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Sex Chromosome Aberrations in Childhood

I. XXY and XXY Mosaicism

By

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In paediatric practice, the XXY chromosomal anomaly is detected unfrequently owing to the paucity and variability of the clinical symptoms. This applies to conditions of mosaicism in particular due to the difficulties of cytogenetical analysis.

Screening tests revealed ten cases of XXY pattern among children with male phenotype. The karyotype was 47, XXY in three cases, 48, XXYY in one case, while the remaining six were mosaics, which shows that mosaicism is more frequent than previously supposed. Hypogonadism, gynaecomastia, mental retardation, i.e. the characteristic features of Klinefelter's syndrome were — separately or jointly — present in all cases of XY/XXY mosaicism.

The familial origin of multiple mosaicism (46,XY/47,XXY/48, XXXY) was proved in one case by the mother's 46, XX/47, XXX mosaicism. Another multiple mosaic 45,X/46,XY/XXY was revealed with the masculine form of Turner's syndrome, still another patient displayed a very rare case of sixfold mosaicism: 45,X/46,XY/46,XX/47,XXY/47,XXX/48, XXXY.

In 1942 KLINEFELTER [13] described the syndrome named after him. The cytogenetic investigations made in the last ten years have elucidated many details concerning the anomaly. It has been demonstrated that the karyotype of patients with this disease is not the normal 46,XY one, but 47,XXY or — rarely — 48,XXXY, i.e., their cells contain one or two supernumerary X chromosomes [1].

In 1959, FORD et al. [10] observed an XXY pattern in a patient with Down's syndrome. This was the first case of mosaicism demonstrated in a human subject.

Examining newborn male infants, MOORE [15] found that the incidence of an XXY chromosomal constitution, the characteristic of Klinefelter's syndrome, was 1 : 400, which was confirmed by others [4, 23]. Cytogenetic examinations made in nearly 10 000 newborn infants in various laboratories during recent years showed the frequency of sex chromosomal aberrations to range between 0.9 and 1.3% [21, 24, 27]. Thus, XXY is not a rare anomaly. These examinations have further revealed that the XXY pattern in boys occurs about four times more frequently than X monosomy in females; the incidence of the latter is

about 0.3% [21, 24]. Of the two chromosomal aberrations, X monosomy is more often detected than X polysomy because the latter is poor in clinical manifestations.

X polysomy, unlike X monosomy, has no striking effect on the patient's phenotype. Individuals with the karyotype XXY have a masculine appearance. The presence of Y at the time of gonadal differentiation, i.e., about the sixth week of intrauterine life, ensures the development of the bipotential primordium into testicles, and the testicular substances induce subsequently (from the tenth week) the growth of male genitals. The only verified result of the XXY anomaly is, according to present knowledge, an epithelial sclerosis of the seminiferous tubules and consequent azoospermatism. All other symptoms are incidental and not characteristic. Since, however, some of these accessory symptoms — insufficient puberty and mental retardation in particular — are strikingly frequent, they are generally regarded as pathognomic. It has been found that the XXY chromosomal aberration is more frequent among the mentally defective than among the normal population [3, 16].

Material

To detect X chromosome anomalies in children we have performed systematic cytogenetic examinations among the patients and outpatients of our institute. The principles of selection, the method of chromosomal examination (including evaluation of the elusive criteria of mosaicism) have been described ersewhere [18, 19].

The present study involved 10 patients ranging in age from 4 to 14 years. Suspicion of Klinefelter's syndrome arose in three cases on account of delayed puberty, in other three cases because of gynaecomastia; a child of 4 years was examined cytogenetically because of a striking hypogonadism, another of 8 years on account of hypogonadism and mental deficiency; still another patient was suspected of male Turner's syndrome, while the tenth case was one of mental retardation and with suspicion of Down's syndrome.

Results

Results are assembled in Table I. The karyotype, as observed in the course of 30 mitoses, showed a chromosomal constitution 47,XXY in three cases and 48,XXYY in one case. Single mosaicism (46,XY/47,XXY) was found in three, multiple mosaicism (46,XY/47,XXY/48,XXXY — 45,X/46,XY/47,XXY and 45,X/46,XY/46,XX/47,XXY/47,XXX/48,XXXY) in three patients. Maternal karyotype determination was made in two cases; in one it was justified by the mother's mental retardation, and in the other because the mother had been exposed to rubella in the second month of pregnancy.

