INTERSEX: A SIMPLIFIED PERSPECTIVE*

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The complexities of modern-day advances in the field of genetics, and in the study of chromosomes with their associated abnormalities, preclude the casual reader from sane comprehension of the problem. Understanding of the vagaries of intersex necessitates a basic grasp of certain aspects of the subject, and this paper will attempt to clarify the position.

Historically, mysticism, superstition and mythology have pervaded the scene. Hermaphroditis, the bi-sexual Greek god, hails from Hermes and Aphrodite. Theoretically, the true hermaphrodite should be capable of the sexual as well as the reproductive functions of both sexes. In humans, such an individual does not exist. It is therefore preferable to substitute the term 'intersex'. Similarly, the term pseudo-hermaphroditism clouds rather than clarifies the issue. A male pseudo-hermaphrodite[1] is an individual with the gonads of a male and the secondary sex characteristics of a female, e.g. the testicular feminizing syndrome. Conversely, the adrenogenital syndrome is an example of a female pseudo-hermaphrodite. The term 'intersex' is again preferable.

Simply, then, sex may be defined as a species dimorphism represented at different planes by chromosomes, gonads, sex ducts, external genitalia, bodily habitus and psychological attitude. It is ever pertinent to view the human organism as a whole, and problems of intersex—despite the fact that the afflictions might be highly localized—evoke repercussions which involve the patient in his entirety. Normality at the different planes is dependent upon each system functioning correctly. The corollary is also true, namely, that if an abnormality exists at one plane, repercussions occur at other planes. In the testicular feminizing syndrome, despite a 46/XY chromosomal complement, this individual is phenotypically female, attractive in appearance, and has well-developed breasts. Either the testes are not producing enough androgens, or perhaps the tissues are resistant to the amounts produced. We have, therefore, an individual who is chromosomally masculine, and therefore has testes, but with external female appearances—a contradiction at the different planes outlined.

This brings us to the definition of the term 'intersex'. Any condition which is associated with a contradiction at the different levels outlined, or which causes difficulty with regard to classifying the individual to one or other gender, may be termed a problem of intersex. The adrenogenital syndrome[2] is characterized by the normal female complement of chromosomes, i.e. 46/XX, but the external genitalia and the bodily habitus show virilizing features; hence there is a contradiction at two levels, and the patient may be termed a problem of intersex.

CLASSIFICATION

Based on the above definitions, we proceed to a simple practical classification.

*Date received: 30 April 1968.

Abnormalities of Chromosomes
1. Super female.
2. Klinefelter's syndrome.[3,4]
3. Turner's syndrome.[2,5]
4. Mosaics.[3,6]

Abnormalities of Gonads
1. Testicular feminizing syndrome.

Abnormalities of the External Genitalia
1. Adrenogenital syndrome.
2. True and pseudo-hermaphroditism.

Abnormalities of Secondary Sex Characteristics
1. Hyperthecosis ovarii syndrome.[7]
2. Stein-Leventhal syndrome.[8]
3. Hirsute female.[9-11]

Abnormalities of Psychological Attitude
1. Homosexual.
2. Transvestite.

Basic to the understanding of these conditions are the following principles.

The chromosomal complement of the zygote (containing the diploid number of 46) determines the sex of the gonad. If the zygote contains 46/xx chromosomes, then the gonad will always be an ovary. Conversely, if the zygote contains 46/xy chromosomes, then the gonad will always be a testis.

The development of the sex ducts and external genitalia, bodily habitus and to some extent psychological attitude depend upon a normally functioning gonad and not upon the chromosomal complement of the zygote. In the testicular feminizing syndrome the karyotype is 46/xy, the gonad is a testis, but the secondary sex characteristics are feminine because the testis fails to masculinize the individual.

In the human species the female gender is close to the neuter state; hence in the absence of 2 X chromosomes as in Turner's syndrome (45/XO) the individual has basic feminine characteristics. In other words, to manifest masculinity, one has to have superadded androgenic hormone. This results in degeneration of the Mullerian system and persistence of the Wolffian system. If the testis fails to produce sufficient or potent androgens, then despite the fact that the karyotype is 46/XY, the Mullerian system will persist and the Wolffian system will degenerate, resulting in an individual phenotypically female, but chromosomally male.

All grades of severity of intersex cases are to be found, but as a guide two main possibilities exist: (*a*) an incomplete masculinized male; and (*b*) a partially masculinized female.

