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The occurrence of gonadal dysgenesis in association with monozygotic twinning*

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Summary. A case is presented of a monozygotic twin pair, discordant for phenotypic sex, in which the female member showed gonadal dysgenesis and chromosomal mosaicism. Review of the pertinent literature reveals that in monozygotic twin pairs, phenotypic and karyotypic concordance is the usual occurrence for Down's and Klinefelter's syndromes, whereas discordance often accompanies gonadal dysgenesis. Mosaicism is a frequent concomitant of gonadal dysgenesis in monozygotic twins. Our case strengthens the probability of a real association between mosaicism and monozygotic twinning in gonadal dysgenesis.

We wish to report another example of gonadal dysgenesis occurring in only one of a pair of monozygotic twins.

Case report

History. The proposita, a Caucasian female, was referred to the University of Washington Hospital in September, 1968 at age 17 for evaluation of primary amenorrhoea, lack of breast development, and short stature.

The patient was one of a set of twins born at full term after an uncomplicated pregnancy. Her birth weight was 2412 g and that of her brother was 3001 g. At the time, the obstetrician noted there was 'only one placenta'. For the first year of the twins' lives, except for the weight difference, the mother could not tell them apart with their diapers on. Their prepubertal development was within normal limits; they were both very good students, and they were healthy throughout childhood.

The male twin underwent normal pubertal development at age 14, with normal male sexual maturation and growth to 168 cm by age 17. The patient, on the other hand, had some growth of pubic and axillary hair at approximately age 14, but she had no growth spurt, breast development, or menses. By age 17, she was notably shorter than her classmates.

Physical examination. Height 144 cm, weight 51·3 kg, blood pressure 120/80. The posterior hairline extended down the midline to the thoracic vertebrae with some further midline hair growth. The palate was arched. The neck was not webbed, and the thyroid gland not enlarged. The right pupil was 1–2 mm larger than the left; both irises were evenly coloured. No cardiovascular abnormalities were noted. The breasts were small, and the nipples and areolas undeveloped. Between the breasts there was a 2×3 cm area of coarse black hair. Black hair grew abundantly on the arms, pubis, abdomen, and the moustache area. There was a moderately-increased carrying angle at the right elbow. The clitoris was enlarged, measuring $3 \times 0{\cdot}7$ cm. The vaginal mucosa appeared hypoestrogenic, being thin and red, with little rugosity. The cervix was small, and the uterus was approximately 4×2 cm; the gonads were not palpable. Neurological examination was grossly normal.

Colour vision, evaluated by the pseudoisochromatic plates of Hardy–Rand–Rittler (1957 edition), revealed moderately severe deuteranopia in both twins. The mother and all other sibs had normal colour vision. (Fig. 1).

Family history (Fig. 2). The twins have a younger brother with first-degree hypospadias; two other sibs and two half-sibs are normal in all respects. The twins' father died in a drowning accident; he reportedly had red–green colour blindness.

Laboratory examinations

The patient's haematocrit was 40%. Twenty-four-hour urinary FSH excretion (ovarian augmentation assay) was 133 IU (normal range 1·8–2·5 IU

