

Mosaicism

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INTRODUCTION

Chromosomal aberrations — numerical or structural — have been demonstrated in various diseases, in some of which the abnormality was one of mosaicism. In these cases the clinical picture is variable and depends on the proportion between cells of differing chromosomal constitution contained in the various tissues and organs. Mosaicism is therefore of theoretical as well as diagnostic interest.

METHOD

Chromosomal examinations were made in leucocyte cultures of peripheral blood by Moorhead's slightly modified technique [31].

REPRESENTATIVE CASES

Case 1. J. B., male, 12 years of age. At the child's birth, the father was 39, the mother 22 years old.

Both parents and two siblings were normal. The patient was moderately developed, his skin showed increased pigmentation, the hair reached deeply down the nape. The

skull was flattened posteriorly, the nasal bridge wide, the ears were below the normal level, the eyes were slanting; the child had epicanthus, irregular teeth and a small penis. His mental power was behind the chronological age. The buccal smear showed the cells to be sex-chromatin positive. Chromosomal examination revealed mosaic Klinefelter's syndrome XY/XXY (Table I, Fig. 1).

Case 2. A. S., female, 36 years of age, was born after a seven-month pregnancy with congenital dislocation of the hip. The family history of four generations contained seven cases of congenital luxation of the hip, six cases of renal or urogenital and five cases of other congenital malformations and a case of chronic myeloid leukaemia. The patient, underdeveloped and lean, had had five pregnancies with three live births, one extrauterine gravidity and one artificial abortion. The nail of the fifth finger of the right, that of the fourth finger of the left hand, and the nails of all toes were missing. The thorax was deformed and there was dextrolateral convex scoliosis, further in the lumbosacral region to the right of the spinal column a fist-sized tumour which was removed and found to be a dermoid cyst. Both kidneys were polycystic, with hydro-nephrosis on the right side. Chromosomal examination revealed 46 normal/47 F-trisomy mosaicism (Table I).

Case 3. A. S., 13-year old daughter of patient No. 2. The girl was tall (177 cm) and exhibited no pathological

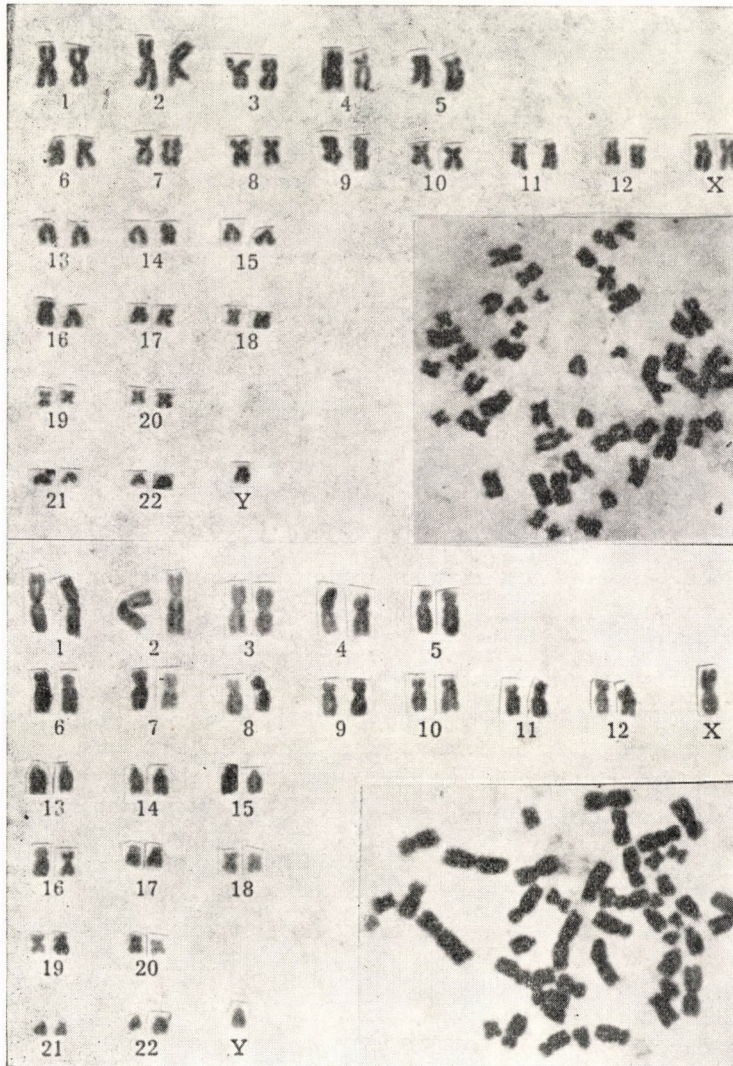


FIG. 1. J. B., male, 12 years old. Mosaic Klinefelter syndrome. Peripheral blood culture. Above: chromosomal pattern XX/Y. Below: normal karyotype from the same culture

changes. Chromosomal examination revealed 46/47 mosaicism (Table I). The supernumerary chromosome belonged most probably to the group F. (For details, see 26). No chromosomal abnormality was found in the two siblings of the patient or in her maternal aunt.