Man has 46 chromosomes in every normal cell. There are 44 autosomes and 2 sex chromosomes. This fact was confirmed with certainty in 1956 when Tjio and Levan[12] discovered for the first time that man possessed 46 and not 48 chromosomes.

Techniques

Present-day studies of chromosomes are accomplished in the following manner. Colchicine is added to a tissue

culture of cells. Mitosis is then arrested, the spindle is destroyed and the chromosomes separate. They swell with the addition of hypotonic saline and are spread by squashing them on a glass slide. After staining, one visualizes the chromosomes as split into two identical chromatids which are adherent at the centromere. The position of the centromere varies for the different chromosomes, but is constant in position for the same chromosome. This, together with the length of each chromosome, enables cytologists to classify them into 7 groups.[13] This arrangement is called a karyotype. (See Fig. 1(b).)

The mature sperm and ovum each contain 23 chromosomes, i.e. 22 autosomes and one sex chromosome (haploid number). This ensures a constant number of 46 with fertilization. Twenty-three chromosomes are therefore lost in mitosis and it is thought that they are condensed in the form of a chromatin mass situated on the inside of the nuclear membrane. This deeply staining plano-convex mass, 1 micron in diameter, containing a high concentration of desoxyribose nucleic acid, is named after its discoverer and is called the Barr[14] body. More than 80% of female cells contain a single Barr body and are said to be chromatin positive. Very few male cells contain a Barr body and are said to be chromatin negative. A simple buccal smear will rapidly ascertain whether the patient is chromatin positive and therefore likely to have a 46/XX karyotype, or chromatin negative with a likely 46/XY chromosomal complement.

CASE REPORTS

Two case discussions serve to illustrate some of the above-mentioned principles.

Case 1

Samuel (Fig. 1), one of 4 normal Bantu siblings, aged 22 years, presented with the request that he would like to be a 'proper man'. His parents had reared him as a male, his friends were males and he had a normal sexual libido towards females. At 14 years of age his voice deepened and the breasts enlarged. He did not shave as there was no facial growth. Erections did occur, but normal coitus was impossible due to a marked chordee. Systematic history was non-contributory.

Examination revealed a healthy individual weighing 113 lb., and 5 ft 2 in. tall. He was slightly built. Systematic examination was normal. The facial contour was somewhat effeminate, with no facial hair. The breasts were small but well developed, with normal nipples and areolae. Axillary hair was normal and there was a male-type, suprapubic escutcheon. There were no masses palpable in the abdomen. There was a small phallus, 1½ in. long, with a small prepuce and marked chordee (Fig. 2). The urethral meatus was of the penoscrotal type, small and elliptical in shape (marked hypospadias). The labioscrotal folds contained no gonads, nor were these palpable in the perineum or inguinal regions. There was no vagina visible. Gonads and a prostate gland were not palpable on rectal examination.

The special investigations performed are shown in Table I.