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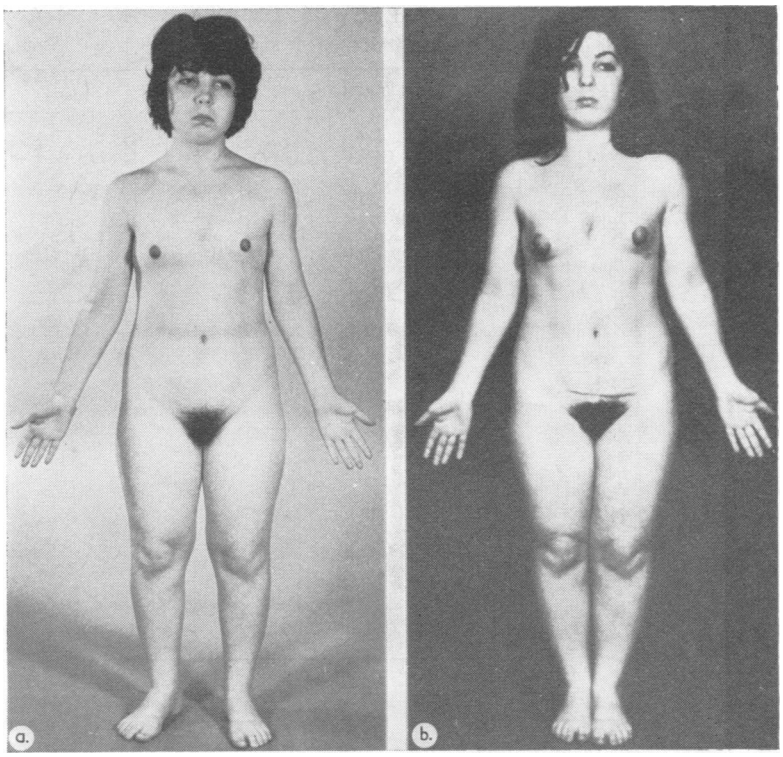

FIG. 1. The patient before (a) and after (b) oestrogen therapy.

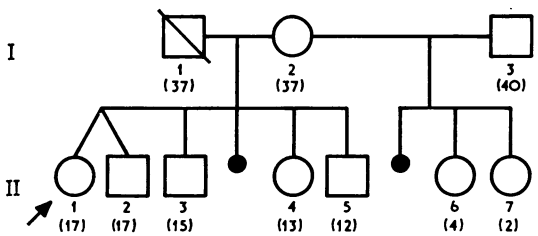

FIG. 2. Family pedigree.

second International Reference Preparation/24 hours); the 24-hour urinary 17-ketosteroid excretion, measured on three occasions, was 5·3 mg, 12·3 mg, and 12·4 mg. Twenty-four-hour urinary oestriol excretion was 3·5 μg on one occasion and 4·0 μg on another occasion (normal range for non-pregnant, reproductive-age women is 4 to 20 μg). Thyroid function studies were normal, as were the levels of blood urea nitrogen, electrolytes, creatinine, alkaline phosphatase, bilirubin, glucose, calcium, phosphorus, and total protein. Radiology revealed a retarded bone age, corresponding to 13½ to 14 years, as well as the following findings consistent with gonadal dysgenesis: generalized hypomineralization; short metacarpals (especially the right fourth); altered relationship of the distal radii and ulnas; relative hypoplasia of the medial tibial condyles with beaking of the medial metaphyses; and slightly increased carrying angle of the elbows. On IVP the right kidney was normal and 12·5 cm long; the left kidney was rotated and enlarged to 16 cm with lateral displacement of the ureter. No abnormalities were detected on ECG or chest radiology.

Thyroid antibodies. No anti-thyroglobulin nor anti-thyroid microsomal (tanned red cell and indirect immunofluorescent tests, respectively) antibodies were found in the blood of either twin. However, anti-thyroid microsomal antibodies were detected at a titre of 1:30 in the mother's serum. The 15-year-old brother had this antibody at a titre of 1:30 and an anti-thyroglobulin antibody titre of 1:2187.

Genetic markers (Table I). When the patient's blood was tested for the markers listed in Table I,

