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Gonadal Dysgenesis With a Familial Character

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Familial gonadal dysgenesis is extremely rare. Several cases of two or three sisters with pure gonadal dysgenesis in the same family have been reported. In 1959, Elliot reported a family in which 3 sisters were affected, and Hauser, in 1963, mentions three other pairs. Von Opitz (*cit.* by Cohen and Shaw, 1965) reports two sisters with the XX karyotype and positive sexual chromatin; Stanescu and Maximilian (1966) studied 3 sisters with the XY karyotype. Similarly, sisters with pure gonadal dysgenesis and XY karyotype, but with gonadal degeneration, have been described.

Frasier (1964) studied a MZ twin pair with bilateral gonadoblastoma; Broggen and Strand (1965) two sisters — one with pure gonadal dysgenesis and the other with bilateral dysgerminoma — and Cohen and Shaw (1965) two sisters with gonadoblastoma.

In 1963, Josso drew up a summary of the familial cases of Turner's syndrome. Part of these cases, however, do not belong to Turner's syndrome, but to pure gonadal dysgenesis or " nonfunctional ovaries ", as sustained by Josso.

Several brothers with testicular dysgenesis have likewise been cited: Overzier, 1956, Aslev and Reinvein, 1958; Sohval and Soffer, 1953; Reiner-Grnja, 1955.

Similarly, families are known in which one of the children presented Klinefelter's syndrome (XY) and the other Turner's syndrome (XO/X isochromosome X) (Padeh, 1964). In 1956, Bassoe reported a similar case, but which was of course not investigated cytogenetically. We had the occasion to study a subject with Klinefelter's syndrome (XXY), whose sister was affected by primary amenorrhea and mental retardation — which however was not studied — (Esanu-Maximilian, *unpubl.*).

The presence in the same family of a brother with congenital anorchidism and an XY karyotype and of a sister with evident clinical phenomena of hypogonadism and an XO/XX/XXX karyotype does not appear to have been mentioned in literature up to the present.

Case I

R.P., aged 40 years, presents marked gonadic, organic and functional deficiency, with deficient sexual differentiation.

The patient has a characteristic edematous, inexpressive *facies*, with reduced pilosity, flat infantile nose and thick lips. Undifferentiated voice. However, he had

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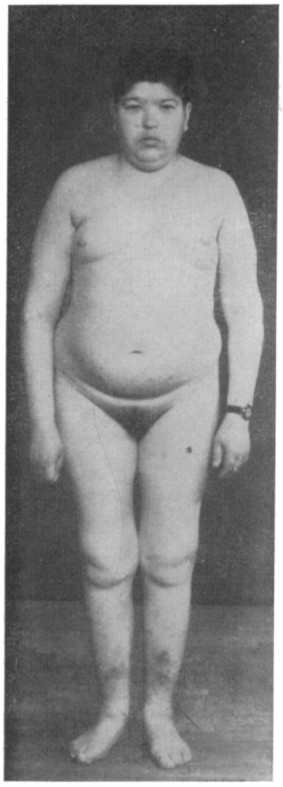

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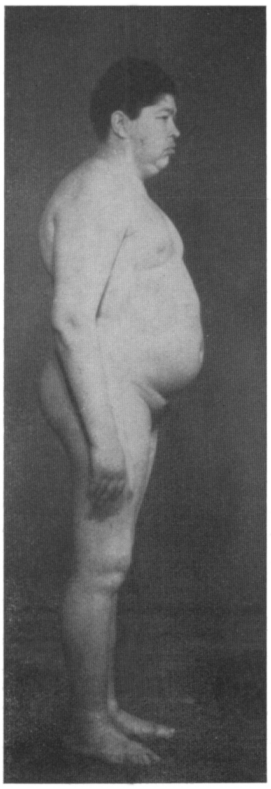

