True Hermaphroditism or Gonadal Intersexuality

Cytogenetic and Gonadal Analyses of 5 New Examples Related to 67 Known Cases Studied Cytogenetically

L. J. BUTLER, G. J. A. I. SNODGRASS, N. E. FRANCE, ALEX RUSSELL, and V. A. J. SWAIN
From Queen Elizabeth Hospital for Sick Children, London

The diagnosis of true hermaphroditism requires the demonstration in one individual of both testicular elements and ovarian tissue embodying primordial follicles. The term 'gonadal intersex' has been advocated for this form of intersexuality (Russell, 1954) in an effort to simplify the nomenclature. Overzier (1963) reviewed the findings in 171 authenticated examples of 'gonadal intersexuality' in the literature. Only 14 of these had been subjected to cytogenetic analysis, though information was available of the nuclear sex in a further 61 cases. Most of the latter were stated to be chromatin positive; likewise 11 of the 14 known karyotypes were 46/XX, the 3 exceptions being made up of one 46, XY, one 45, XO/46, XY mosaic, and one 46, XX/46, XY mosaic. 6 cases subsequently described by Jones, Ferguson-Smith, and Heller (1965) were all 46/XX. Linked to the 23 examples with chromosomal analysis which had by then accumulated, their appraisal served to emphasize the predominantly high frequency of an apparently normal female karyotype despite the existence of testicular material.

Since the advent of cytogenetic techniques, more cases of intersexuality are being subjected to comprehensive study incorporating bilateral gonadal biopsy. Gonadal intersexuality is thus being identified more frequently. We are now in a position to review the cytogenetic and correlated findings of 67 examples extracted from the literature, to which we related the situation defined in our own series of 5 proven cases. In 4 of these, cytogenetic study was also extended to gonadal cultures: from the ovotestis when present, otherwise from both gonads. One of these showed a familial chromosomal variant, while 2 had an unusual karyotype aberration directly linked to their gonadal constitution.

Case Reports

Case 1. This child, birthweight 3426 g., was the result of a full-term normal delivery. No hormone preparations were taken prenatally, but the mother suffered rubella when 4 months pregnant. There was no relevant family history. Two male sibs aged 6 and 4 years and a female sib aged 3 years were normal.

External features of intersexuality were noted at birth, but 17-ketosteroid estimations conducted during the first 3 years did not support an adrenal disorder. By the age of 3 years, however, an increase in clitoral size was noticeable. Her height was then at the 25th centile level, and her weight on the 50th centile. She was a normally proportioned, plump, and intelligent little girl with no abnormalities except for the genitalia.

External genitalia. At the age of 3 years the phallus was large, 3 cm. in length, and with a well-developed glans and prepuce bound down tightly in chordee (Fig. 1). A urethral groove on its ventral surface extended from a small perineal opening at the base, presumed to be the orifice of a urogenital sinus. The labio-scrotal folds were small and fused, and no gonads were palpable.

Internal genitalia. A small firm mid-line structure, approximately 1 cm. long, was palpable rectally in the usual position of the uterus. A perineal sinogram showed free flow of the radio-opaque medium into the bladder, and no vagina was seen. Laparotomy revealed a small acutely anteverted uterus with fallopian tubes and gonads attached to the broad ligaments; the upper segment of the vagina was defined, though its probable union with the urethra was not seen. The *right gonad* was small and spherical, and was composed of solid seminiferous tubules separated by loose connective tissue, without interstitial cells, merged with typical ovarian tissue (Fig. 2). The *left gonad* was flat and crenated, consisting only of ovarian tissue in which were numerous primordial follicles; the ova appeared to be degenerate with marked vacuolation of cytoplasm and nuclei. No hilus cells were seen.

Investigations. The range of blood urea, proteins,

calcium, phosphorus, sodium, potassium, and chlorides was normal. Further estimations of 17-ketosteroids (0.63–0.70 mg./24 hr.) and 17-ketogenic steroids (3.10–4.55 mg./24 hr.) were also within normal limits. A buccal smear was chromatin positive.

Cytogenetic studies. Cultures of peripheral blood, and of tissue from the ovotestis, yielded only cells with a normal female complement 46/XX.

Progress. The right gonad was removed at 5 years. The phallus was resected at 8 years and the adjacent skin folds were fashioned into a vaginal introitus. The phallus, with glans well developed, measured 4.6 cm. in length with a diameter of 1.2 cm. Well-developed corpora cavernosa and spongiosa were defined on section.

Case 2. This child, the result of a normal pregnancy and birth, was normal apart from evidence of intersexuality including perineal hypospadias. A two-stage repair of the hypospadias was completed by the age of 3 years. At 9 years he was found to be on the 75th centile for height and weight, while his bone age was normal.

External genitalia. At birth there was perineal hypospadias marked by an adequate urethral orifice within a bifid scrotum, together with moderate chordee and some fibrous contracture along the dorsal surface of the penis (Fig. 3). Neither testis could be palpated in scrotum or inguinal canals. At 9 years of age, the penis was normal in size but the scrotum was small and the testes could not be located.

FIG. 1.—Case 1. External genitalia (age 3½ yr.) showing enlarged phallus and urethral opening between fused labial folds.

