A Study of Chromosomes in Ten Sexually Abnormal Patients[1)]

By

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(With 2 Text-figures and 2 Tables)

Subsequent to the pioneer work on the chromosomes of Turner's syndrome by Ford *et al.* (1959) and Klinefelter's syndrome by Jacobs and Strong (1959), it was reported that various types of abnormal sexual development in man were associated in most cases with the abnormalities of sex-chromosome constitution. Since 1959, over 400 cases of congenital disorders involving sexual anomalies have been screened for chromosome abnormalities in the Makino laboratory, in order to obtain criteria for understanding chromosomal changes in assocation with disease states. Chromosomal data from 300 cases collected in a period from 1959 to 1963 were summarized in one condenced paper by Makino (1964).

As a link in the same project, the present authors have undertaken a chromosome survey in sexually abnormal patients. The present paper reports the chromosome constitutions of ten sexually abnormal cases. They are represented by three sibs diagnosed as male pseudohermaphroditism (nos. 8–10), 2 cases of congenital absence of vagina (nos. 2 and 4), one case each of hypogonadism (no. 1), uterine hypoplasia (no. 5), oligomenorrhea and hypomenorrhea (no. 3), primary amenorrhea (no. 6), and testicular feminization (no. 7).

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Materials and Methods: Chromosome observations were carried out on cells from short-term leucocyte cultures from peripheral blood of patients. In two cases (nos. 9–10), fibroblasts which were obtained from a very small skin biopsy specimen and cultivated for 50 days provided materials for study. Chromosome slides were made based on both cultured leucocytes and fibroblasts according to the air-drying method of Rothfels and Siminovitch (1958) with a slight modification.

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Ten to 43 cells were chromosomally scanned in each case, with particular attention toward the number of small acrocentrics and the existence of the Y chromosome in metaphase plates. Among them 2 to 8 well-spread chromosomes were karyotyped.

Table 1. Chromosomal findings in ten sexually abnormal patients under study

Case no.	Chromosome counts					No. of cells obs.	No. of cells anal.	Chrom. constitution
	<45	45	46	47	>47			
1	—	1	22	—	—	23	3	46-XX
1-M	—	1	16	—	—	17	3	46-XX
1-F	—	—	12	—	—	12	3	46-XY
2	—	1	25	—	1	27	3	46-XX
2-M	—	3	30	—	—	33	1	46-XX
2-F	—	—	16	—	—	16	3	46-XY
3	—	—	21	—	—	21	6	46-XX
4	—	—	12	—	—	12	2	46-XX
5	—	—	10	—	—	10	2	46-XX
6	—	6	37	—	—	43	8	46-XX
7	—	—	10	—	—	10	3	46-XY
8	—	—	12	1	—	13	3	46-XY
9	—	—	21	1	—	22	3	46-XY
9*	1	—	9	—	—	10	3	46-XY
10	1	—	23	—	—	24	2	46-XY
10*	—	—	2	—	—	2	1	46-XY
8, 9, 10 -M	—	—	21	—	—	21	2	46-XX
8, 9, 10 -F	1	1	28	—	—	30	4	46-XY

M: mother, F: father, *: fibroblast cultures derived from skin biopsies.

Cytological Findings

Diagnosis and clinical features of patients with sex abnormalities considered here are presented in Table 2. In addition three parents of the following cases, no. 1, no. 2 and nos. 8 to 10, were chromosomally studied. The mother of case 1 with normal phenotype cast three spontaneous abortions in the past. The remaining two persons were clinically normal.

Results of chromosomal observations in the above subjects are summarized in Table 1. It was shown that all the subjects under study were found to possess a normal chromosome number of 46.