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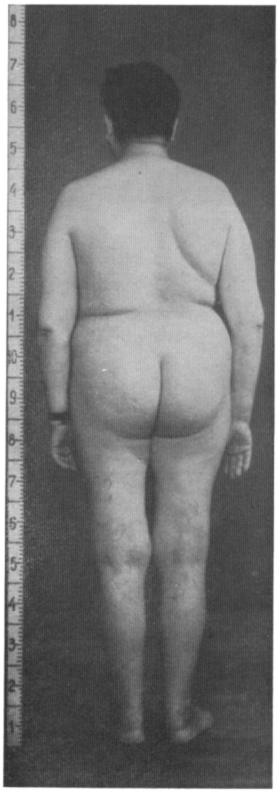

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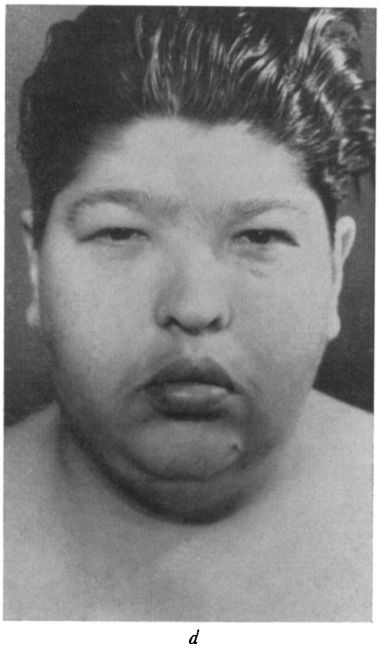

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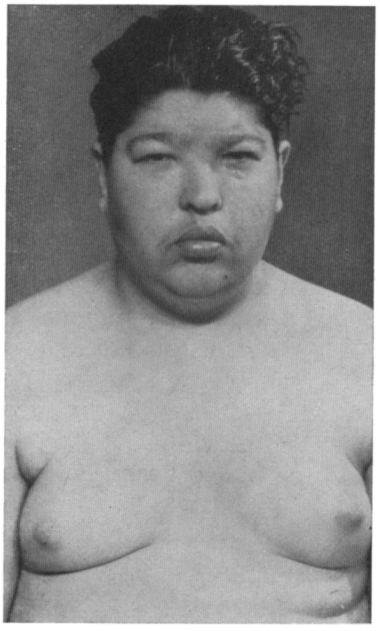

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Fig. 1*a*, *b*, *c*, *d*, *e*. R. P. 40 years. Note lipodystrophic eunichism body shape

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abundant hair, an aspect frequently noted in hypogonadism, with frontal insertion of the female type and occipital insertion of intermediary type. Adiposity was of the superior type, but also predominated on the abdomen. The lower extremities were very thin, due to the underdeveloped musculature. Skeletal differentiation was of the macroskel type: long legs, narrow shoulders, broad hips. The a-a/tro/tro index

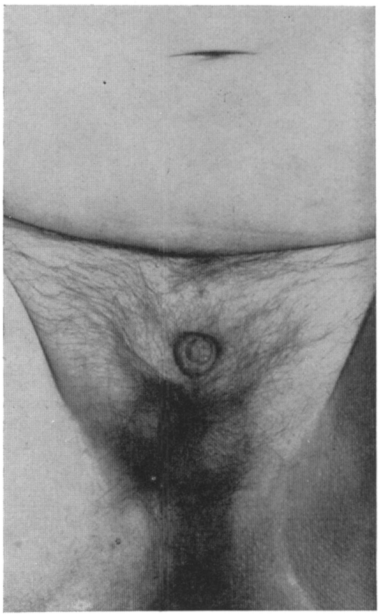


Fig. 2. R. P. Note the straight pubic pilosity, the small penis and the absence of the bursae

was equal to 101.4, within the limits of female variations. The thigh/weight index = 62.4 was however android and reflected the tendency to upper deposition of adiposity. The presence of gynecomastia, predominant on the left, was also noted.

The *genital examination* showed straight pubic pilosity of the prebuscent female type, absence of the bursae and pigmentation, the scrotal region hardly outlined. The small penis (1 cm) was difficult to identify in the adipose panniculus. The testicles could not be palpated or detected either by rectal touch or following surgical exploration of the inguinal ducts.