Internal genitalia. Laparotomy at the age of 11 years revealed a uterus measuring 5×2.5 cm. Fallopian tubes without fimbriated ends and the gonads were attached to the broad ligament. The left gonad was spherical, 2 cm. in diameter and pale yellow. Histologically it consisted of infantile testicular tissue. The right gonad was composed of irregularly-shaped cells forming rounded masses resembling seminiferous tubules. Among these cells were small groups of large

FIG. 2.—Case 1. Right gonad (age 5 yr.) showing both testicular and ovarian tissue. (×75.)

FIG. 3.—Case 2. External genitalia (age 1 yr. 5 mth.) showing bifid scrotum.

pale cells resembling ova while other cells were reminiscent of ovarian hilus cells (Fig. 4). Two years later this gonad was removed together with the uterus and vagina. It measured $2.0 \times 0.9 \times 0.6$ cm., and was pale and firm and encased in fibrous tissue. Section showed central calcification and possible early seminoma transformation (Fig. 5). Members of the Testicular Tumour Panel and Registry [(Institute of Urology, London)] unanimously agreed that the right gonad was an ovotestis. At this time the left gonad was anchored at the internal inguinal ring. The lower part of the vagina was not exposed.

FIG. 4.—Case 2. Right gonad (age 11 yr.) showing rounded masses of cells resembling seminiferous tubules among which are ova. ($\times 190$.)

Investigations. A buccal smear was chromatin negative; urinary gonadotrophins less than 6 mouse units; urinary excretion of 17-ketosteroids (3.0 mg./24 hr.) and of 17-ketogenic steroids (5.0 mg./24 hr.) were normal for the age.

Cytogenetic studies. Cells from peripheral blood culture and tissue cultures of skin, vagina, and right gonad revealed a consistently normal male karyotype 46/XY.

Progress. By the age of 13 years considerable penile enlargement had occurred and the glans was well developed. The scrotum, though small, was rugose and there was a moderate growth of pubic hair. The voice had obviously deepened and his psycho-sexual orientation was clearly that of an aggressive young male.

Case 3. The second child of a 28-year-old mother and 30-year-old father. Apart from mild pre-eclamptic toxæmia, the antenatal period was uneventful and no hormonal medication was taken by the mother at any stage. Delivery occurred normally at term and the birthweight was 3397 g. Anomalous genitalia were noted. At the age of 4 months he appeared to be normally proportioned for his age.

External genitalia. At the age of 4 months the phallus was normal in size but bound down in chordee and associated with a marked degree of perineal hypospadias, the urethral meatus opening low between labio-scrotal folds (Fig. 6). The right fold contained a normal sized gonad, but no gonad could be detected on the left side.

FIG. 5.—Case 2. Right gonad (age 13 yr.) showing possible early seminoma transformation. ($\times 190$.)

Internal genitalia. Laparotomy at the age of 5 years showed a unicornuate infantile uterus with a single left fallopian tube; the anatomy of the vagina was not determined. The gonad attached to the left broad ligament was histologically a normal ovary with primordial follicles, Graafian follicles, and small follicular cysts. The right gonad consisted of a few poorly-developed seminiferous tubules lying in dense cellular connective tissue in the wall of an epidermoid cyst lined by stratified epithelium. The right vas deferens ran into the uterine wall.

Investigations. During the first few weeks of life, a buccal smear examination showed 10% of cells with typical sex chromatin. Excretion of 17-ketosteroids (0.1 mg./24 hr.) and 17-ketogenic steroids (0.8 mg./24 hr.) was normal for the age. At the age of 5 years the buccal smear showed 38% chromatin positive nuclei.

Cytogenetic studies. Chromosomal mosaicism was seen in cells obtained from cultures of peripheral blood, skin, right testis, left ovary, left fallopian tube, and uterus (Table I). Two types of cells were present. Those with 46 chromosomes had an apparently normal female chromosome pattern 46/XX, while those with 47 were similar except that there was an additional member of group G interpreted as a Y chromosome. Thus the latter had the Klinefelter's syndrome constitution of 47/XXY, and the karyotype diagnosis was 46, XX/47, XXY.

Progress. It was decided to rear the child as a boy. The hypospadias was therefore repaired by the Denis Browne method, and when the child was 6½

years old a total hysterectomy was performed to remove the infantile uterus, fallopian tube, and left gonad.

Case 4. This child, birthweight 2491 g., was the only child of normal parents. Pregnancy was uneventful and the mother received no hormonal medications at any time. Milestones were normal but clitoral enlargement was noticed at 1 month. She was essentially feminine in outlook until the age of 6 years when she

FIG. 6.—Case 3. External genitalia (age 2 yr. 2 mth.) showing phallus bound down in chordae. The urethral meatus lies between labio-scrotal folds, the right fold containing a gonad.