TABLE I

BLOOD AND SERUM GROUP STUDIES

Locus	Mother	Female Twin	Male Twin	Brother	Sister	Brother
Blood-group antigens						
ABO	O	O	O	O	O	O
Rh	C+D+E−c+ e+V−Cw−	C+D+E−c− e+V−Cw−	C+D+E−c− e+V−Cw−	C+D+E−c− e+V−Cw−	C+D+E−c+ e+V−Cw−	C+D+E−c− e+V−Cw−
MNSs	M+N−S−s+	M+N−S−s+	M+N−S−s+	M+N−S−s+	M+N−S−s+	M+N−S−s+
P	P_1+	P_1+	P_1+	P_1+	P_1+	P_1+
Lutheran	Lu(a−b+)	Lu(a−b+)	Lu(a−b+)	Lu(a−b+)	Lu(a−b+)	Lu(a−b+)
Kell	K−k+Kp (a−b+)Js(a−)	K−k+Kp (a−b+)Js(a−)	K−k+Kp (a−b+)Js(a−)	K−k+Kp (a−b+)Js(a−)	K−k+Kp (a−b+)Js(a−)	K−k+Kp (a−b+)Js(a−)
Lewis	Le(a−b+)	Le(a−b+)	Le(a−b+)	Le(a−b+)	Le(a−b+)	Le(a−b+)
Duffy	Fy(a+b+)	Fy(a−b+)	Fy(a−b+)	Fy(a+b+)	Fy(a−b+)	Fy(a−b+)
Kidd	Jk(a+b+)	Jk(a+b−)	Jk(a+b−)	Jk(a+b+)	Jk(a+b−)	Jk(a+b−)
Diego	Di(a−)	Di(a−)	Di(a−)	Di(a−)	Di(a−)	Di(a−)
Xg	Xg(a+)	Xg(a+)	Xg(a+)	Xg(a+)	Xg(a+)	Xg(a+)
Serum proteins						
Hp	2-1	2-1	2-1	2-1	2-1	2-1
Tf	C	C	C	C	C	C
Gc	1-1	1-1	1-1	1-1	1-1	1-1
Blood cell enzymes						
PGM_1	2-2	2-1	2-1	2-2	2-1	2-1
AcPh	A	BA	BA	BA	BA	BA
PGD	A	A	A	A	A	A
AK	1	1	1	1	1	1
PHI	1	1	1	1	1	1
Pep A	1	1	1	1	1	1
Pep B	1	1	1	1	1	1
GSR	Usual	Usual	Usual	Usual	Usual	Usual
G6PD	B	B	B	B	B	B
DPNH diaph	Usual	Usual	Usual	Usual	Usual	Usual
ADA	1	1	1	1	1	1
Colour vision	Normal	Deuteranopia	Deuteranopia	Normal	Normal	Normal

there was no evidence of two separate cell populations. Tests on the blood of the other family members showed that the phenotypes of the patient and her twin brother could have been discordant in at least seven systems (Rh, MNSs, Duffy, Kidd, PGM_1, Hp, and colour vision); however, in all of these, they were concordant. This fact alone indicates that the probability of monozygosity is greater than 0·99.

Cytogenetics (Fig. 3). Bilateral buccal smears from the patient showed no X-chromatin bodies, but Y-chromatin bodies were observed in her buccal smear and lymphocytes. X- and Y-chromatin patterns of the patient's full sibs and their mother were consistent with phenotypic sex.

All but one of 50 phytohaemagglutinin-stimulated blood lymphocytes examined from the male twin contained 46 chromosomes, and karyotypes were normal 46,XY. The one cell with 45 chromosomes lacked a Y. Forty of 50 blood cells from the patient were intact, with 46 chromosomes and five G-group members; seven cells contained 45 chromosomes and three had less than 45. Only one of

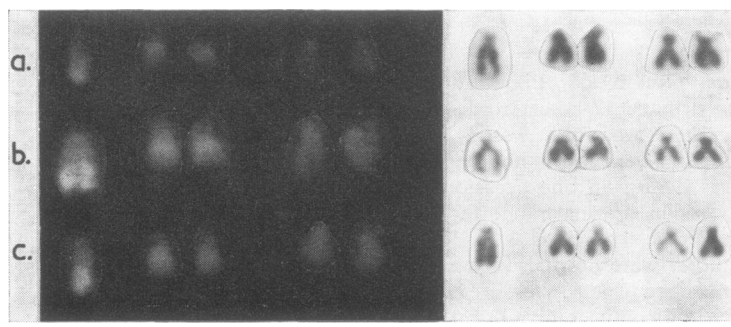

FIG. 3. Composite of G-group chromosomes (Y,21,22) of the patient (a), her male twin (b), and her younger brother (c). (QM and tetrachrome stains.)