Mammography revealed fibroglandular tissue on the left side.

Endocrine examination. Hypophysis: sella turcica of normal size. Thyroid: clinical hypothyroid elements, basal metabolism = + 1.9%, PBI = 2.6 gamma 1% ccm. Adrenals: faciotroncular adiposity; blood pressure: 160/110 mmHg.

Hormonal determinations. Total gonadotropin urinary elimination: lo to 20 m.u./24 h, FSH 5 to lo m.u./24 h (Dekanski method, with separation according to Butt and Crooke).

Chromatography of the estrogens gave the following values: estrone 1.51 μg/24 h; estradiol 1.51 μg/24 h and estriol 5.55 μg/24 h (Brown method, 1955).

17 total KS values were 8.89 μg/24 h (Drekter method, 1952).

Chromatography of 17 KS (Beaulieu method, 1961): DHA 0.54 μg/24 h; androsterone 0.68 μg/24 h; etiocholanolone 0.92 μg/24 h; 11 oxi 0.57 μg/24 h; total values 2.71 μg/24 h. A/E ratio = 0,7.

Explorative laparatomy confirmed the absence of the testicles, but showed the presence of the deferent ducts.

Cytogenetic findings. Absence of sexual chromatin in the cells of the buccal mucosa. The karyotype determined in the bone marrow by the direct method was XY.

The patient had two sisters, one of whom presented evident hypogonadism phenomena.

Case 2

B.M., aged 42 years, with primary amenorrhea, a manifest hypogonadic morphotype, was surprisingly like her brother; the same facies, the same faciotroncular distribution of obesity, the same lipodystrophic eunuchism.

The *genital examination* showed reduced pubic pilosity with hardly any waves; marked hypoplasia of the external genitalia, unformed clitoris, hardly outlined nymphae, marked hypotrophy of the cervix and uterine body.

Endocrine examination. Hypophysis: sella turcica within normal limits, with narrowed entry. Thyroid: infiltered integuments, cold extremities, basal metabolism = + 8.3%, PBI = 2.8 gamma/1% ccm; adrenals: faciotroncular obesity, abdominal apron; 17 KS = 10.8 mg/24 h; 17 CHCS = 9.20 mg/24 h.

Hormonal determinations. Vaginal cytology with the presence of basal type cells showed estrogen deficiency; total urinary gonadotropin elimation 10 to 20 m.u./24 h, FSH 5 m.u./24 h (Dekanski method, with separation according to Butt and Crooke), LH 7 rabbit unit/24 h (Friedman method).

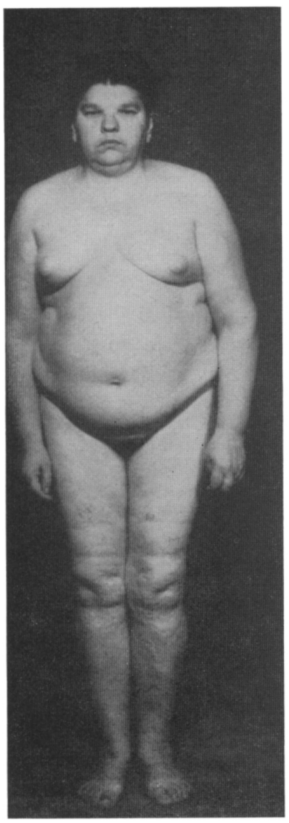
Chromatography of estrogens gave the following values: estrone 3.5 μg/24 h, estradiol 1.5 μg/24 h and estriol lo μg/24 h (Brown method, 1955).

Chromatography of 17 KS (Beaulieu method, 1961): DHA 1.20 mg/24 h, androsterone 2.79 mg/24 h, etiocholanolone 1.47 mg/24 h, 11 oxi 2.24 mg/24 h; total value 7.70 mg/24h; A/E ratio = 1.8.

Appraisal of 5 α *testosterone metabolism* 24 hours after the administration of 75 mg testosterone propionate showed dominant metabolism towards etiocholanolone with decrease of the ratio to 0.6, a common aspect in estrogen deficiencies, after bilateral ovariectomy (Ciocîrdia, 1966).