Case 4. T. P., female, 16 months old. Both parents and a sibling were normal.

The father was 28, the mother 32 years of age when the patient was born. The baby was underdeveloped, had slanting eyes, epicanthus, hypertelorism and a flat nasal bridge; the tongue was large, the palate gothic and the maxilla hypoplastic, the neck was short, with nuchal folds, the hands were short and broad, the fingers short, showing clinodactyly. The middle

TABLE I

	Number of chromosomes (peripheral leucocyte culture)			Type of chromosomal aberration	Clinical pattern
	45	46	47		
1	—	11	13	XY/XXY	Hypogonitalism, mental deficiency
2	3	20	21	Normal/F trisomy	Multiple developmental anomalies
3	5	42	27	Normal/F trisomy	Normal
4	1	13	26	Normal/21 trisomy	Several symptoms of Down's syndrome. Mental deficiency.
5	4	29	17	Normal/21 trisomy	Few symptoms of Down's syndrome. Normal mental development
6	22	77	1	Normal/E monosomy (?)	Atresia ani, anorectal fistula, tracheal diverticulum Cry like mewling.
7	1	84	9	Normal/22 trisomy	Microcephaly, deformity of ears, hypotonic abdominal muscles, clubfoot

phalanx of the fifth finger was short, the skin normal to touch, the muscle tone normal. The baby was paying attention to the surroundings but could neither sit nor stand. Chromosomal examination revealed 21-trisomy/normal mosaicism (Table I, Fig. 2).

Case 5. I. B., male, 11 years of age. The father was 42, the mother 40 years of age when the child was born. Both parents and two siblings were normal. The patient showed normal growth. The forehead was low, the eyes were slanting; the patient had epicanthus, the middle phalanx of the third and fifth fingers was short, with clinodactyly (Fig. 3). The left testicle was not palpable. No other symptom pointing to Down's disease was observed. Intelligence was normal. Chromosomal examination revealed 21-trisomy/normal mosaicism (Table I).

Case 6. A. S., female, 2 weeks old. She was admitted with anal atresia, ano-rectal fistula, tracheal diverticulum. The baby's

cry sounded like mewling. Chromosomal examination (Table I, Fig. 4) showed 45 chromosomes in 22 per cent of the cells in peripheral leucocyte culture. The missing chromosome seemed to belong to group E in some cells and appeared to be the chromosome X in others. This could not be decided with certainty since no autoradiogram was carried out (Fig. 4).

Case 7. H. S., a one-week old premature female baby, had microcephaly, deformed auricles, hypertonic abdominal muscles and a typical clubfoot (Fig. 5). An inflammatory, scaling dermal lesion on the lower extremity improved spontaneously in a few days. Chromosomal examination revealed 46/47 mosaicism. The supplementary chromosome belonged to chromosome 22 (Table I) [23].