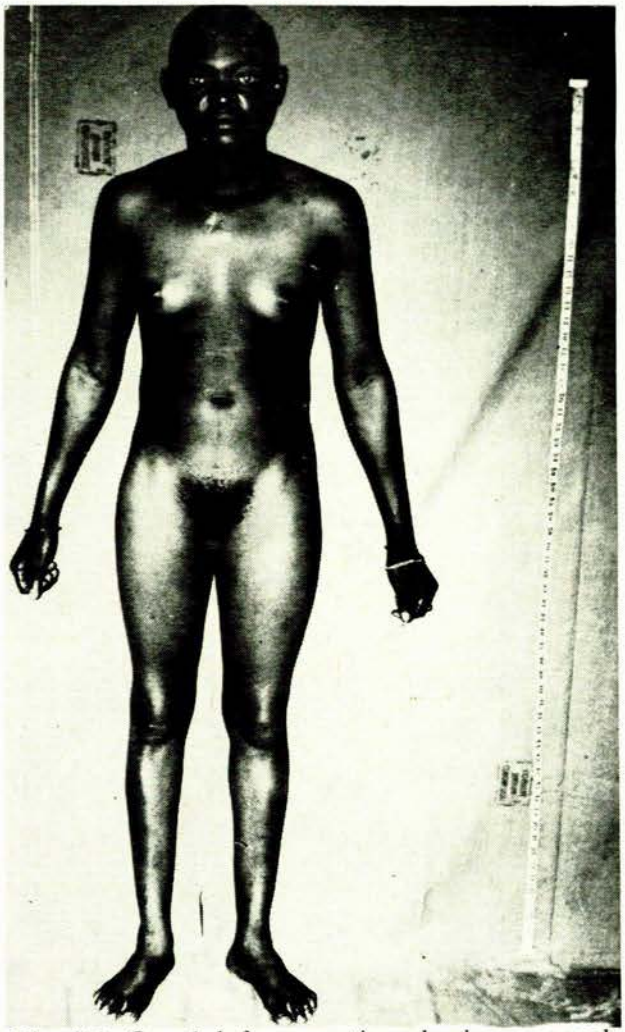

Fig. 1(a). Case 1 before operation, showing a general female body habitus with breast development and a small phallus.

TABLE I. SUMMARY OF FINDINGS IN 2 CASES

Examination	*Samuel*	*Obed*
F.S.H.	6 - 12 m.u.u.*	6 - 12 m.u.u.
17-OH-steroids	12 mg./24 hr	8·0 mg./24 hr
17-ketosteroids	8·0 mg./24 hr	9·2 mg./24 hr
Total oestrogens	27 μg./24 hr	57 μg./24 hr
X-ray of the chest	Normal	Normal
Blood count, urea, electrolytes	Normal	Normal
Urinalysis	Normal	Normal
Blood sugar	102 mg./100 ml.	79 mg./100 ml.
Pelvic pneumogram	Gonads both sides	Tumour L. side. Gonad R. side. Uterus
Buccal smear	Chromatin +ve	Chromatin +ve
Chromosomes	46/XX	46/XX
Cystogram	Normal bladder and urethra. No urogenital sinus	Normal bladder and urethra. No urogenital sinus
Pathology	R. side: ovotestis, vas deferens. L. side: normal ovary, normal tube. Vestigial uterus	R. side: ovotestis. L. side: dysgerminoma. Normal uterus and cervix, normal upper ⅓ vagina ending blind

*m.u.u. = mouse uterine units.

A diagnosis of intersex was made and, to use the older terminology, this patient was a true hermaphrodite. There were features consistent with the male and female genders. Careful psychological assessment over a matter of months favoured a strong masculine orientation. There was no doubt that Samuel wanted his breasts removed and his phallic abnormality corrected so that he could live a normal masculine life.

A laparotomy was to be performed. If the gonads were ovaries, or ovatestes, then they would be removed as they were contrary to the future anticipated sex. If they were testes, then the chance of malignancy was present. Morris[15] described 7 malignant tumours in 82 cases. Overzier[16] described 10 malignancies in 128 recorded cases.

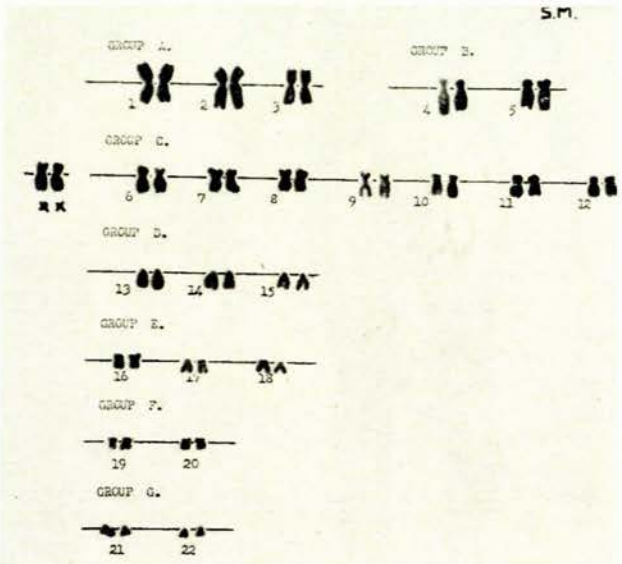

Fig. 1(b). Karyotype of case 1. There are 44 autosomes and 2 sex chromosomes (XX in group C), being the normal complement for a normal female, or for the majority of true hermaphrodites.