Positive *sexual chromatin.* In 3% of the cells 2 chromatin corpuscles were found. The presence of drumsticks was noted. The karyotype was determined in a peripheral blood culture according to the Moorhead method.

N. of chromosomes	44	45	46	47	48
N. of cells studied	1	17	32	21	—



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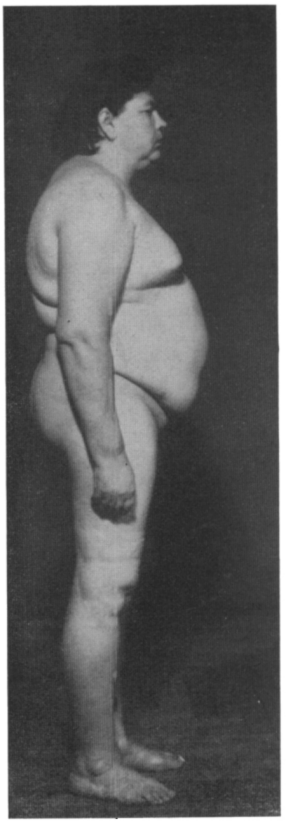

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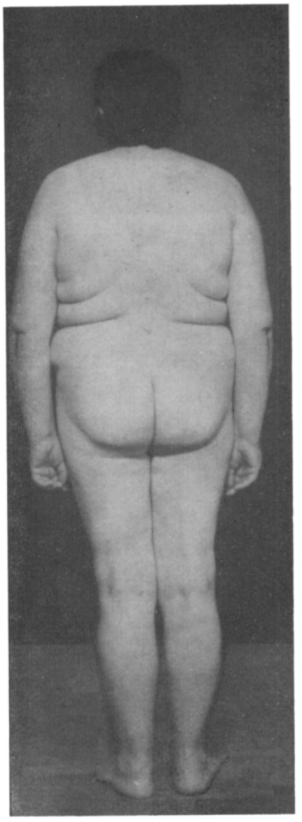

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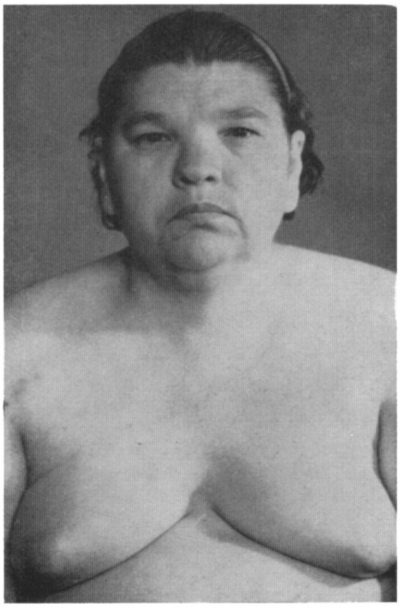

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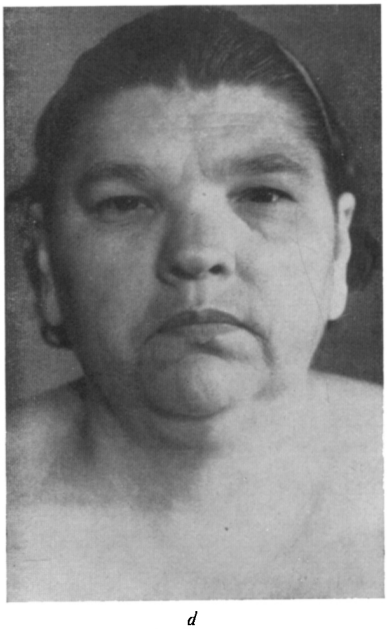

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Fig. 3*a*, *b*, *c*, *d*, *e*. B. M. 42 years. Note the same body shape