TABLE II

DERMATOGLYPHIC FINDINGS

Digital ridge counts

	Left (radial/ulnar)					Right (ulnar/radial)					Total Ridge Count
	5	4	3	2	1	1	2	3	4	5	
Patient	0/8	0/8	2/0	20/0	0/16	20/0	0/0	0/1	15/0	15/0	115
Twin	0/5	0/23	0/3	3/0	0/19	19/4	0/0	1/0	23/0	4/0	100
Brother	9/13	7/15	0/10	6/0	0/17	17/14	0/9	11/0	11/10	16/10	125
Brother	0/4	0/6	4/0	4/0	0/15	20/16	0/6	4/0	7/0	7/0	77
Sister	0/17	12/24	0/15	14/0	0/20	21/0	0/14	11/0	24/0	18/0	178

Palmar formulae*

	Left	Right
Patient	11.X.7.3 – t',t' – L^{u}.O.O.V.O	11.0.7.4 – t' – O.O.O.O.O
Twin	11.X.7.4 – t' – O.O.O.V.O.	11.7.7.5′ – t' – O.O.O.O.1^{d}
Brother	10.X.6.3(2) – t' – O.O^{sm}.V.O	11.10.8.3 – t' – O.O.O.L^{d}.O
Brother	10/7.8.7(6).3 – t' – O.O.O.O.L^{d}	11.11(10).9(8).4 – t' – O.O.O.L^{d}.O
Sister	9.7.5′.3(2) – t' – O.O.O.O.L^{d}	11(10).8.7(6).3 – t' – O.O.O.L^{d}.O

* Main line terminations D.C.B.A.—axial triradius position—pattern areas hypothenar —thenar interdigital one $(1_1).1_2.1_3.1_4$ (Cummins and Midlo, 1961).

these 10 hypomodal cells lacked a G-group member and the rest had random chromosome loss. Karyotypes of intact cells from the patient were indistinguishable from those of her twin. No late-labelled X was found on radioautographic study, and the presence of the Y chromosome in the patient's blood cells, those of her twin, and those of another brother was confirmed by fluorescence. Lymphocyte karyotypes of the patient's mother and full sibs were consistent with phenotypic sex. All chromosomes appeared morphologically normal. Specifically, the morphology and fluorescence of the patient's Y chromosome did not differ from that observed in her twin and her non-twin brother.

Morphology of ejaculated spermatazoa of the male twin appeared normal. A fluorescent Y-chromatin body was noted in 450 of 1000 mature sperm cells.

Dermatoglyphics (Table II). Although dermatoglyphic traits common to all the sibs were observed, the increased similarities of the main line coursings and pattern shapes on both the hands and feet of the patient and her twin were remarkable when contrasted with their sister and brothers. These similarities were emphasized particularly when main lines and patterns differed as, for example, the right hand main line C which was absent in the patient and which, while present in her twin, recurved almost at the triradial point to form a very small loop distal, ie, while formulated differently both palms expressed the same genetic tendency to suppression at this point. This C-line suppression was complete in both of their left palms and was seen only unilaterally in one brother.

Operative and pathological findings (Fig. 4a and 4b). Because of the risk of gonadal neoplasm in phenotypic females with a Y chromosome (Fathalla, Rashad, and Kerr, 1966; Taylor, Barter, and Jacobson, 1966; Barr, *et al*, 1967; Josso *et al*, 1969), the patient underwent laparotomy, with removal of both fallopian tubes and gonads. The uterus was not removed, so that periodic hormonal withdrawal bleeding could later be induced. Histologically, the right gonad was a streak of fibrous tissue with some ovarian stroma. The left gonad consisted mainly of fibrous stroma, but there was a focus of seminiferous tubules which contained

TABLE III

CHROMOSOME ANALYSIS OF CELLS FROM BLOOD, GONADS, AND TUBES

	Blood	R. Gonad	L. Gonad	R. Tube	L. Tube
No. of cells counted	50	103	52	49	100
No. of cells karyotyped	11	14	5	19	12
Cell lines	46,XY	45,X	45,X	45,X(66%)/46,XY(34%)	45,X(97%)/46,XY(3%)