DISCUSSION

In mosaicism, cells with discrepant chromosomal patterns may be of the

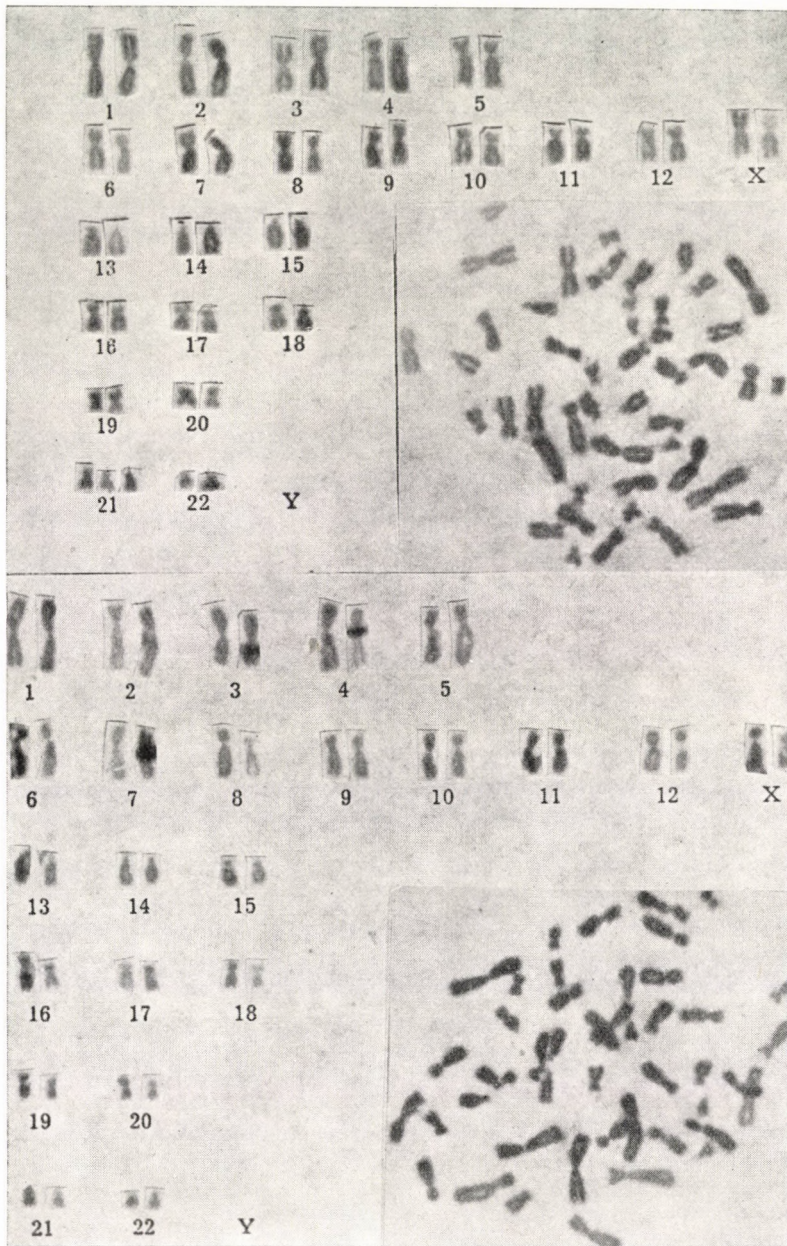


FIG. 2. T. P., female, 16 months old. Mosaic Down's syndrome. Peripheral blood culture. Above: 21-trisomy. Below: cell with normal chromosomal pattern from the same culture



FIG. 3. I. B., male, 11 years old. Mosaic Down's syndrome. Note slanting eyes, epicanthus and clinodactyly

same or of a different genotype. Individuals of the latter category are termed chimerae. The difference in genotype may be due to somatic crossing-over, point mutation, or microscopic chromosomal aberration [8]. This study is concerned with the last-mentioned abnormality.

It was in connection with Klinefelter's syndrome that the first case of human chromosomal mosaicism was described [11].

Some cells showed the pattern XXY, characteristic of the said syndrome, others contained the normal male sex chromosomes. Chromosomal mosaicism has since been described in numerous other diseases, and some of the most important observations are listed in the following.

Ovarian dysgenesis: XO/XX [12]; XO/XXX [22]; XX/XXX [14]; XX/XXX/XXXX [5]; XO/XX/XXX [18]; XO/XX-isochromosome [25]; XX/Xx (deletion) [14]; Xx/XX/XXx [1]; XO/X + fragment [10].

Testicular dysgenesis: XX/XXY; XY/XXY, XO/XXY [6]; XXXY/XXXXY [17]; XY/XXY/XXxY [21].

True hermaphroditism: XX/XY [3, 15, 42,]; XO/XY [19]; XX/XXY [38]; XO/XX/XY [43].

In cases of the considerably less frequent autosomal mosaicism, the following chromosomal patterns have been observed: partial 6-12 trisomy [35, 46]; 13-15 trisomy [4, 41], 17-18 trisomy [2, 20, 28] and 21-trisomy [7, 48].

The origin of chromosomal mosaicism is still obscure. Two spermatozoa may fertilize one ovum [15, 42], but it probably happens more frequently that after fertilization more than the normal number of chromosomes gain access to a cell owing to disturbed mitosis (postzygotic nondisjunction). This cell becomes then the ancestor of a cell population with abnormal chromosomal constitution. Again it may happen that during mitosis a chromosome or part thereof