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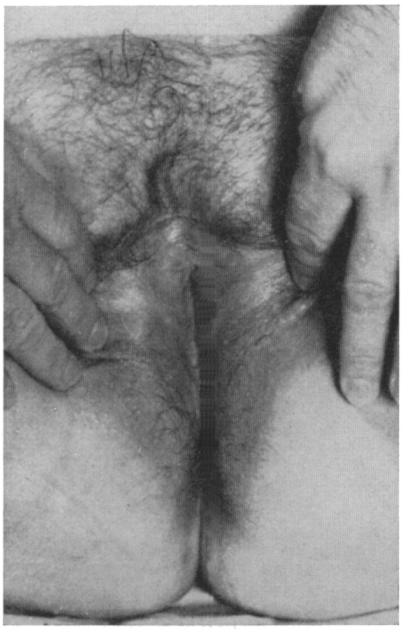

Fig. 4. B. M. marked hypoplasia of the external genitalia

The primary amenorrhea, marked hypoplasia of the genital tract, orientation of the metabolism of testosterone towards etiocholanolone, similar to that occurring in the absence of the gonads, suggest the existence of estrogen deficiency due to gonadic dysgenesis — an aspect confirmed by the karyotype mosaic.

The case was not confirmed operatively as the patient refused the operation.

Dermatoglyphs

Digital. R.P.: ulnar loop 1st, 4th and 5th fingers of both hands; radial loop on the 2nd finger of the right hand, arches on the remaining fingers. B.M. presents the same location and the same pattern as her brother. The difference between the two consists in the number of digital ridges, which is 100 in the brother and 55 in the sister. Moreover, in both there was an increased number of vertical or horizontal white lines on the 1st, 3rd, 4th and 5th finger of both hands.

Palms. In both brother and sister the left hand had the same palmar formula (3 p. 5.7. 9/8) and pattern on the 4th interdigital space. R.p.: carpal arch in the hypothenar region due to the higher position of *t*; B.M., transverse sulcus on the left hand. Right hand formula, R.P.: 4.5.7.9.; B.M.: 5.7.9.8.; R.P. a loop in the 3rd interdigital space; B.M. a loop in the 4th interdigital space.

Discussion

Congenital anorchidia is one of the rarest gonadal disturbances. The number of cases reported is comparatively small. According to Sadi (1964), there are 19 known cases. According to Vague (1958), however, the number of cases is almost 30. Subsequently, at least 8 more were added, and only a few of these were studied cytogenetically.

In 1964, Milcu studied a child with genital infantilism and negative sexual chro-

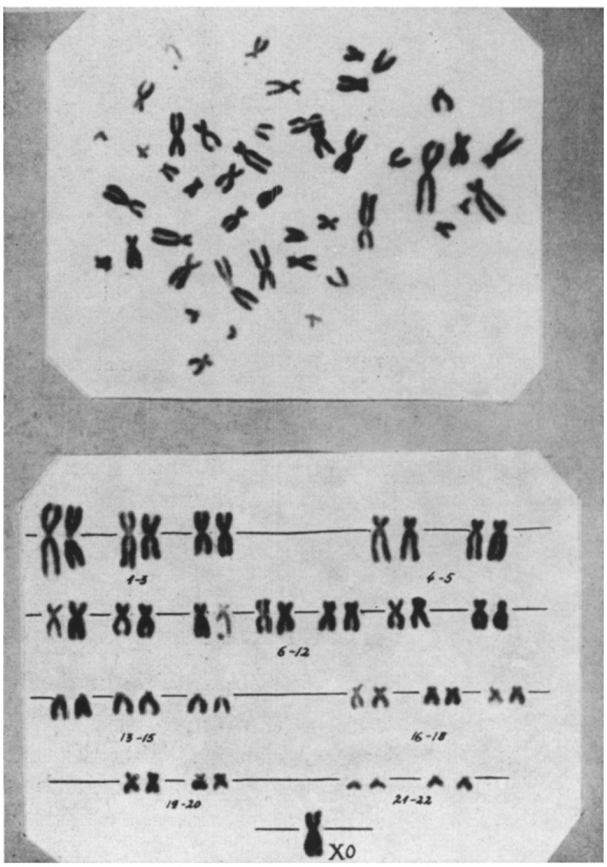

Fig. 5. Cell with chromosome complement 45/XO

matin. The karyotype was XY (1964*a*). Later on in the same year (1964) he reported another 3 cases with the same karyotype.