TABLE I
Chromosome Findings in Cases 3 and 4

Case No.	Tissue Cultured	Chromosome Count					Karyotype Diagnosis and Percentage
		<45	45	46	47	>47	
3	Blood	2	2	11	11	0	46, XX (62.5%) and 47, XXY (37.5%)
	Testis	3	1	21	7	0	
	Ovary	2	1	26	9	0	
	Fallopian tube ..	1	2	8	8	0	
	Uterus	1	2	14	13	0	
4	Blood	0	10	13	0	0	45, X, G-, t(Gq : Yq) + (64%) and 46,XXp, G-, t(Gq : Yq) + (36%)
	Skin	4	31	14	0	3	
	Ovary	1	32	18	0	3	
	Testis	4	11	2	0	0	

began to pursue more masculine activities though without aggressive behaviour. The clitoris continued to enlarge, her voice deepened at the age of 12 years and pubic hair appeared one year later. Body hair generally increased and facial acne appeared. By the age of 15 years she was shaving twice weekly; there was neither breast development nor menstruation though a profuse white vaginal discharge was persistent. Treatment with cortisone for 8 months did not modify the hirsutism.

FIG. 7.—Case 4 (age 15½ yr.). Note masculine build and male distribution of body hair.

At the age of 15½ years she was considered unduly introvert and was a stocky, well-built muscular adolescent with a deep voice (Fig. 7). Her height was 162 cm. and weight 49 kg. The thorax was broad and male in configuration, with well-developed pectoral musculature. No breast development was evident and there was a notable depletion of fat over hips, thighs, and pectoral areas. The limbs were conspicuously hirsute, and there was thick hair on the chest and lower back. Pubic hair was of male distribution.

External genitalia. The clitoris and labia majora were large and the introitus with intact hymen was situated rather posteriorly. The median raphe extended from the base of the clitoris to the posterior junction of the labia, interrupted half-way by the urethral orifice. No gonads were palpable in the labia majora or inguinal regions.

Internal genitalia. A vaginogram showed a normal-sized vagina, absence of cervix, and a bicornuate uterus, with its long axis pointing first posteriorly and then anteriorly. At laparotomy, the fallopian tubes appeared normal. The left gonad was 2 cm. in diameter with a cystic area laterally. Following examination of a frozen section, it was removed in its entirety. It consisted almost completely of seminiferous tubules with moderate nodular hyperplasia of the Leydig cells; several dysgenetic tubules were present in one part of the section. The right gonad was streak-like and a small biopsy specimen showed that it consisted of ovarian stroma in which two primordial follicles were found; no hilus cells were recognized.

Investigations. Skeletal age was slightly in advance of her chronological age. Radiologically the sella turcica was normal. The visual fields were normal. The blood pressure was 150/100 mm. Hg. Routine blood and urine biochemistry produced normal results. Excretion of 17-hydroxycorticosteroids was much raised (21.8 mg/24 hr. and 29.8 mg./24 hr.) on two occasions when the child was 13 years old. The 17-ketosteroids were similarly raised at these times (29.7 mg./24 hr. and 19.3 mg./24 hr., respectively). At the age of 15

FIG. 8.—Case 4. Karyotype of cell from skin with 45 chromosomes. Note $t(Y:G)$ translocation chromosome in group G (21–22) (arrow).

years corresponding values were at the upper limit of normal for the age. A diminished adrenal response to exogenous ACTH was also noted. A buccal smear was chromatin negative.

Cytogenetic studies. Cultures were established from peripheral blood, skin, and both gonads. The chromosome counts (Table I) indicate mosaicism with modal counts of 45 and 46. Cells with a 45 complement contained 3 chromosomes in group G (21–22), 5 chromosomes in group F (19–20), and 15 in group C (X 6–12). Morphologically one 'F' group chromosome was very unusual, with one set of arms consistently closely parallel compared with the usual divergence of the other pair of arms. This marker segment was interpreted as representing most of the long arms of the Y chromosome, the other arm presumably being the long arms of the missing G (21–22) chromosome. The final karyotype diagnosis is therefore 45,X,G-, $t(Gq Yq)+$ (Fig. 8). Cells with 46 chromosomes could be interpreted in the same way except that an additional acrocentric intermediate in size between D and G chromosomes was

present. From the dimensions of the long arms, this chromosome was interpreted as representing mostly the short arms of an X. In one or two cells, the short arm telomere had an indistinct outline suggestive of satelliting, and obviously this chromosome could have been derived from the same sequence of fusions which gave rise to the $t(Gq Yq)$ chromosome. The karyotype diagnosis is therefore 46,XXp, G-, $t(Gq Yq)+$ (Fig. 9).

A more detailed description of the chromosome situation in this child including autoradiographic analysis and familial studies will be reported elsewhere.

Progress. The clitoris was subsequently amputated and treatment started with oestrogens. At the age of 18 years she still shaved her face frequently, but breast development was satisfactory and there was monthly withdrawal bleeding. Her appearance was acceptably feminine and she was of normal intelligence. Now, at the age of 20½ years she is still psychologically disturbed by her condition but is able to work adequately. She has recently undergone further plastic surgery on the external genitalia.

FIG. 9.—Case 4. Karyotype of cell from right ovary with 46 chromosomes. Note small acrocentric chromosome in group C (X-6-12) and the translocation chromosome in group G (21-22) (arrows).

FIG. 10.—Case 5. External genitalia (age 1 yr. 10 mth.) showing hypoplastic penis with a urethral opening at its base and absence of scrotum.