Prenatal and perinatal data are listed in Table II, the more important clinical data in Table III. Dermatoglyphic features of the patients are compared to those of normal children in Table IV. Values for urinary excretion of various steroid metabolites are listed in Table V.

TABLE I

Details of chromosome examinations

No. Name age (yrs)	Number of observed mitoses	Number of chromosomes					Karyotype
		45	45	46	47	48	
1. T. S. 4	30	2	1	1	26	0	47,XXY
2. G. H. 8	31	1	1	5	24	0	47,XXY
3. B. C. 14	31	0	1	0	30	0	47,XXY
4. P. V. 12	37	0	1	3	2	31	48,XXYY
5. T. I. 13	73	0	0	56	17	0	46,XY/47,XXY
6. J. T. 13	82	3	0	66	13	0	46,XY/47,XXY
7. L. J. 14	80	1	1	67	11	0	46,XY/47,XXY
8. B. N. 13	77	2	0	20	45	22	46,XY/47,XXY/ 48,XXXY
9. B. H. 12	94	8	15	62	9	0	45,X/46,XY/ 47,XXXY
10. J. B. 14	1. 25 2. 42	5 6	5 22	3 3	10 10	1 1	45,X/46,XY/46,XX/ 47,XXY/47,XXX/ 48,XXXY

CASE REPORTS*

1. *TSO31266.* Conspicuously undeveloped external genitals. Cytogenetic examination at the age of 4. Karyotype: 47,XXY.

2. *GH181062.* The child was 8 years of age when examined (Fig. 1). Cryptorchism on the left side had previously been corrected by the administration of 2×1500 units of Choriogonin. Psychomotor retardation requires regular psychological care. Karyotype: 47,XXY.

3. *BC220354.* A cryptorchism on the right side had first been treated with 15×500 units of Choriogonin. Later on the apparently intact testicles and epididymis were brought down surgically into the scrotum Cytogenetic examination at the age of 14 was performed on account of delayed puberty and mental retardation. Karyotype: 47,XXY. Physical examination at 16 years of age showed pubic hair which, though in keeping with the chronological age, was of the feminine type; bean-sized, compact testicles were found in the scrotum (Fig. 2).

4. *PVO60955.* The child was operated at the age of 3 on account of right-side cryptorchism. Cytogenetic examination at the age of 12 was performed on account of hypogonadism and serious mental deficiency. The secondary sex characters have appeared at the age of 14, with

* Names and birth dates are given according to the Chicago nomenclature.

TABLE II

Prenatal and perinatal

	T. S. 4 yrs	G. H. 8 yrs	B. C. 14 yrs	P. V. 12 yrs	T. I. 13 yrs
Karyotype	47,XXY	47,XXY	47,XXY	48,XXYY	46,XY/ 47,XXY
Mother's age	34	20	29	23	27
Father's age	52	24	30	27	34
Results of previous pregnancies			First: healthy male Second: artificial abortion		First: normal male Second: spontaneous abortion Third: normal female
Results of subsequent pregnancies				Four normal	
Weight at birth	2300	3000	3000	3800	3850
Notes					Mother obese

feminine-type pubic hair (Fig. 3). Karyotype: 48,XXYY (Fig. 4).

5. *TI101053*. Although the external genitals were normally developed at the age of 13, obesity, bilateral gynaecomastia and mental retardation justified a cytogenetic examination. Examination at 15 showed normal puberty with unchanged gynaecomastia. Karyotype: 46,XY/47,XXY.

6. *JT111053*. Both members of a pair of twins from the first marriage of the mother are schizophreniacs.

The child was examined at the age of 13 on account of obesity and gynaecomastia. The pubic hair was scanty, the reproductive organs were normal, the breasts swollen and glandular; gynaecomastia was still present two years later. Oestrogen excretion was above normal (Table V). Karyotype: 46,XY/47,XXY.