Steeno (1965) added 2 new cases with an XY karyotype.

All these cases appear to suggest disappearance of the testicles in the 8th week

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of intrauterine life. If disappearance of the gonads had taken place earlier, an individual with female genital organs would have developed.

The origin of these disorders is unknown. It is assumed that sometimes at least anorchidia is the result of a mutation. Several cases lend support to this assumption. In 1956, Overzier cited a family in which two individuals exhibited the same anomaly.

Ciampolini (1962) studied 3 patients, of whom one had a brother with severe hypoplasia and unilateral ectopy. These cases led Ciampolini to assume, in accord

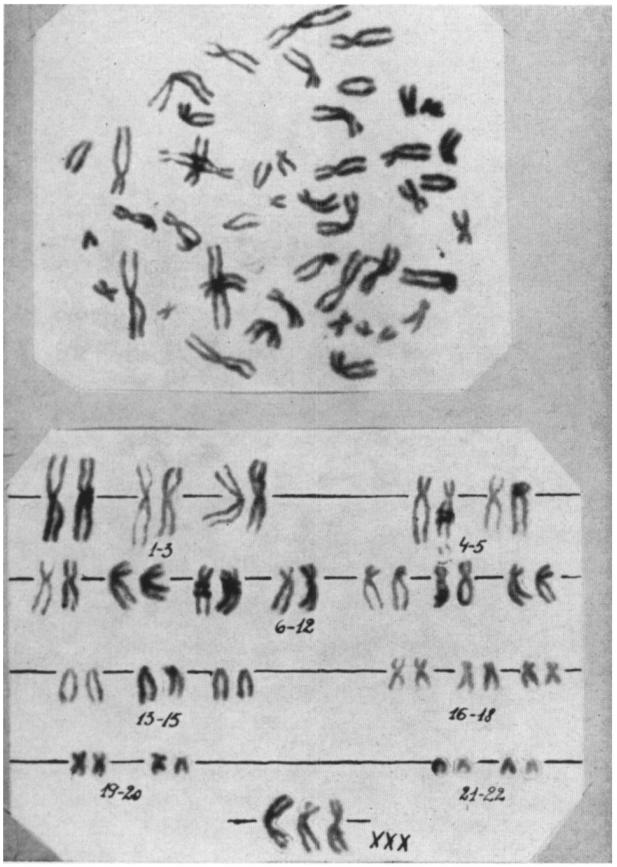

Fig. 6. Cell with chromosome complement 47/XXX

with Andreani (1961) that the same genetic anomaly may bring about varied gonadic disturbances.

The XO/XX/XXX form of mosaicism is comparatively rare. Approximately 15 cases have been reported in literature. It is difficult to class them systematically, however, because in most cases essential data are missing from the description (laparatomy, histologic examination of the gonads and sometimes even evidence of their

morphologic aspect). Notwithstanding, several general considerations may be made on the basis of the existing findings.

Wu Min and coworkers (1964) report a typical case of Turner's syndrome. Most cases exhibit typical Turner aspects, sometimes numerous and intense, in other cases few and discrete. In Bianchi's case (1963), the Turner signs are important: statural hypotrophy, shield chest, cubitus valgus, genital infantilism. In Carr's case (1962) these aspects were reduced to statural hypotrophy and a short neck; Jacobs and coworkers (1960) report a case (case 1) in which the only evocative signs were cutaneous naevi. Most cases exhibit statural hypotrophy, sometimes very accentuated (Rothenbuchner's case was 132 cm high at the age of 17) (1964). Moreover, normal cases without any morphologic anomaly have also been observed (Milcu *et al.*, *unpubl.*; Jacobs *et al.*, case 2, 1960).

The external genital organs are generally hypoplasic, with deficient secondary sexual characters. In Jacobs' first case (1960), absence of the vagina was found, but with hypertrophy of the clitoris. Hypoplasia of the uterus is noted in most cases.