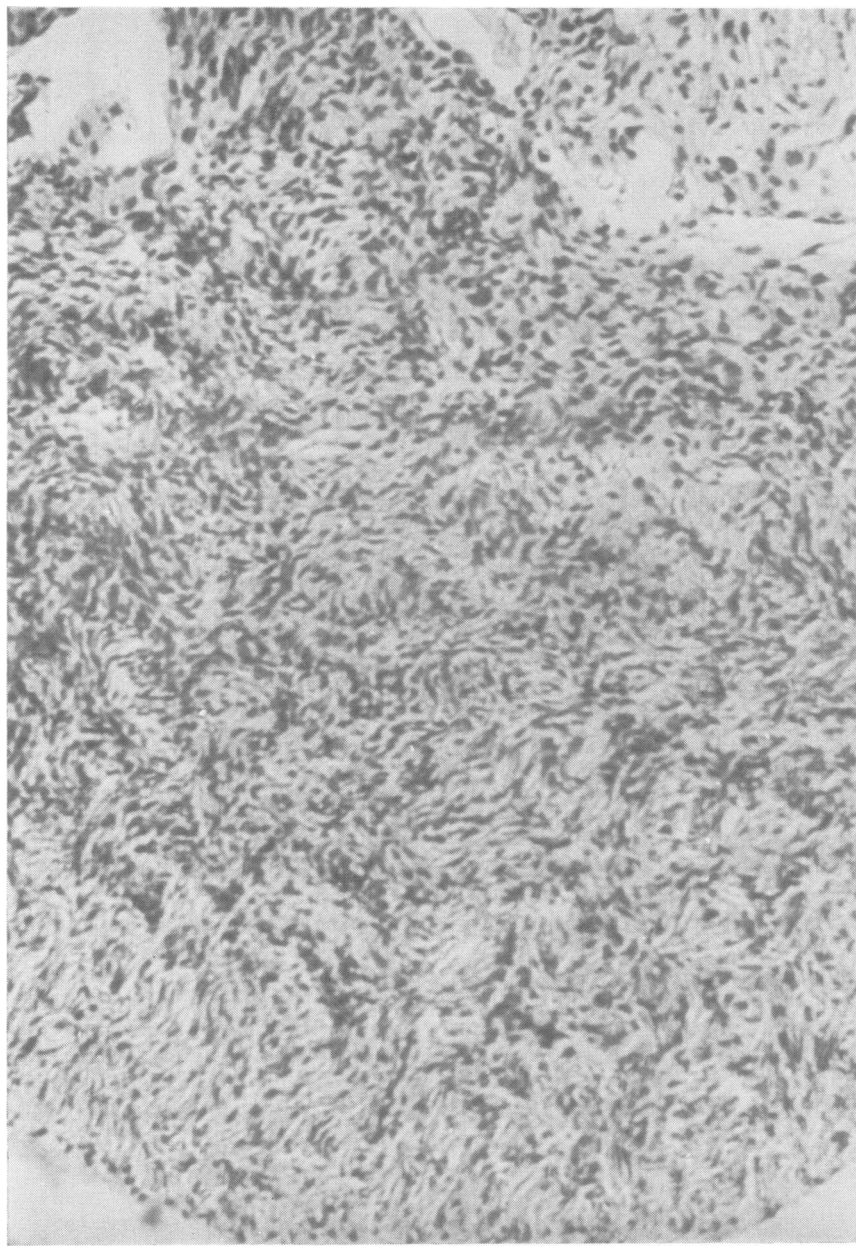

FIG. 4a. Right gonad, microscopic section (× 100).