7. *LJO10152*. First examined at the age of 14 on account of symmetric gynaecomastia. The patient was taller than the average and displayed a feminine constitution. The breasts were glandular and, the mammillae were surrounded by a strongly pigmented areola 5 cm in diameter (Fig. 5). Urinary oestrogen output was abnormally high (Table V). Exam-

data of the patients

	J. T. 13 yrs	L. J. 14 yrs	B.N. 13 yrs	B. H. 12 yrs	J. B. 14 yrs
Karyotype	46,XY/ 47,XXY	46,XY/ 47,XXY	46,XY/ 47,XXY/ 48,XXXY	45,X/ 46,XY/ 47,XXY	45,X/ 46,XY/ 46,XX/ 47,XXY/ 47,XXX 48,XXXY
Mother's age	39	18	39	28	22
Father's age	39	29	42	36	39
Results of previous pregnancies	First marriage: One pregnancy: schisophreniac twins. Second marriage: second, third, fourth, fifth pregnancies artificial abortions		First pregnancy, normal female Second, third, fourth pregnancies artificial abortion		normal male
Results of subsequent pregnancies				normal female	normal female
Weight at birth	3500	3600	3000	3400	3100
Notes		Both parents obese	Parents obese. Mother: 46,XX/ 47,XXX	Parents short stature	Mother: 46,XX

inations for a possible tumour were negative. At the age of 15, the degree of gynaecomastia had not changed but oestrogen excretion had diminished. At 18 years, the swelling of the breasts was unchanged, while the pubic hair has turned into a regular male character; oestrogen excretion was the same as 3 years before. Karyotype: 46,XY/47,XXY.

8. *BNO80155*. Admitted at the age of 13 on account of obesity, the boy was subjected to cytogenetic examination because of delayed puberty and mental retardation. Body height and weight were above the average. No sign of puberty; the penis was small, scrotum and testicles were underdeveloped.

The boy was a mediocre student. I.Q.: 0.71. The epiphyses were not ossified and the intravenous pyelography disclosed renal agenesis of the right side. The condition showed no change at the age of 15 (Fig. 6). Karyotype: 46,XY/47,XXY/48,XXXY.

Chromosomal examination of the mentally retarded mother revealed a 46,XX/47,XXX mosaicism. The chromosomal anomaly seemed to be familial. The presumable development of the child's mosaicism is schematically illustrated in Fig. 7.

TABLE III

Clinical

	T. S. 4 yrs	G. H. 8 yrs	B. C. 14 yrs	P. V. 12 yrs	T. I. 13 yrs
Obesity	—	+	+	—	+
Insufficient puberty			+	+	—
Retention of testis	bilateral	left	right	bilateral	—
Gynaecomastia	—	—	—	—	+
Mental deficiency	—	+	+	+	—
Body weight (kg)	14	34	45	36	72
Height (cm)	99	132	157	145	156
Notes				Short fingers and toes	

TABLE IV

Dermatoglyphic features of the patients

No., Name	P. I.	T. R. C.	RC-$_{a-b}$	atd angle	AD index	
					left	right
1. T. S.	15	91	71	87	10	11
2. G. H.	9	108	95	88	5	8
3. B. C.	9	81	84	93	8	11
4. P. V.	18	152	74	85	10	9
5. T. I.	16	112	67	126	9	7
6. J. T.	16	158	65	73	11	11
7. L. J.	18	181	89	115	8	10
8. B. N.	9	128	80	79	8	10
9. B. H.	13	120	66	84	5	7
10. J. B.	4	16	64	121	10	10
$\overline{X}$	12.7	114.7	75.5	95.1	8.4	9.4
200 normal boys $\overline{X}$	12.6	137.6	82.8	85.3	8.3	9.7

P.I. = palmar index
T.R.C. = total ridge count
R.C. = ridge count
L = loop pattern
r = radial
u = ulnar

s ymptoms

	J. T. 13 yrs	L. J. 14 yrs	B. N. 13 yrs	B. H. 12 yrs	J. B. 14 yrs
Obesity	+	—	+	—	—
Insufficient puberty	—	—	+	+	—
Retention of testis	—	—	—	—	—
Gynaecomastia	+	+	—	—	
Mental deficiency	—	—	+	—	+
Body weight (kg)	45	64	64	35	50
Height (cm)	142	178	158	138	165
Notes			Left renal agenesis	Pterygium cubitus valgus; fused vertebrae	Mongoloid constitution

in comparison to 200 normal children

Hypothenar		Transverse line		Karyotype
left	right	left	right	
L_r	L_r	—	—	47,XXY
L_r	L_r	—	—	47,XXY
—	L_r	—	—	47,XXY
—	—	—	—	48,XXYY
—	L_u	—	—	46,XY/47,XXY
—	—	—	—	46,XY/47,XXY
L_u	—	—	+	46,XY/47,XXY
L_r	L_r	—	—	46,XY/47,XXY/48,XXXY
—	L_u	+	+	45,X/46,XY/47,XXY
—	—	—	—	45,X/46,XY/46,XX/ 47,XXY/47,XXX/48,XXXY
40	60	1.0	2.0	
32.8	33.5	1.5	1.0	

