five other apparent ‘females’, known to be infertile may also have had testicular feminization syndrome (Fig. 3).

On examination of our patient RL, bilateral inguinal herniae were present and within each, a gonad was palpable. The external genitalia were those of a normal female infant. There was no other abnormality. The karyotype was 46XY.

Surgical exploration confirmed the presence of inguinal herniae and these were excised. Biopsy of each gonad showed them to contain histologically normal testicular tissue.

The testes were left in situ so that they would feminize the patient at ‘puberty’. Subsequently they should be removed because of the high risk of neoplasia (Federman, 1967).

Patients EK and RL are examples of abnormalities at 2 (Fig. 1).

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**Fig. 3. Pedigree of patient RL (arrow). An aunt (asterisk) also had the testicular feminization syndrome; other individuals thought to have this disorder are indicated by the same symbol.**
(3) The True Hermaphrodite

The true hermaphrodite is an individual in whom there is both ovarian and testicular tissue. In most the karyotype is 46XX (Jones et al, 1965). One explanation for the presence of testicular tissue in a genetic female has been suggested by Ferguson-Smith (1966). He postulates interchange of that fragment of the Y chromosome which carries the testes determining gene(s), with the homologous part of the X chromosome. This anomaly, which probably arises during paternal meiosis, is designated Xv. Cells with the karyotype 46XXv are not however, discernible using present cytogenetic techniques.

In the true hermaphrodite there is a wide spectrum of phenotypic manifestations in both internal and external genitalia; some patients are feminized, while in others almost normal male genitalia are present.

Patient PC—born in 1970, was the fifth child in an otherwise normal family. At birth the diagnosis of CAH was suggested by the presence of a large phallus with a single small opening at its base and no palpable gonad. However there was no pigmentation of the genital or areolar skin and no dehydration.

Plasma electrolytes and the urinary 17-oxosteroid excretion were normal. Chromosome analysis of leucocytes showed a mosaic of 45X and 46XY cells. CAH was therefore excluded.

It was decided to rear the child as a girl, because the external genitalia were so poorly masculinized. The phallus was reduced in size. The labia separated easily and distinct urethral and vaginal orifices were identified. Since no gonad was palpable it was necessary to explore the pelvis, in order to remove testicular tissue which would masculinize the patient at 'puberty'.

Laparotomy was deliberately postponed until 3 years of age so that the pelvic organs could be more easily identified. At operation a normal uterus, tubes and two gonads were found. A vas deferens was also present in the right pelvis. Germ cells were absent on frozen section of each gonad and both were removed. Further histology showed the right gonad was an ovotestis and the left a fibrous 'streak'. Patient PC is therefore an example of abnormality 3 (Fig. 1).

DISCUSSION

Examples of the 3 groups of intersex have been described and current ideas on their pathogenesis and management outlined. In each the earliest physical signs were ambiguous genitalia.

Congenital adrenal hyperplasia (CAH) due to the 21-hydroxylase enzyme deficiency, is the commonest cause of ambiguous external genitalia in the newborn. Its incidence in some communities is as high as 1 in 5,000 live births (Hubble, 1966). The affected infant is a female, whose external genitalia have been masculinized by adrenal androgens before the sixteenth week of gestation. The internal genitalia are normal. One explanation is that they differentiate before the fetal adrenal glands become functional at 12 weeks (Hamilton, 1972). Similar changes in the infant's external genitalia have been described, when progestogens were given to mothers early in pregnancy because of recurrent abortion (Wilkins, Jones, Holman and Stempfel, 1958). CAH should be promptly diagnosed because of the mortality associated with the salt-losing syndrome which is present in one-third of patients with this enzyme defect. Vomiting and diarrhoea occur during the first two
weeks of life and such infants may erroneously be thought to have gastroenteritis. Since this defect is inherited as an autosomal recessive trait, males are also affected. However, since their only genital abnormality may be congenital enlargement of the penis, too frequently they are overlooked. This is well illustrated by the family history of patient MM. A male sib developed severe vomiting and diarrhoea and died at 3 weeks of age presumably of salt loss.

The male pseudohermaphrodite may also present in early life with ambiguous genitalia. The types of genital abnormalities vary considerably as illustrated by the two patients described. Patient EK had arrested masculinization, probably the result of a defect in testosterone secretion by the fetal testes. The absence of female internal genitalia suggests that Müllerian suppressor substance was active. Several hereditary defects in testosterone biosynthesis are now recognised (Visser, 1974). Even in patients with undescended testes per se, recent studies have shown elevated plasma concentrations of follicle stimulating hormone, which is a sensitive indicator of mild hypogonadism. This might suggest that even in this relatively minor genital abnormality, a primary testicular defect is its cause (Lee, et al, 1974).

The syndrome of testicular feminization was diagnosed in early infancy in patient RL. More commonly it presents in adult life with amenorrhoea or infertility. The cause may be a deficiency of the enzyme 5α-reductase within the nuclei of the end organ cells. This enzyme normally transforms testosterone into its more potent metabolite, dihydro-testosterone, which stimulates protein synthesis within these cells (Bruchovsky and Wilson, 1968a; 1968b). The result of this biochemical defect is a life-long resistance to the action of both endogenous and exogenous testosterone (French, et al, 1965). An identical disorder has been produced experimentally in male rats, treated during fetal life with the anti-androgen, cyproterone acetate (Neumann, et al, 1970). The genetic basis of this disorder, which occurs about once in 100,000 of the population (Taylor, 1974), is a point mutation. Various studies have still not resolved whether this occurs on an autosome or on the X chromosome (Polani, 1970).