Case 5. This patient, birthweight 3001 g., was the first child of a mother aged 22 and father aged 24. Pregnancy was normal, there was no maternal irradiation before or during pregnancy, and the mother took no drugs. Normal delivery occurred at term when his abnormal genitalia were noted. At 9 months he was admitted to hospital for investigation. Apart from the genitalia no abnormalities were observed and a buccal smear was chromatin negative.

External genitalia. The penis was hypoplastic, with labia on each side and a urethral opening at its base (Fig. 10). There was no scrotum but a swelling was observed in the left groin.

Internal genitalia. Urethrography revealed no urethral diverticulum. A cord-like unicornuate uterus was seen at laparotomy; only the right fallopian tube was present leading to a white streak-like structure, representing the *right gonad*. Histologically this proved to be a hypoplastic ovary with typical ovarian stroma. There were a few small collections of granulosa cells and occasional ova. The *left gonad* was situated

FIG. 11.—Case 5. Karyotype of cell from peripheral blood showing 46 chromosomes and the unusual marker C9 in group C (X-6-12) (arrow).

in the left inguinal canal and consisted of infantile testicular tissue showing a tendency for the seminiferous tubules to branch. It is probable that the vagina joined the urethra but this was not ascertained.

Cytogenetic studies. Cells were obtained from cultures of peripheral blood and skin. The modal number was 46 and the karyotype was normal except for one chromosome in group C (X-6-12). This chromosome had a very marked secondary constriction in the long arm near the centromere and was considered to be a morphological variant of chromosome No. 9 (Fig. 11). However, this degree of variation has not been observed previously either in this laboratory or in the literature. The same chromosome was subsequently observed in a female sib of the propositus, the father, and one of his brothers, paternal transmission proving that this is an autosome. The karyotype diagnosis here is interpreted as 46, XY mar 9. A more detailed description of the chromosome situation is planned elsewhere.

Progress. It was decided to rear the child as a male and the first stage in the plastic repair of the hypospadias

was performed when he was 4 years old. Right gonadectomy and hysterectomy will be performed in the future.

Discussion

Since 1959 there have been reports of 67 cases of true hermaphroditism in the literature with full chromosome studies, and these together with the 5 new cases reported here form the basis of the present survey. Some of these cases have been included in previous reviews by Overzier (1963); Guinet *et al.* (1965); and Jones *et al.* (1965). The diagnosis of the condition depends on the histological examination of the gonads, and the testicular and ovarian tissue can be present either as separate gonads or composite ovotestes. As these two types of gonadal tissue induce the development of the respective Wolffian and Müllerian duct systems, it is understandable that many patients show features of intersexuality.

In this paper we shall use the classification of the form of the external and internal genitalia as proposed by Overzier (1963). The five categories are as follows.

Type I:—‘purely female’ form; *Type II*:—common external urethral and vaginal orifice; *Type III*:—urogenital sinus with slight clitoric enlargement; *Type IV*:—internal urogenital sinus and phallus with penile urethra or hypospadias; *Type V*:—‘purely male’ form with or without a uterus which may be well developed or rudimentary.

Fusion of labial folds or bifid scrotum is usually associated with Types IV and V.

The classification of the nature and position of the gonads which we shall use is that devised by Sasaki and Makino (1960). Six groups are recognized (Table II).

TABLE II
Gonadal Classification of True Hermaphrodites

Group	Gonad One Side	Gonad Opposite Side
1	Ovary	Testis
2	Ovotestis	Ovotestis
3	Ovary	Ovotestis
4	Testis	Ovotestis
5	Ovotestis	No gonad
6	Ovotestis	Not examined

The references to the published cases together with the chromosome findings are arranged in Table III under the appropriate gonadal group. For completeness our own patients are also included. Working tables were constructed to record the data on the gonadal and genital findings of all cases. The results of the analyses form the basis of the clinical discussion which follows under the headings external genitalia and internal genitalia including gonads. Extensive comparisons are made between our data on the clinical features from the series as a whole and similar findings recorded by Overzier (1963). His figures have been modified, however, to exclude cases with chromosome studies, thus avoiding duplication. The chromosome findings are discussed in a separate section which also includes reference to non-hermaphrodite cases where the chromosome findings are relevant.

The *external genitalia* in the gonadal intersex have displayed all gradations from male to female pattern, though almost all carry some element of intersexual malformation. In those subjected to full cytogenetic analysis there were four individuals, all with 46/XX chromosome pattern, in whom the configuration of the external genitalia was entirely

normal male (Bregman *et al.*, 1963; Roberts and Khajavi, 1964; Rosenberg, Clayton, and Hsu, 1963, Case 2) or normal female (O'Mahony, 1966). In all other patients some external genital abnormality was present. Those reared as females were usually described as having an enlarged clitoris with or without fused labio-scrotal folds, while those reared as males were said to have hypospadias, usually with a bifid scrotum. Of 29 reared as females, 19 were stated to have enlargement of the clitoris while 5 were recorded as examples of hypospadias. 28 of 35 reared as males and 6 of 7 in whom the sex of rearing was not stated also had hypospadias. Approximately half the cases (35/72) had either fused labio-scrotal folds or a bifid scrotum and a vagina was defined in 32 cases. Though a urogenital sinus was mentioned in only 14 individuals, this feature was probably more frequent than the figures suggest. In his review, Overzier (1963) showed that among the 49 reared as females, 104 as males, and 3 indeterminate, the most frequent urogenital type was Type IV. Here a uterus coexists with a phallus having a penile urethra or hypospadias and an internal urogenital sinus. 69 (40.5%) were of this type and a further 71 were placed in adjacent categories (Types III–V).