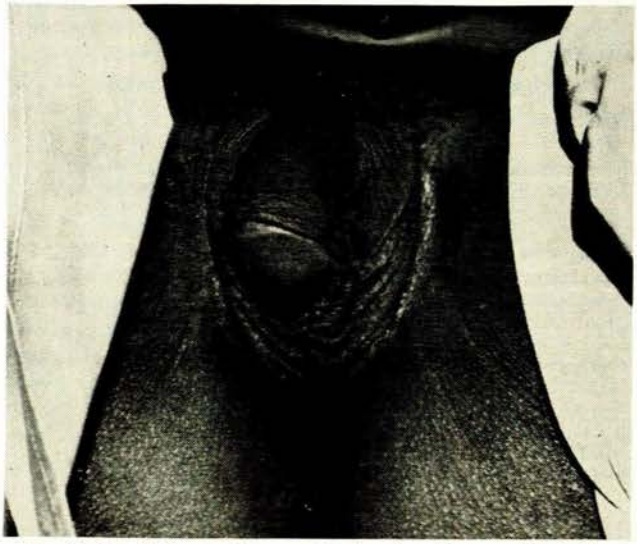

Fig. 2. Genital area in case 1, showing the small phallus with chordee, labioscrotal folds, the absence of scrotal or perineal gonads and a hidden penoscrotal type of hypospadias.

Laparotomy revealed a normal ovary and tube on the left side and an ovotestis on the right (Fig. 3). The uterus was represented by a nodule. These tissues were removed *in toto*.

Histology revealed a normal ovary on the left side. A number of primordial, developing and cystic follicles were evident. The right gonad showed features consistent with an ovotestis. The ovarian portion exhibited normal primordial, plus developing, follicles, while the testicular portion showed the presence of well-developed tubules and occasional islands of interstitial cells. There was no evidence of spermatogenesis.

Six weeks after he had recovered from his laparotomy both breasts were excised through an infra-areolar incision. With postoperative drainage by suction a good result was obtained. Methyltestosterone, 10 mg., was given 3 times a day to stimulate masculinity. Noticeable results were evident only after about 3 months of therapy. The phallus enlarged by about 25%. A 10 lb. increase in weight and a more masculine demeanour also resulted. The chordee was treated by excision of the fibrous attachment and primary closure of the well-mobilized penile skin.

It must be emphasized that the patient returned each time after discharge from hospital eager to have his next operation. His reorientation was gradual, determined and punctuated with extreme gratitude.

Case 2

Obed (Fig. 4), aged 26 years, one of 5 normal Bantu siblings, was admitted to the ward within a week of Samuel. He requested rectification of his sexual status. His history was similar to case 1. He was reared as a male by his parents, enjoyed the company of males, had a normal sexual drive towards females but was unable to experience coitus due to a small phallus tethered by a marked chordee. At 12 years of age his breasts grew, but menstruation never commenced. Psychological orientation was strongly masculine, so much so that he more than once threatened suicide if his status was not corrected.

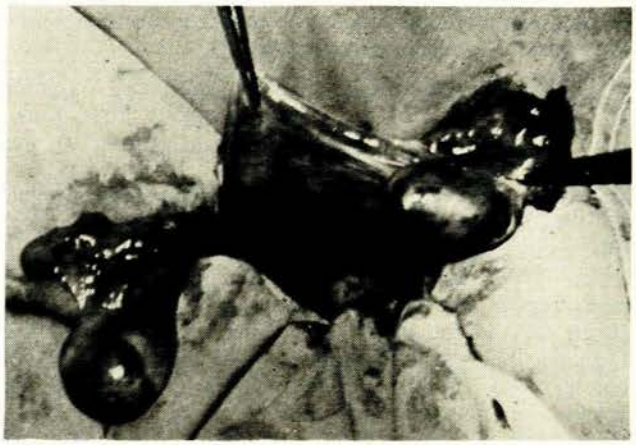

Fig. 3. Case 1. Laparotomy shows an ovary and a tube on the left side, with an ovotestis and a vas deferens on the right side. A small vestigial uterine nubbin is shown below the central forceps.