Four phenotypically female patients, one case with testicular feminization and three sibs clinically diagnosed as male pseudohermaphroditism, were subjected to karyotype analyses. It was found that they had an apparently normal male complement, consisting of 44 autosomes and an XY-complex (Fig. 1). The

Table 2. Clinical and diagnostic features in ten sexually abnormal patients under study

Case no.	Age & legal sex	Diagnosis	Clinical features
1	4y F	Hypogonadism	Fused labia majora; tiny clitoris-like protrusion; defect of vaginal ostium and testes; sex chromatin, 24%.
2	1y3m F	Congenital absence of vagina	Defect of vagina and vaginal ostium; enlarged clitoris; sex chromatin, 15%.
3	24y F	Oligomenorrhea and hypomenorrhea	Underdeveloped uterus; normal external genitalia; 17-KS, 7.0 mg/day; 17-OHCS, 3.8 mg/day.
4	23y F	Congenital absence of vagina	Primary amenorrhea; height, 150.0cm; weight, 54.0 kg; rudimental uterus and vagina (5 cm in length); PBI, 4.8 r/dl; 17-KS, 10.6 mg/day; 17-OHCS, 6.7 mg/day; sex chromatin, 32%.
5	27y F	Uterine hypoplasia	Primary amenorrhea; male type pubic hair; Underdeveloped uterus; normal-sized ovaries; gonadotropin, 8u/day; PBI, 8.5r/dl; 17-KS, 1.3 mg/day; 17-OHCS, 1.3 mg/day; sex chromatin, 32%.
6	17y F	Primay amenorrhea	Primary amenorrhea; normal external genitalia; underdeveloped uterus; hypophyseal hypofunction; sex chromatin, 30%.
7	17y F	Testicular feminization	Primary amenorrhea; height, 163.0cm; weight, 40.0 kg; female type external genitalia with normal sized clitoris; internal organs of male type except for the remnant of vagina (3 cm in length); scanty pubic hair; female-like breast; PBI, 10.0 r/dl; 17-KS, 2.0 mg/day; 17-OHCS, 1.2 mg/day; sex chromatin, negative.
8	18y F	Male pseudo-hermaphroditism	Underdeveloped breast; male type body hair and pubic hair; enlarged clitoris; internal organs of male type; defect of vagina; uterus being not detected; PBI, 7.5 r/dl; 17-KS, 10.1 mg/day; 17-OHCS, 2.1 mg/day; sex chromatin, negative.
9	16y F	Male pseudo-hermaphroditism	Underdeveloped breast; enlarged clitoris; male type body hair and pubic hair; internal organs of male type except for the remnant of vagina (4cm in length); PBI, 6.9 r/dl; 17-KS, 14.5 mg/day; 17-OHCS, 6.0 mg/day; sex chromatin, negative.

Table 2. (Continued).

10	15y	F	Male pseudo-hermaphroditism	Underdeveloped breast; male type body hair and pubic hair; enlarged clitoris; internal organs of male type except for the remnant of vagina (2 cm in length); PBI, 6.1 r/dl; 17-KS, 9.1 mg/day; 17-OHCS, 4.8 mg/day; sex chromatin, negative.

y: year. m: month. F: female.

other patients were found to possess a normal female complement with the XX sex-mechanism (Fig. 2).