Thus the *internal genitalia* usually include a uterus, and indeed there were only 6 cases in this series in which its absence was stated, failure to mention it marking 10 cases. In 25 the uterus was considered of normal size and shape, in 18 it was hypoplastic, and in 12 unicornuate. Descriptions of the tubular structures associated with the uterus and gonads were rather variable, but in the vast majority, there was at least reference to fallopian tubes. An epididymis was specifically mentioned in 17 cases.

Using the Sasaki and Makino (1960) classification of the gonadal arrangement, Table IV shows the total numbers comprising the different groups both from our survey and from the review by Overzier (1963). 61 of 223 (27.5%), with a separate ovary and testis, qualified for group 1, but the majority (72.5%) had at least one ovotestis, or both ovary and testis occupying the same side. An analysis of the situation of ovarian and testicular tissue shows non-uniformity of distribution (Table V). Whereas ovarian tissue was found with approximately equal frequency on each side, testicular material was more frequently observed on the right, the difference proving statistically significant. Some interference in the descent of the testicular material is to be expected because of the high frequency of an ovotestis, and it has

TABLE III
Chromosome Findings in Reported Cases of True Hermaphroditism

GROUP 1: Ovary on one side, testis on other side.			
Blank <i>et al.</i> (1964)	46, XX/48, XXY	O'Mahony (1966)	46, XX
Bregman <i>et al.</i> (1963)	46, XX	Ponté <i>et al.</i> (1967)	45, XO/46, XY
Brögger and Aagenaes (1964)	46, XX/46, XY	Ribas-Mundo and Prats (1965)	46, XX/46, XY/ 47, XXY
Corey <i>et al.</i> (1967)	46, XX/46, XY	Sakatoku <i>et al.</i> (1964)	Case 2 46, XY
Deminatti and Maillard (1967)	{ 46, XX/46, XY 45, XO/46, XX + fragment	Schmidt <i>et al.</i> (1966)	46, XY
Saint Aubert <i>et al.</i> (1968)		Segni and Grossi-Bianchi (1965)	46, XX/46, XY
Dewhurst <i>et al.</i> (1965)		Shearman <i>et al.</i> (1964)	46, XY
Eliachar <i>et al.</i> (1962)	46, XY	Turpin <i>et al.</i> (1962)	46, XX/47, XXY
Ferguson-Smith <i>et al.</i> (1960)	Case 1 46, XX/47, XXX	This report	Case 3 46, XX/47, XXY
Gordon <i>et al.</i> (1960)	46, XX		Case 4 { 45, X, G-, t(Gq Yq) +/ 46, XXp, G-, t(Gq Yq) +
			Case 5 46, XY, mar 9
Jones <i>et al.</i> (1965)	Case 3 46, XX		
GROUP 2: Ovotestis on both sides			
Bernheim <i>et al.</i> (1966)	46, XX	McGovern and Marshall (1962)	Case 2 46, XX
Clavero <i>et al.</i> (1965)	46, XX/47, XXY	Roberts and Khajavi (1964)	46, XX
Grumbach, Morishima, and Chu (1960)	46, XX	Rosenberg <i>et al.</i> (1963)	Case 1 46, XX
Jones <i>et al.</i> (1965)	Case 2 46, XX	Rosenberg <i>et al.</i> (1963)	Case 2 46, XX
Lejeune <i>et al.</i> (1966)	46, XX/46, XY	Sandberg <i>et al.</i> (1960)	46, XY
Manuel <i>et al.</i> (1965)	46, XX/46, XY	Tazaki, Ikeda, and Omori (1964)	46, XX
McGovern and Marshall (1962)	Case 1 46, XX		
GROUP 3: Ovary on one side, ovotestis on other side.			
de Assis, Epps, and Bottura (1960)	46, XX	Josso <i>et al.</i> (1965)	46, XX/46, XY
Domenici and Romeo (1962)	46, XY	di Lorenzo, Ciampalini, and Lotti (1964)	46, XX
Ferguson-Smith <i>et al.</i> (1960)	Case 2 46, XX	Lonsdale <i>et al.</i> (1963)	46, XY + fragment
Friedberg and Rosenberg (1965)	46, XX	McGovern and Marshall (1962)	Case 3 46, XX
Grouchy <i>et al.</i> (1964)	46, XX/46, XY	Merrill and Ramsey (1963)	46, XX
Guinet <i>et al.</i> (1965)	46, XX	Overzier (1963)	46, XX
Harnden and Armstrong (1959)	46, XX	Root <i>et al.</i> (1964)	46, XX
Hung <i>et al.</i> (1966)	46, XY	Sakatoku <i>et al.</i> (1964)	46, XX
Ishizuka, Chihara, and Narita (1964)	46, XX	Sato <i>et al.</i> (1964)	45, XO/46, XY
Jones <i>et al.</i> (1965)	Case 1 46, XX	Waxman <i>et al.</i> (1962 a, b)	{ 46, XX/46, XY 46, XX
Jones <i>et al.</i> (1965)	Case 5 46, XX	Gartler <i>et al.</i> (1962)	
Jones <i>et al.</i> (1965)	Case 6 46, XX	This report	Case 1 46, XX
GROUP 4: Testis on one side, ovotestis on other side.			
Crossfield (1962)	46, XX	Márquez Monter <i>et al.</i> (1966)	46, XX
Fraccaro <i>et al.</i> (1962)	46, XX/47, XXY/49, XYYYY	Rosenberg <i>et al.</i> (1963)	Case 3 46, XX
Hungerford <i>et al.</i> (1959)	46, XX	This report	Case 2 46, XY
Jones <i>et al.</i> (1965)	Case 4 46, XX		
GROUP 5: Ovotestis on one side, no gonad on other side.			
Court Brown <i>et al.</i> (1964)	46, XX	Overzier (1964)	46, XX/46, XY
Dewhurst, Warrack, and Casey (1963)	46, XX	Sasaki and Makino (1960)	46, XX
Knorr <i>et al.</i> (1968)	46, XX/47, XXY	Schuster and Motulsky (1962)	45, XO/46, XY/46, XX
GROUP 6: Ovotestis on one side, other side not examined.			
Hirschhorn <i>et al.</i> (1960a, b)	45, XO/46, XY	Solomon and Green (1963)	46, XX