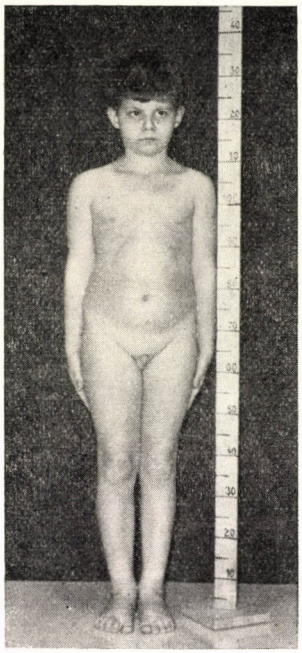

FIG. 1. G. H., 8 years; karyotype 47,XXY

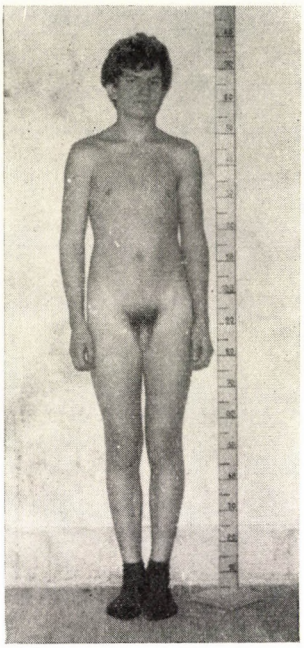

FIG. 2. B.C., 14 years; karyotype 47,XXY

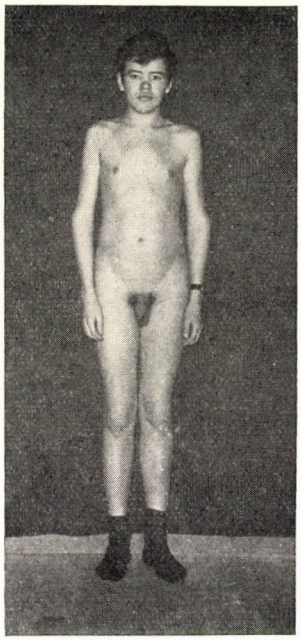

FIG. 3. P.V., 12 years; karyotype 48,XXYY

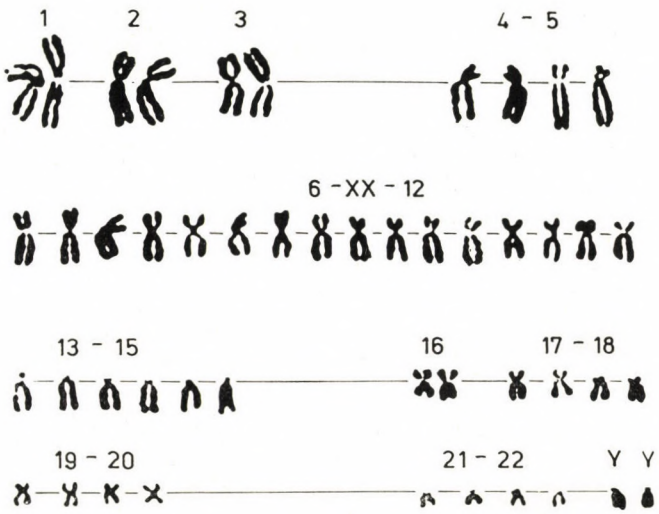

FIG. 4. Pathologic karyogram of P.V.

TABLE V

Urinary excretion of steroid metabolites in 24 hrs

	B. C.	P. V.	T. I.	J. T.	L. J. 14 yrs	L. J. 15 yrs	B. N.	J. B.	Normal value
Ketosteroids (mg per day)									
17-KS	11.0	9.3	10.0	10.8	8.4	13.3	6.6	5.0	2.2—12.2
Ketogenic steroid		1.6		3.8	8.4				3.0— 9.5
11-OH-etiocholanolone		0.6			0.8	1.4	0.6	0.2	0.4— 0.6
11-OH-androsterone		0.4			1.1	2.0	0.5	0.8	0.5— 1.6
11-keto-etiocholanolone		0.1			0.9	1.5	0.1	0.4	0.6— 2.3
Dehydroepiandrosterone		0.0			0.0	0.0	0.0	0.3	0.1— 2.3
Etiocholanolone		0.0			2.1	3.9	0.3	0.7	0.4— 2.8
Androsterone		0.4			2.1	3.1	0.7	0.9	0.3— 3.4
Oestrogens (μg per day)									
Oestrone			2.1	10.0	17.5	3.6		4.0	0.0— 2.5
Oestradiol			2.1	16.0	27.1	0.0		0.3	0.3— 2.1
Oestriol			2.5	6.0	9.6	4.9		1.8	1.5— 4.1