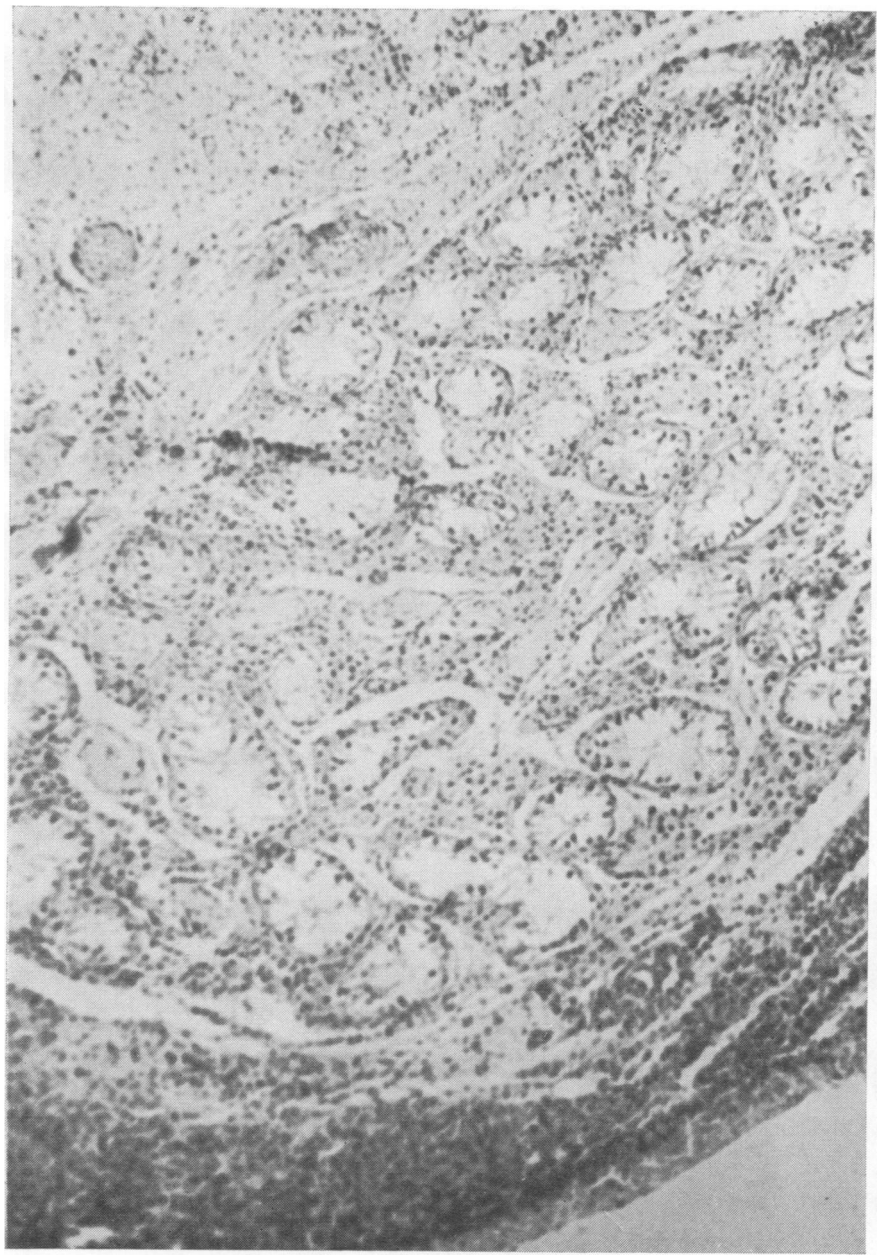

FIG. 4b. Left gonad, microscopic section (× 40).