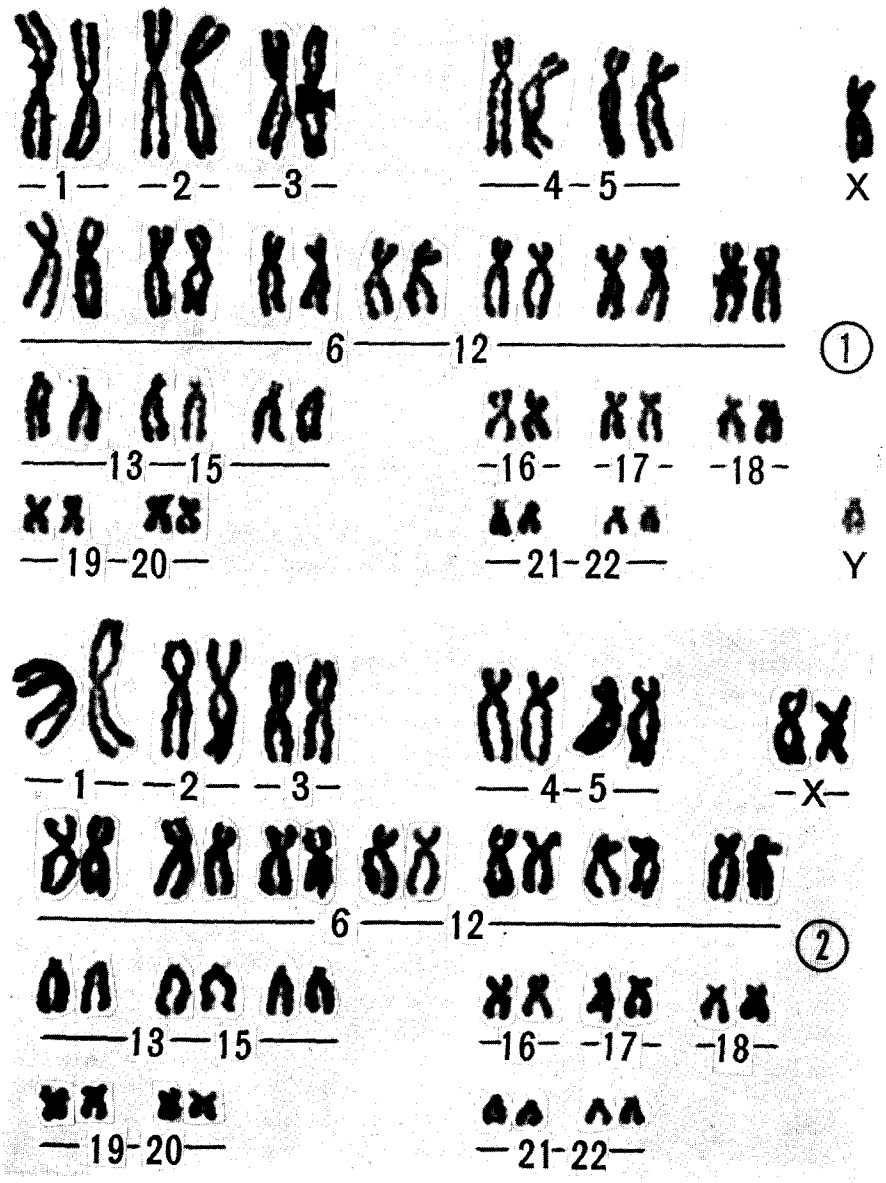
It was observed in case 6 that 6 out of 43 cells examined showed 45 chromosomes. Karyotype analyses of cells with 45 chromosomes revealed the occurrence of a random loss of certain chromosomes in them, withont evidence for chromosomal mosaicism.

Discussion

Recently, many individuals with sex anomalies other than Klinefelter's or Turner's syndromes involving psuedohermaphroditism, testicular feminization, atresia vagina, primary amenorrhea, adrenogenital syndrome and so on, have been studied with respect to their chromosomal conditions. Most of them were found to possess a karyotype of a normal chromosome constitution (for reference, see Makino 1964). Three sibs diagnosed as male pseudohermaphroditism here concerned also had an apparently normal male complement of chromosomes. Recent literature refers to many cases in which various types of chromosomal mosaicism occurred in sex-chromatin-negative patients or in male pseudohermaphrodites (Schuster and Motulsky 1962, De la Chapelle and Hortling 1962, Warkany *et al.* 1962, Makino *et al.* 1964, *etc*).

It was reported that the patients with primary amenorrhea showed sex-chromosome aberrations at a relatively high frequency (Jacobs *et al.* 1961, Reitalu *et al.* 1965). Further, Philip *et al.* (1965) described a patient of a similar type who had an enlarged chromsome no. 1. In the present study, 7 patients who were generally noted as primary amenorrhea (nos. 3–10) were found to have an apparently normal chromosome complement, without showing any detectable change or chromosomal mosaicism.

All patients studied here were found to possess karyotype of a normal chromosome constitution without any identifiable abnormality, indicating that the sex-determination in them was not genetically disturbed. It seems likely that the abnormal sex differentiation may occur in association with some environmental factor (or factors) which caused unbalanced secretion of endocrines and affected the course of development at a critical stage after the sex had been normally determined (Makino 1964).



Figs. 1–2. Karyotype analyses in patients with sex abnormalities. 1: Case no. 8 with male pseudohermaphroditism. 2: Case no. 6 with primary amenorrhea.

Further chromosomal studies of primary amenorrhea patients are now in progress, and results will be given in another paper.

Summary

Ten patients with sexual abnormalities and three parents were studied with respect to their chromosome constitutions. Three sibs with male pseudohermaphroditism and one case of testicular feminization were found to possess a normal male chromosome complement, consisting 44 autosomes and an XY sex-constitution. The remaining six patients with various sexual abnormalities showed 46 chromosomes and an XX sex-complement.

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