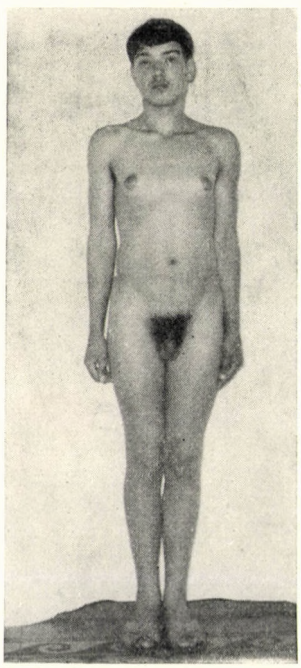

FIG. 5. L.J., 14 years; karyotype 46,XY/47,XXY

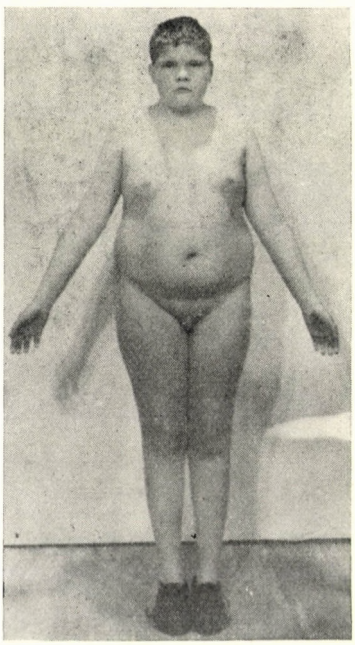

FIG. 6. B.N., 13 years; karyotype 46,XY/47,XXY/48,XXXY

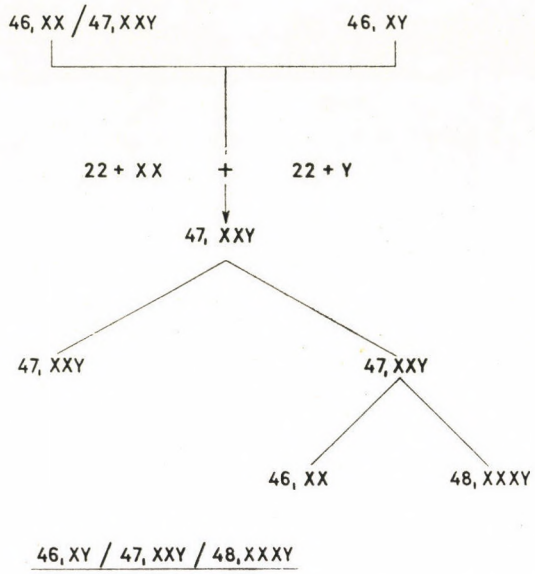

FIG. 7. Diagrammatic illustration showing the development of multiple mosaicism in B.N.