The true hermaphrodite is probably the rarest of the intersex disorders, though Polani (1970) found 339 patients in the world literature since 1899. The genitalia in general reflect the incomplete effectiveness of the fetal testes in suppressing Müllerian and stimulating Wolffian development. Hence a uterus is almost constantly present, while differentiation of the other ducts usually corresponds to the adjacent gonad (Guinet, 1965). Three-quarters of the reported patients have been reared as males, though some degree of hypospadias is often present. The diagnosis may then be delayed until early adult life, when gynaecomastia develops or menstruation occurs.

In many true hermaphrodites the karyotype appears to be 46XX. An explanation for this chromosome pattern, in the presence of testicular tissue, has already been given. A mosaic karyotype, 45X/46XY, as in patient PC, has been found in 20 per cent of true hermaphrodites (Polani, 1970). This abnormality is probably related to anomalous cell division around the time of fertilization.

All infants with ambiguous genitalia require immediate hospital referral for diagnosis and initial management. The clinical approach to such a patient should
include a full history, with particular reference to the family history. Three of our patients had a close relative with the same disorder.

Clinical examination should note the state of hydration. Pigmentation of the genital and areolar skin suggests increased ACTH secretion, the result of cortisol deficiency in CAH. The genitalia should be carefully examined. If a gonad is palpable in the external genitalia or groin, it is likely to be a testis or ovotestis. Since a normal ovary is rarely found outside the pelvis, the presence of a palpable gonad, associated with ambiguous genitalia, clearly excludes female pseudohermaphroditism. An inguinal hernia in an apparently female child should alert one to the possibility of testicular feminization, because herniae of this type are exceptional in normal female infants.

In the newborn with ambiguous external genitalia, immediate laboratory investigations for the diagnosis of CAH should be carried out, since this is the only intersex disorder in which the survival of the child is jeopardized. In the salt-losing type of 21-hydroxylase deficiency, the urinary chloride concentration is marked by elevated sodium and chloride; the plasma potassium is raised. In the absence of excess salt loss these investigations are normal. Although the 24-hour urinary pregnanetriol is increased in older patients, this may not be the case in the newborn with this disorder, because of differences in the metabolism of 17α-hydroxy-progesterone in early life (Forsyth, 1974). Elevation of the urinary 17-oxosteroids (17-ketosteroids) indicates androgen excess; the mean value at this age is less than 1.0 mg/24 hours (Forsyth, 1974). In the other intersex disorders discussed all these investigations are normal.

Chromosome analysis of leucocytes should be carried out. This will distinguish the male pseudohermaphrodite (46XY) from the female pseudohermaphrodite (46XX). True hermaphrodites show a variety of karyotypes. Although the most frequently reported is 46XX (Polani, 1970), mosaics, as in patient PC, may also be found. Chromosomal analysis is more accurate than the Barr body preparation, particularly in the newborn female, where false negative results may mislead (Hamilton, 1972).

Once the diagnosis has been established, the child is assigned to the appropriate sex and a forthright explanation given to the parents. Ideally this should be done as early as possible, since the sex of rearing and gender identification, which is ingrained in early life, are important determinants of psycho-sexual orientation (Money, Hampson and Hampson, 1955).

A female infant with CAH, in whom the external genitalia alone are masculinized, should be reared as a girl. If adequate cortisone is given both excess ACTH and androgens are suppressed. The size of the phallus may then regress. If this does not occur, it should be reduced in size surgically before school entry. At operation, care should be taken to preserve the sensitive tissue of the glans. Pubertal development is normal, but before menarche a separate vaginal orifice should be ensured. Provided corticosteroid therapy is begun soon after birth, anomalies in the patient’s gender role should not appear in adult life (Ehrhardt, Evers and Money, 1968). The female infant with CAH will become a normal, fertile adult.
When parents are known to be carriers of this gene defect, diagnosis in late pregnancy of an affected infant may be possible, by assay of the pregnanetriol concentration in amniotic fluid (Jeffcoate, et al, 1965).

Since fertility is almost never possible in the other groups of intersex, the child should be reared in the sex appropriate to the external genitalia, regardless of the karyotype. It is therefore a simple decision to rear the child with testicular feminization syndrome as a girl, because the external genitalia are completely feminized. It is important that the testes remain in situ to feminize the child at 'puberty'. Female secondary sex characteristics are probably produced by testicular oestrogens, since prepubertal removal prevents feminization (Morris and Mahesh, 1963).

In other male pseudohermaphrodites and in the true hermaphrodite, if the phallus is small with no penile urethra, so that micturition in the normal male fashion is impossible, then the infant should also be reared as a girl. The phallus should be reduced to the size of a clitoris and testicular tissue removed to prevent masculinization at 'puberty'. This policy was followed in patients EK and PC. Each will require oestrogen therapy to promote breast development in their teens. On the other hand, some of these patients may be more masculinized, with virtually normal male external genitalia. Here the decision would be to rear as a boy. Removal of ovarian tissue and internal female organs is then essential.

When sex of rearing is assigned on such criteria, much psychological morbidity, as occurred in the sib of patient EK, may be averted and the controversial question of reassignment of sex will not arise (Armstrong, 1968).

When the diagnosis of intersex is made, subsequent sibs should be delivered in a hospital where facilities are available for its full investigation.

Summary

Four newborn infants with intersex are described. The pathogenesis, differential diagnosis and management are discussed.

Congenital adrenal hyperplasia in a female is the commonest cause of ambiguous external genitalia. This is the only intersex disorder in which survival of the child is at risk. A palpable gonad virtually excludes this diagnosis. With adequate treatment, sexual development and fertility are normal. Hence females with adrenal hyperplasia should be reared as girls.

In the other intersex disorders, since fertility need not be considered, the sex of rearing is determined by the functional capacity of the external genitalia.

Optimal early management of infants with ambiguous genitalia renders anomalies of gender role unlikely in adult life.

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