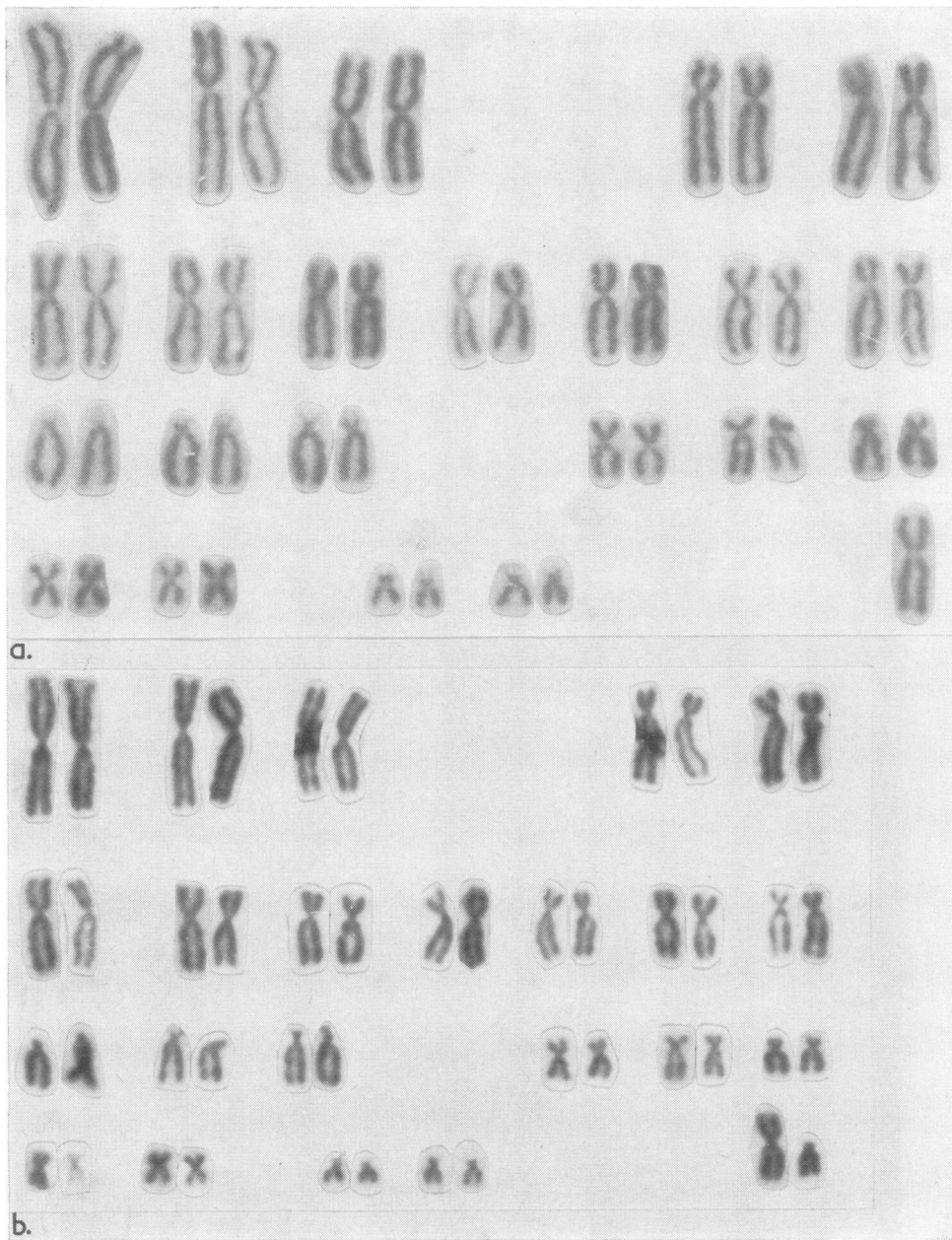

FIG. 5. 45,X karyotype (a) and 46,XY karyotype (b) in the fallopian tube of the patient.

Sertoli cells. In addition, one small area of calcification surrounded by granulosa cells, which possibly might represent gonadoblastoma was noted.

Karyotypes of cultured cells from both gonads were uniformly 45,X but cultures of the fallopian tubes consisted of a mixture of 45,X and 46,XY cells: the percentage ratio of 45,X to 46,XY was 66 to 34 on the right and 97 to 3 on the left (Fig. 5 and Table III).

After surgery, cyclic therapy with Enovid E produced withdrawal menstrual bleeding, some degree of breast development, and deposition of fat over the hips and buttocks. Yearly follow-up examinations have shown adequate feminization of all oestrogen-sensitive tissues and good psychological adjustment to her condition.

Discussion

Only one of 50 examined blood lymphocytes from the proposita and one of 50 from her co-twin were compatible with a 45,X karyotype. Thus blood mosaicism, a feature of some previous cases of monozygotic twins with discordance for gonadal dysgenesis, was not readily apparent in either member of our twin pair. However, chromosomal mosaicism was evident in cultivated cells from the proposita's rudimentary gonads and fallopian tubes. Since no tissue other than blood was studied in the phenotypically normal male co-twin, we cannot confidently exclude the presence of a minor 45,X cell line.