* Groups refer to the gonadal classification of Sasaki and Makino (1960).

been observed in all positions from a high retro-abdominal location to full descent. In our survey, testicular tissue was present in the scrotum or labio-scrotal fold in 27 of 71 instances; it was inguinal in 19 and abdominal in 25. Of the 22

separate testes, 13 had descended into the scrotum or labio-scrotal fold. Testicular development judged by microscopical examination was almost always very poor, and there were few records of germ cells being identified in the tubules.

TABLE IV
Known True Hermaphrodites Classified According to Arrangement of Gonads

Group	Gonad One Side	Gonad Opposite Side	Known Cases			Total
			*Overzier (1963)	This Review	This Series	
1	Ovary	Testis	40	18	3	61
2	Ovotestis	Ovotestis	39	13	0	52
3	Ovary	Ovotestis	42	22	1	65
4	Testis	Ovotestis	12	6	1	19
5	Ovotestis	No gonad	13	6	0	19
6	Ovotestis	Not examined.. .. .	5	2	0	7
Total			151	67	5	223

* Only cases without chromosome analysis are included to avoid duplication.

To summarize the genital findings in our own patients, in 4 there was either an enlarged clitoris or phallus, associated in 3 with perineal hypospadias; a hypoplastic penis coexisted with perineal hypospadias in the remaining example. 4 had either fused labia or a bifid scrotum but a vagina and urogenital sinus were defined only in 2. A uterus and fallopian tubes (unilateral in Case 4) were found in all. Only in 2 children was there evidence of gonadal descent, and this proved to be a testis in each.

Congenital malformations of other organ systems were rare and without any consistent relationships. They included agenesis of right kidney (Roberts and Khajavi, 1964); congenital heart disease (Fraccaro *et al.*, 1962); minor anomalies of the lumbo-sacral spine (Jones *et al.*, 1965); pes planus and short hallux (Lonsdale, Mercer, and McCullagh, 1963); bilateral anophthalmia (Root *et al.*, 1964).

Analysis of the *chromosome findings* in true hermaphroditism shows that of the 72 cases studied, 38 (53.5%) are 46/XX, 9 (12.5%) are 46/XY, and 24 (32.5%) show mosaicism for the sex chromosomes (Table VI). The proportion of

abnormal karyotypes (34%) is probably rather high because during recent years the abnormal ones are more likely to have been published. Nevertheless anomalies of the sex chromosome complement form a significant contribution to the aetiology of the condition and in this report 2 of 5 cases have abnormal karyotypes. Table VI shows that chromosome mosaics form the greater proportion of group 1 hermaphrodites. In all the other categories, a normal female karyotype predominates. XX/XY mosaicism is particularly significant; 10 of the 15 known examples being proven to be true hermaphrodites. From a genetical point of view they form an interesting group because of the substantial evidence from blood group and serum protein marker studies that they often arise from double fertilization. Waxman and his associates (Waxman *et al.*, 1962b; Waxman, Gartler, and Kelley, 1962a; Gartler, Waxman, and Giblett, 1962) were the first to observe two populations of red cells for the MNS and Rh systems in such an individual. Similarly Zuelzer, Beattie, and Reisman (1964) and Myhre

TABLE V
Distribution of Gonadal Tissue

Author	Testis		Ovary	
	Left	Right	Left	Right
Overzier (1963)	68	111	101	107
This series ..	35	55	53	51
Total	103	166	154	158
Statistics	$\chi^2 = 14.7$; $p < 0.001$		$\chi^2 = 0.051$; $0.8 < p < 0.9$	

* One degree of freedom.