The aspect of gonads — although investigated in very few cases — appears varied: " Streak gonads " (Jacobs *et al.*, 1960 — case 2; Bianchi *et al.*, 1963); dysgenetic gonads; asymmetrical gonadal dysgenesis (Milcu *et al.*, unpubl.) and probably almost normal ovaries, as the patient had her menses (Rotenbuchner *et al.*, 1964).

A backward psycho-intellectual development was sometimes noted (Jacobs *et al.*, 1960 — case 1 and 2; De Toni *et al.*, 1964).

In general, the clinical aspect of the patients with XO/XX/XXX mosaicism is fairly varied. The developmental aspect of the genital tract and sexual characters are certainly the consequence of ovarian dysgenesis. The intensity of the latter, the possibility of asymmetry, the intensity and number of malformations appear to be linked to the distribution and proportional combination of the three different chromosomial lines in the organism.

In the case of patient B.M., the presence and, to all likelihood, exclusive predominance of XO line in the gonadal development bud, explain the agonadic hormonal aspect and this, in turn, accounts for the eunichism aspect. Although the mosaicism is complex and formed of the three XO/XX/XXX lines, the absence of morphologic malformations appears to combat the action of the XO line in other structures. The same stands true for XXX line which does not appear to have influenced the psychointellectual development in any particular way. This mosaic has been encountered in women with varied somatic malformations, with deficient secondary sexualization and gonadal dysgenesis, almost constantly sustained by laboratory data or histologic analysis of the ovaries.

Explanation of the family association in our cases is not clear. If the patients had a normal karyotype, the disorders observed could be assumed to have been caused either by a mutation or by environmental factors, in which case the role of heredity is almost inexistent.

The presence of a XO/XX/XXX mosaic is sufficient to account for gonadal dys-

genesis and, implicitly, to render improbable the intervention of gene mutations or of mesologic conditions.

The presence in the same family of two cases of gonadal dysgenesis appears to have occured by mere chance.

Summary

The Authors report on a case of congenital anorchidism, confirmed by laparatomy, with negative sexual chromatin and an XY karyotype. One of his two sisters, with primary amenorrhea, presented marked hypoplasia of the genital tract, positive sexual chromatin and in 3% of the cells with 2 chromatine corpuscles, XO/XX/XXX karyotype. The presence in the same family of two cases of gonadal dysgenesis appears to have occurred by mere chance.

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RIASSUNTO

Gli Autori presentano un caso di anorchidismo congenito, verificato mediante laparatomia con cromatina sessuale negativa e cariotipo XY.

Una delle sorelle del candidato, con amenorrea primaria, presenta accentuata ipoplasia dell'apparato genitale, cromatina sessuale positiva e, nel 3% delle cellule, 2 corpuscoli di cromatina; cariotipo: XO/XX/XXX.

La presenza, nella stessa famiglia, di due casi con disgenesia gonadica, sembra fortuita.

RÉSUMÉ

Les Auteurs présentent un cas d'anorchidisme congénital, vérifié laparatomiquement, avec chromatine sexuelle négative et caryotype XY.

L'une des sœurs du proband, avec aménorrhée primaire, présente hypoplasie marquée du tractus génital, chromatine sexuelle positive et, dans 3% des cellules, 2 corpuscules chromatiniques; caryotype: XO/XX/XXX.

La présence dans la même famille des deux cas de dysgénésie gonadique semble fortuite.

ZUSAMMENFASSUNG

Die Verff. veröffentlichen einen, durch Laparatomie überprüften Fall mit kongenitalem Anorchidismus, negativem Sexual-Chromatin und Karyotyp XY.

Eine der Schwestern des Kranken weisst primäre Amenorrhoe, ausgeprägte Hypoplasie der Genitalien auf, positives Sex-Chromatin; in 3% der untersuchten Zellen werden 2 Chromatinkörperchen gefunden. Karyotyp XO/XX/XXX.

Das Vorhandensein in derselben Familie dieser beiden Fälle mit Gonadendysgenesie ist wahrscheinlich zufällig.