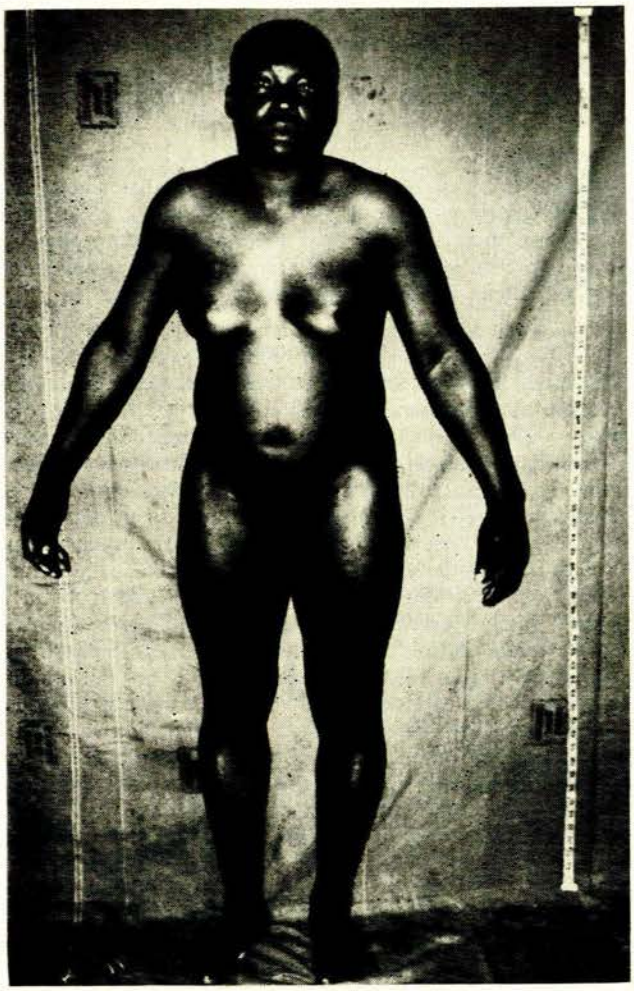

Fig. 4. Case 2, showing a more effeminate body configuration, with typical female escutcheon, fat distribution and breast development.

General examination revealed an individual phenotypically female with rounded body contours, 4 ft 6 in. tall, 120 lb. in weight, with blood pressure of 110/60 mm.Hg. There was no facial hair and the voice was effeminate. The breasts were well developed, the axillary and pubic hair was of the female type. There was a small phallus with a very small prepuce (Fig. 5). It resembled a hypertrophied clitoris and was tethered by a chordee. A small elliptical external urinary meatus opened at the base of the phallus. The labioscrotal folds contained no gonads. Rectal examination revealed a tumour mass 3 in. × 3 in. on the left, a normal-sized gonad on the right side and a small uterus. There was no vagina visible on external examination, and dye introduced into the external urinary meatus entered the bladder and failed to outline the vagina. The special tests performed are shown in Table I. A diagnosis of intersex was made with a strong leaning towards a feminine bodily disposition, but with equally strong masculine psychological orientation. The tumour on the left side was likely to be a dysgerminoma as these are common in cases of intersex.

The plan of action was similar to case 1. At laparotomy a lobulated, solid, grey tumour measuring $3\frac{3}{4}$ in. × $2\frac{3}{4}$ in. × $1\frac{1}{2}$ in. was found, in place of the left gonad. The capsule appeared to be intact. A normal tube was present on this side. The opposite gonad appeared to be an ovary adjacent to a normal tube. The uterus was small and a broad ligament extending on each side to the pelvic sidewall was present. A total hysterectomy and a bilateral salpingo-oöphorectomy with a removal of the tumour was

Fig. 5. Genitalia of case 2, showing a smaller phallus, marked chordee, with a scrotal type of hypospadias. The labioscrotal folds are devoid of gonads. There is no vaginal opening.

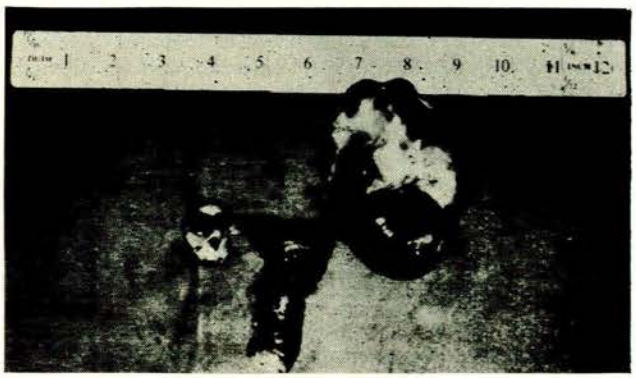

Fig. 6. Operative specimen of case 2, showing a dysgerminoma and normal fallopian tube on the left, with a normal tube and ovotestis on the right side. The uterus and cervix are of the prepubertal type.

performed (Fig. 6). A long prepubertal type of cervix was encountered when cutting across the vaginal vault. The latter ended blindly and was 1¼ in. long.