TABLE VI
Gonadal Classification and Karyotype Diagnosis

Group*	XX	XY	Mosaics	Others	Totals
1	4	5†	12‡	0	21
2	9	1	3	0	13
3	16	2	4	1	23
4	5	1	1	0	7
5	3	0	3	0	6
6	1	0	1	0	2
Totals	38	9	24	1	72

* Groups refer to gonadal classification of Sasaki and Makino (1960) (see text and Table II).

† Includes from this report unusual familial marker No. 9.

‡ Includes from this report complex mosaic with t(Gb Yq).

et al. (1965) have shown two cell populations for ABO, Se, Jk^a, and haemoglobin and for ABO, and Jk^a, respectively, in their cases, while the patient of de Grouchy *et al.* (1964) had a double phenotype for haptoglobin (Hp 2-1 and Hp 2-2).

The majority of XO/XY mosaics, on the other hand, are not true hermaphrodites, for in those cases with mixed gonadal dysgenesis, the ovarian tissue consists only of stroma without follicles and is similar to that found in XO Turner's syndrome (Ferguson-Smith, 1965). Nevertheless 3 cases are reported with definite ovarian and testicular tissue in one or both gonads (Hirschhorn, Decker, and Cooper, 1960a, and b; Sato *et al.* 1964; and Ponté *et al.*, 1967).

Eight examples of XX/XXY mosaicism have been reported. Those of Botella-Llusia (1960)—cited by Guinet *et al.* (1965), Turpin, Lejeune, and Breton (1962), Clavero *et al.* (1965), and Knorr *et al.* (1968) were true hermaphrodites, but the patients described by Ford *et al.* (1959), Hayward (1960), and Hecht *et al.* (1966) had features of Klinefelter's syndrome with gonads, presumed to be testes, descended into the scrotum. No details of the gonadal and urogenital findings of the eighth patient were given in the paper by Raha, Sarkar, and Mukherjee (1967). However this case was interesting because an anomaly of ABO blood group inheritance could point to the presence of two genetically different populations of cells.

Case 3 in this paper is closely similar to the patient described by Turpin *et al.* (1962), having a similar configuration of the external and internal genitalia with an ovary on the right and testis on the left. A very similar mosaic form, XX/XXYY, was reported by Blank *et al.* (1964). Clinically this child was also similar to the above cases, except that the position of the ovary and testis was reversed.

Triple stem cell mosaics giving rise to true hermaphroditism include XX/XY/XXY (Ribas-Mundo and Prats, 1965); XX/XXY/XXYY (Fraccaro *et al.*, 1962); and XO/XY/XX (Schuster and Motulsky, 1962). The chromosomal constitution of the 11-year-old boy with hypospadias reported by Siebner and Schöck (1964) XO/XY/XXY/XX, had the potential of producing true hermaphroditism. However, he proved to have 'mixed' gonadal dysgenesis with a right testis and left ovarian streak.

Other abnormal karyotypes reported include XX/XXX (Ferguson-Smith, Johnston, and Weinberg, 1960), XO/XX + fragment (Dewhurst *et al.*, 1965), and XY + fragment (Lonsdale *et al.*, 1963).

Two further cases, described by Sarkar *et al.* (1966), were stated to have abnormal karyotypes.

However, the illustrations of chromosomes leave considerable doubt about the karyotype diagnosis, and consequently these cases have been excluded from this survey.

However, mosaicism by no means accounts for all true hermaphrodites despite multiple tissue culture studies in some cases (Root *et al.*, 1964; Shearman *et al.*, 1964; Jones *et al.*, 1965; Hung *et al.*, 1966; Case 2—this report). There must be some other explanation to account for the predominance of normal karyotypes, and it has been suggested by Ferguson-Smith (1966) that X-Y chromosomal interchange might play a significant role. Cytological evidence of the phenomenon is not yet available, and in any case a small translocation would be difficult to detect by present methods. However, he has pointed out the existence of one or two instances of anomalous inheritance of the Xg blood group which would fit the hypothesis. Translocations involving the Y chromosome and an autosome have been observed. Schultz and Passen (1963) described a child with 46 chromosomes and a t(Yq+ : 1p(or q) —) translocation. His multiple anomalies were probably due to the partial deletion of chromosome No. 1 in the cells lacking the Y- translocation chromosome. Another child with multiple anomalies, including a very small penis and only a small right testis in a complete scrotum was reported to have 47 chromosomes by Nakagome, Smith, and Soukup (1968). The additional chromosome with a median centromere was composed of the long arms of a second Y and a segment of unknown origin. Again most of the anomalies were probably attributable to the duplicated autosome segment.

There are two further reports of individuals with Y translocation in whom anomalies are restricted to the urogenital system. The first, described by van den Berghe *et al.* (1965), concerned a man of short stature with hypogonadism who developed gynaecomastia after puberty. Testicular biopsies showed degenerative changes of the tubules and Leydig cell hyperplasia. His karyotype with 46 chromosomes contained a translocation t(2p— : Yp+). The second case (Federman, Davidoff, and Ouellette, 1967) was shown at laparotomy to possess a uterus and hypoplastic fallopian tubes, the right tube being associated with an ovarian streak and the left with a testis lacking evidence of spermatogenesis. Chromosome studies performed on a wide range of tissues revealed that the child was an unusual mosaic with 45/X cells and 45/X, D,- t(Dq : Yq) + cells.