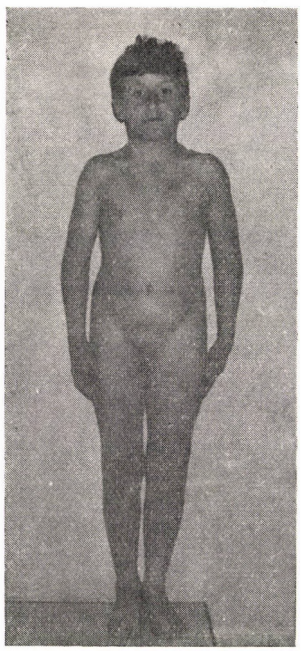

FIG. 8. B.H., 12 years; karyotype 45,X/46,XY/47,XXY

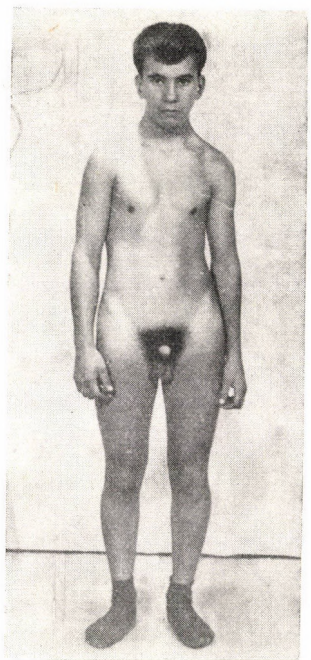

FIG. 9. J.B., 14, years; karyotype 45,X/46,XY/46,XX/47XXY/47,XXX/48,XXXY

9. *BHO91257*. The boy originated from a family of low stature. At the age of 12, his growth was well behind the mean for his age. Physical examination disclosed a short neck, slight pterygium, ptosis, cubitus valgus, multiple vertebral anomalies and absence of pubertal signs (Fig. 8). Two years later, the condition was unchanged. Karyotype: 45,X/46,XY/47,XXY.

10. *JB130755*. Cytogenetic examination was carried out at the age of 14 on account of mental retardation (I.Q., 0.73) and a phenotype suggestive of Down's syndrome. Development of the reproductive organs was in keeping with the chronological age, and the puberty was normal (Fig. 9). Urinary oestrogen output was above normal (Table V). Maternal karyotype: 46,XX. The autoradiographically verified sixfold mosaicism of the child showed the pattern of 45,X/46,XY/46,XX/47,XXY/47,XXX/48,XXXY. Fig. 10 presents a schematic illustration of the development of this extremely rare form of mosaicism that must have been due to multiple mitotic disturbances. Details of this case will be presented elsewhere [20].

Discussion

Data regarding the frequency of the various forms of sex chromosomal mosaicism are insufficient because technical factors make it difficult to diagnose such anomalies in the course of screening examinations [14, 18, 19, 26]. Our observations showed that the majority of our cases is associated with mosaicism; this does not tally with the recent data according to which the frequency of sex chromosomal disorders manifesting themselves with mosaicism is fairly constant. The rate is stated to amount to 30% in Turner's syndrome, and to 10% in Klinefelter's syndrome [7].

According to present knowledge, mosaicism and the single-line chromosomal aberration originate at different points of time. The latter usually results from a non-disjunction

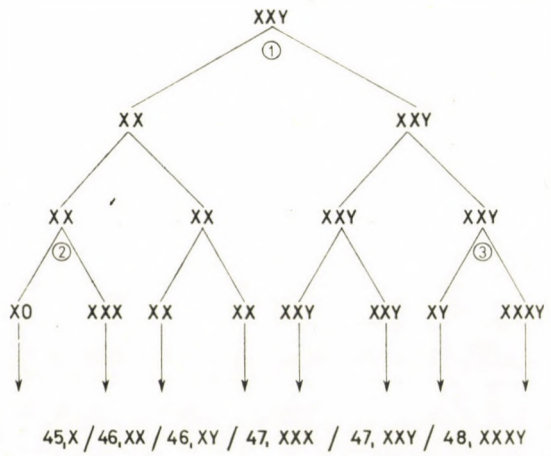

Fig. 10. Diagrammatic illustration showing the development of sextuple mosaicism in patient J.B.

of the paternal or maternal gamete. Mosaicism, on the other hand, results from a disturbance in the mitosis of the zygote, a disturbance that may occur at the very first cell division or at any other time in the course of life. The significance for the phenotype of the mitotic disturbance depends on its time, site and duration. A congenital deformity of a given organ can be due to chromosomal mosaicism only if the latter had already existed at the time of organogenesis [18].

The ratio of cells with a pathologic karyotype may change from organ to organ as a result of cell migration and differentiation in the embryo; selective proliferation may give rise to such changes in prenatal and also in postnatal life [6, 9].

It follows that mosaicism diagnosed in some tissue at a given phase of extrauterine life need not truly reflect the interproportion of cells of different karyotypes at the time of organogenesis. Whether the deficit or surplus of certain genes, the chromosomal deficiency or surplus had been present in the ootid already or whether the aberration was of a somewhat later origin, makes presumably no difference for the growing organism. If a syndrome which corresponds or is similar to the classical clinical manifestation of the chromosomal aberration associated with mosaicism, it is reasonable to assume a correlation between the pathologic karyotype and phenotype. No sharp clinical distinction between the two types is at present possible. So-called "formes frustes" do occur in cases of chromosomal mosaicism, but the mosaicism need not be a less serious and prognostically more favourable anomaly.