Histology of the left gonad confirmed the presence of a dysgerminoma-seminoma type of tumour. An area showing normal early corpus luteum in the stage of vascularization was present. Because of this area of normal ovarian tissue it was considered that the tumour might be a seminoma originating from the testicular portion of an ovotestis. The opposite gonad was an ovotestis. The ovarian portion was well developed with primordial follicles, normal developing follicles and occasional corpora fibrosa and corpora albicantia. In the testicular portion the tubules exhibited quite marked thickening and hyalinization of their basement membranes. Occasional small islands of interstitial cells were present. The uterine endometrium showed an early secretory picture.

Despite the histological evidence of previous ovulation in the ovary, there was no haematocolpos or haematometra at operation, suggesting the absence of uterine withdrawal bleeding. Two months later the breasts were reduced in size to masculine proportions. A subsequent operation to elevate the nipples was necessary. The chordee was freed some months later. At the time of writing, both patients have been admitted for construction of penile urethrae. Case 2 was given a course of deep X-ray therapy to the abdomen and pelvis in view of the presence of a dysgerminoma.

THE ORIGIN OF CHROMOSOME ANOMALIES

During meiosis chromosomes come together, material is exchanged and they separate. When this process functions abnormally, chromosomal anomalies occur, which differ according to the type of mechanism involved producing the abnormality.

Non-disjunction

This is probably the commonest abnormality involving chromosomes and is responsible for the occurrence of the super female, Turner's and Klinefelter's syndromes. During gametogenesis the two sex chromosomes which have come together fail to separate, so that one daughter cell will have 22 autosomes and no sex chromosome.

Translocation

There is normally an exchange of material between like chromosomes when these come together in meiosis. When material is exchanged of different pairs an imbalance of genetic material will result.

Mongolism is an example, where the patient has 3 of No. 21 chromosome, trisomy 21, an autosomal abnormality arising due to non-disjunction. This was first described by Lejeune *et al.* in 1959.[17] Translocation of chromosome 21 which becomes attached to a chromosome of group 13 - 15 can also produce the abnormality. The latter type is familiar and can be inherited by the offspring.

Isochromosome Formation

When the chromosomes break and rejoin, the 2 long arms and the 2 short arms join each other respectively. This causes 2 isochromosomes, each with 2 arms that are exact duplicates of each other. This condition may be associated with an atypical Turner's syndrome.[18]

Deletion

Part of one chromosome is missing. Jacobs *et al.*[19] described two women suffering from primary amenorrhoea, one of whom had deletion of a short arm and the other a long arm of the X chromosome.

Duplication

When part of one chromosome is transferred to its opposite partner without an equal exchange of material occurring, then a segment of the latter chromosome will have representation from 2 chromosomes (duplication) and the other will have none at all (deletion).

DISCUSSION

Thorough clinical assessment, psychological evaluation, endocrine estimation and chromosome studies are obligatory. The management ultimately depends upon the psychological sex of rearing, and this usually corresponds with the patient's sexual orientation. Disasters have occurred in the past where the new sex has been determined by the karyotype rather than the patient's psycho-sexual orientation. Usually it is easier to convert to a female phenotype by amputation of the phallus, construction of a new vagina, especially using the Williams technique,[20] and by stimulating breast development with oestrogen compounds. This, however, should not be the guiding principle. If it is decided to convert to the masculine gender, then breast amputation, phallic and urethral construction and androgen treatment should be employed. These operations should not be undertaken lightly, and prolonged observation and discussion with thorough mental assessment will avert incorrect orientation.

SUMMARY

The terms sex and intersex are defined. A practical classification of intersex is presented. Four important principles in the understanding of these conditions are discussed. The normal chromosomal pattern in man and the Barr body are discussed. Two cases of intersex are presented with details of investigations and management. The origins of chromosomal anomalies are defined.

I should like to thank Dr P. C. Hauptfleisch, Superintendent of Natalspruit Hospital, for permission to publish; Prof. S. Shippel for the pathology reports; and Dr E. Wilton for the chromosome studies.

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