Further evidence of translocations between the Y chromosome and a D or G group chromosome was presented by Genest, Bouchard, and Bouchard

(1967a, b). In their study of a family containing a male with Down's syndrome they discovered that the Y chromosome in a number of individuals had distinct satellites attached to the ends of the long arms. This terminal region was often involved in satellite association with other acrocentrics. Finally, Ferrier *et al.* (1967) have described the complex situation in a family in which both a translocation and XO/XY/XXY mosaicism have occurred. Because of the tendency for meiotic and mitotic non-disjunction of the Y chromosome in this family, the authors postulate that the additional material translocated to the short arms of a D (13-15) chromosome represents part of the Y.

Our fourth case is of special import in that she represents the first known example of true hermaphroditism associated with a Y-autosome translocation. The single cell line 45/X, t(Gq:Yq) would probably have produced a male intersex with testes or possibly mixed gonadal dysgenesis. However, the presence in the second cell line of the additional chromosome, probably composed of the short arms of X, could explain the occurrence of both testicular elements and ovarian tissue containing follicles.

In conclusion, though the normal female karyotype predominates, chromosome abnormalities are frequently encountered in true hermaphroditism, and these almost invariably involve sex chromosome mosaicism. The chromosome complements of the cell lines which form the mosaic are important. For example primordial cells with XX or XXX would be expected to form ovarian tissue when present as the sole cell line in a non-mosaic female individual, and, likewise, XY, XXY, and XXYY cells would give rise to testicular tissue in a non-mosaic male individual. In mosaics with a mixture of such potentially 'male' and 'female' cells, features of intersexuality are likely to be evident and both types of gonadal tissue could well be present. This is confirmed in the majority of patients with XX/XY and XX/XXY mosaicism.

The presence of ovarian tissue with follicles in the three XO/XY mosaics is more difficult to explain because an XO cell line, as in Turner's syndrome, produces only rudimentary streak gonads devoid of follicles. Presumably these cases must be considered in the same light as the normal males (46, XY) with true hermaphroditism. Equally it is difficult to explain testicular development in patients with a normal female karyotype (46, XX). The X-Y interchange proposal is an attractive theory but cytologically difficult to prove. In the foregoing discussion, however, we have also presented evidence that the Y chromosome

can be involved in translocations at least with autosomes, and that true hermaphroditism can be associated with a Y-autosome translocation, as in our Case 4. Despite the consequences of X-inactivation, it is reasonable to speculate that ovotestes would be observed more frequently in individuals with a single 46, XX cell line than in the mosaic forms where separate cell lines could give rise more readily to separate testes and ovaries. This is borne out by the data. In the group 1 true hermaphrodites with a separate ovary and testis only 4/21 (19%) are 46, XX while 12/21 (57%) are mosaics. In all other groups with at least one ovotestis, the normal female 46, XX karyotype predominates over mosaic forms (34/51, 66.5% and 21/51, 23.5% respectively).

Summary

The presence of both testicular tissue and ovarian tissue with follicles in the same individual (true hermaphroditism or gonadal intersexuality) is a rare condition. Since the introduction of chromosome studies only 67 well-documented cases have been reported. In this paper we review the clinical, gonadal, and cytogenetic findings in all those cases and describe fully our own series of 5 patients. Though there was wide variation in the form of the external and internal genitalia, 40.5% of cases conformed to urogenital Type IV, with enlarged phallus, bifid scrotum, perineal urethral orifice, vagino-urethral fistula, and uterus. The majority (72.5%) had at least one ovotestis, or testis and ovary on the same side. Testicular tissue, often with reduced germ cells, was more frequently observed on the right, the difference being statistically significant.

Chromosomally more than half (53.5%) were normal females (46, XX), 12.5% were normal males (46, XY), and most of the remainder (32.5%) were sex chromosome mosaics. The last included a significant proportion of 46, XX/46, XY and 46, XX/47, XXY mosaics, though not all individuals with these karyotypes are true hermaphrodites. Our own series included a 46, XX; a 46, XY; a 46, XX/47, XXY mosaic; a 46, XY with an unusual familial group C marker in which the uncoiled secondary constriction region may be duplicated; and finally a mosaic with possible XO/XXp mosaicism combined with a t(Y:G) translocation. Abnormal karyotypes noted in the literature are reviewed and the possibility of translocations involving the Y chromosome are discussed. Known cases of Y-autosome translocations are surveyed, but one case in this report appears to be the sole

true hermaphrodite to have this type of translocation.

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Addendum

Parental karyotype analyses in Case 4 showed the mother to be a normal female (46, XX); the father had 46 chromosomes with deleted Y and t(G:Y) translocation in all cells.

Correspondence to Dr. L. J. Butler, Queen Elizabeth Hospital for Children, Hackney Road, London E2.