The causes of chromosomal mosaicism are unknown, but among possible predispositions are parental thyroid autoimmunity or structural chromosome aberrations. For example, in some cases X/XY mosaicism has been associated with structural abnormalities of the Y chromosome (Starkman and Jaffe, 1967; Caspersson *et al*, 1971; LoCurto *et al*, 1972). However, fluorescence studies demonstrated identical and apparently normal Y chromosomes in both twins reported here. While it was not possible to examine the father's Y, essentially the same information was provided by the Y chromosome of the non-twin male sib. The proposita's mother and a normal sib had thyroid antibodies and there are data to suggest that the presence of thyroid autoimmunity in a woman predisposes her to a child with a post-zygotic chromosomal abnormality such as XY/X mosaicism (Fialkow, 1966; Fialkow and Uchida, 1968).

The proposita and her twin brother had discordant phenotypes, an observation reported in most previously described monozygotic twin pairs when gonadal dysgenesis is involved (Turpin *et al*, 1961; Mikkelsen, Frøland, and Ellebjerg, 1963; K. Benirschke and M. M. Sullivan, personal communication; Edwards, Dent, and Kahn, 1966; Shine and Corney, 1966; Jacobs, 1969; Ross, Tjio, and Lipsett, 1969; Potter and Taitz, 1972). In apparent contrast to this are the findings of phenotypic and karyotypic *concordance* reported in most—but not all (Nielsen, 1967)—monozygotic twin pairs with Down's or Klinefelter's syndrome and in one pair with XYY (Zellweger, 1968; Nicolis *et al*, 1972; Rainer, Abdullah, and Jarvik, 1972). Since mosaicism occurs in most monozygotic twins with gonadal dysgenesis, both events, twinning and the chromosomal disorder, arose post-zygotically. On the other hand, the abnormalities leading to some, and perhaps to many cases of trisomy 21, XXY and XYY are prezygotic, when concordance in monozygotic twin pairs is more apt to occur.

Mosaicism, detected in our case as well as in several other cases of monozygotic twins discordant for gonadal dysgenesis (Mikkelsen *et al*, 1963; Edwards *et al*, 1966; Ross *et al*, 1969) was also present in at least five (Turner and Zanartu, 1962; Russell *et al*, 1966; Ferrier, Ferrier, and Kelley, 1970; Muller *et al*, 1970; van der Horst, Frankel, and Grace, 1971) and probably six (Lemli and Smith, 1963) of the nine reported monozygotic female twin pairs concordant for sex chromosomal aneuploidy.*

Furthermore, in our opinion, the reported data for the three remaining twin pairs (Decourt *et al*, 1964; Klempman, 1964; Riekhof, 1972) are not sufficient for accurate assessment of mosaicism. Thus, we are unaware of any monozygotic twin pair definitely concordant for non-mosaic 45,X. At least in part, this finding can be explained by severe selection *in utero* against 45,X fetuses, especially in twin pregnancies.

The association between monozygotic twinning and chromosomal mosaicism may not be unique to gonadal dysgenesis. Although mosaicism has not been reported frequently in monozygotic twins with Down's or Klinefelter's syndrome, one should be cautious in interpreting results of studies in which adequate techniques for the detection of mosaicism and zygosity were not applied. In any event, the findings in our case, when added to previous reports, strengthen the probability that in gonadal dysgenesis there is real association between mosaicism and monozygotic twinning (Nance and Uchida, 1964; Benirschke and Kim, 1973a and b). It is

* The twins reported by Turner and Zanartu (1962) have been cited as non-mosaic 45,X, but the cytological findings as partially indicated in the title, 'Ovarian dysgenesis in identical twins: discrepancy between nuclear chromatin patterns in somatic cells and in blood cells', strongly suggest mosaicism.

likely that the association is based on some fundamental relationship, but a more definitive answer requires intensive study of more cases of phenotypically normal as well as abnormal monozygotic twin pairs.

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