The proportion of pathologic cells in mosaic aberrations does not permit prognostic conclusions.

Not only the evaluation but also the diagnosis of mosaicism is difficult. The chances of its detection are enhanced by increasing the number of cells to be examined. There is, however, no exact rule as to the minimum number of mitoses that suffices for the demonstration of mosaicism after the possibly widest elimination of all technical shortcomings. The guiding principle is to examine in suspicious cases as many cells as possible [18].

The clinical manifestations in patients 5, 6 and 7, all of whom exhibited the mosaic karyotype 47,XXY, were the usual ones seen in Klinefelter's syndrome. Delayed puberty and mental deficiency were the most frequent symptoms observed in these cases. These two symptoms were not invariably present in the patients with gynaecomastia. The 17-KS values were normal in all examined cases [2]. Normal values in this respect have been described by FEHÉR et al. [5, 28]. Examination of the ketosteroid fractions revealed no pathologic metabolite excretion in patients 4, 7, 8 and 10, but urinary oestrogen output in patients 6 and 7 was as high as in fertile women (Table V). Gynaecomastia was pronounced in these two cases. A similar observation has been reported by ZUPPINGER et al. [29].

The phenotype of patient No. 9 was suggestive of the male form of Turner's syndrome. Only a few of the observed mitoses disclosed X monosomy. Since the patient's phenotype was not that usual in Klinefelter's syndrome, the pathogenic role of the observed cell population (47, XXY) was obscure in this case. [17]

The phenotype of patient No. 10 was suggestive of Down's syndrome. As no testicular biopsy was performed, it is impossible to tell whether there was a tubular degeneration due to the supernumerary X chromosomes found in some of the cells. Other characteristic symptoms of Klinefelter's syndrome such as delayed puberty and gynaecomastia, were not observed in this case.

PENROSE [22], HUNTER [12] and HOLT [11] compared the dermatoglyphic features of Klinefelter patients with those of normal individuals and also with patients displaying Turner's syndrome. They found that the surplus of X chromosome diminished, while its absence increased pattern intensity and the number of dermal ridges. It is, however, only by statistical evaluation that the differences can be expressed. Table IV contains the important dermatoglyphic parameters of our patients with reference to the mean values for 200 normal male children from Budapest. Deviations between the two groups did not seem to be significant, but the number of examined cases was not sufficient for statistical evaluation.

It should be noted that the Beckman score in the dermatoglyphic pattern of patient No. 10 was not pathognomonic. The low index of pattern intensity and the low value of total ridge count seemed to correspond to phenomena characteristic of Klinefelter's syndrome [11]. The observed dermatoglyphic features need not necessarily have been due to the presence of the accessory X chromosome, as shown by the fact that, although the cells of the mother showed the normal karyotype, the pattern intensity of her fingers and her value of total ridge count were likewise low.

The family history, such as the age of the parents, details of previous pregnancies, etc., is hardly contributory from the diagnostic point of view. Nevertheless, in 6 cases the age of the father, in 3 cases that of the mother and in 2 cases that of both parents was over 30 years (Table II). These data lend further support to the well-known fact that the more advanced the parents' age, the higher the probability of polysomic aberrations in the offspring.

It is clear that it is difficult to establish a reliable diagnosis of Klinefelter's syndrome. Only a histologically verified degeneration of the seminiferous tubules reveals the anomaly before sexual maturity. The final proof, i.e., azoospermatism, must be expected only after the customary time of sexual maturity, and it is understandable why Klinefelter's syndrome is usually detected only in connection with sterility examinations [8,25].

Mass screenings are unsuitable for the detection of Klinefelter's syndrome and mosaicism because sex-chromatin determinations provide no conclusive proof [14]; their normality does not exclude mosaicism, while the examination of a few cells is not sufficient for karyotype determination. To examine the chromosomal complement of 50 or more cells per individual on a mass scale is as yet impossible so that all we can do at present is to make detailed analyses in each suspicious case. There is hardly any premonitory and no unmistakable diagnostic sign. Retarded puberty, hypogonadism, cryptorchism and gynaecomastia are the symptoms which, if accompanied by mental retardation, make cytogenetic examination imperative.

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