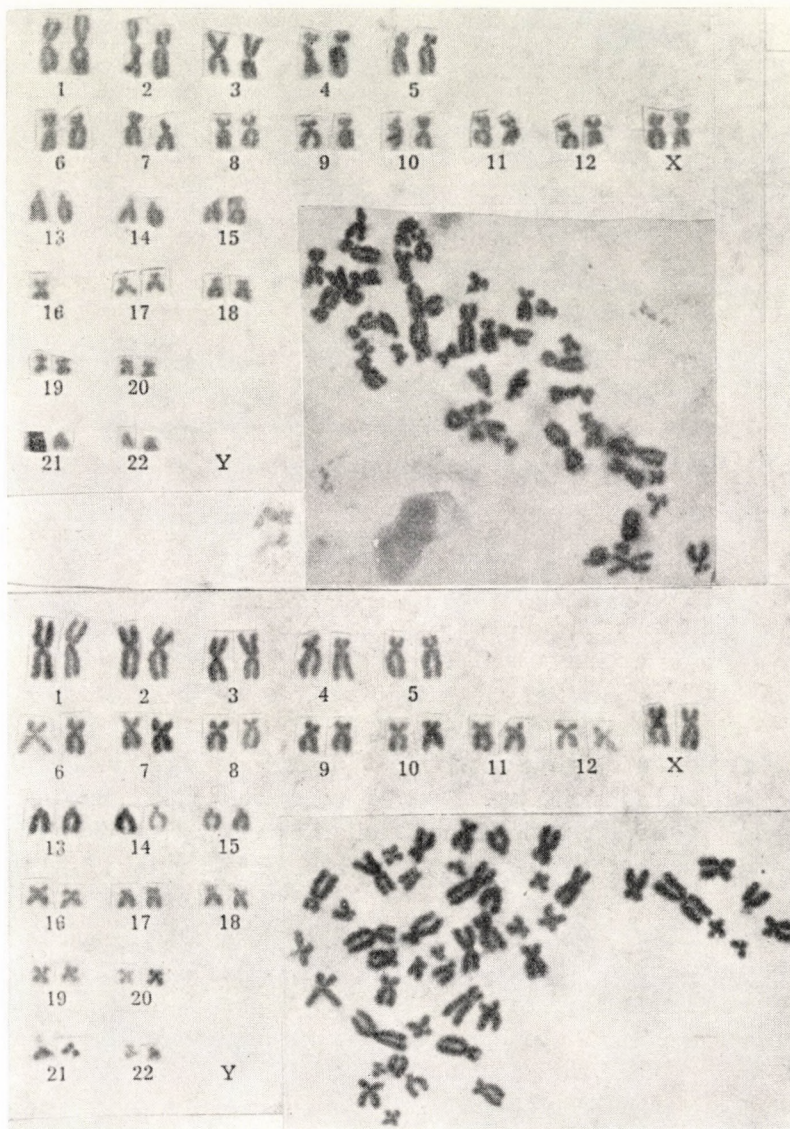


FIG. 4. A. S., female, 2 weeks old. Multiple congenital anomaly. Peripheral blood culture. Above: E-monosomy. Below: cell with normal chromosomal pattern from the same culture

fails to gain access to one of the newly formed cells (anaphase lag) so that two kinds of cells are born. Mosaicism may further result of some structural aberration (deletion, translocation,

isochromosome, inversion) occurs in a cell during intrauterine or extrauterine life and if it survives, the cell continues to proliferate. To a mechanism if this nature points the pres-

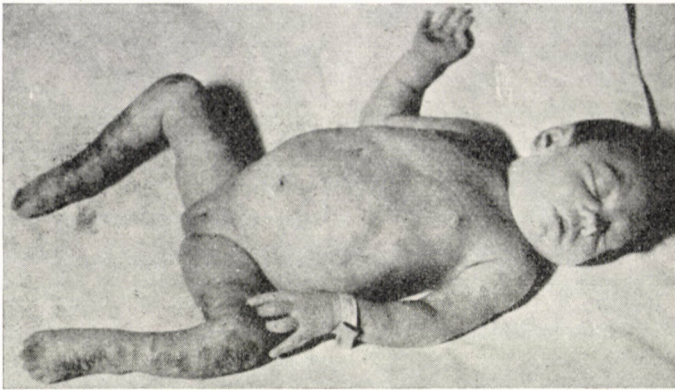


FIG. 5. H. S., female, 7 days old. Mosaic 22-trisomy. Note microcephaly and clubfoot

ence of chromosome Ph₁, demonstrable only in myeloid cells in cases of myeloid leukaemia. Chromosomal mosaicism may arise if foreign cells find their way into the foetus by blood transfusion [27] or from the blood of the mother or a twin by way of placental circulation. To this mechanism are due certain cases of mosaicism observed in true hermaphroditism [47].

The incidence of mosaicism is unknown. Among our 234 chromosomal examinations done in the period 1960 to 1966, there were 7 cases of mosaicism. The percentage of abnormal cell divisions is presumably higher than the observed one: if the resulting cells are eliminated, no mosaicism develops. This seems to be corroborated by the observation that the incidence of chromosomal abnormalities is much higher in spontaneously aborted fetuses than in infants, and this explains why certain chromosomal aberrations observed in aborted fetuses are not encountered *in vivo* [36, 45]. The high

incidence of mosaicism in some families shows that the susceptibility to it may be inherited. What is inherited is probably the reluctance of the chromosome to separate at mitosis (increased satellite association [15, 16, 39, 49, 50]). We were dealing with familial mosaicism in the above cases Nos. 2 and 3.

It occurs in mosaicism that cells originating from various tissues (blood, bone, fibroblasts) display different chromosomal patterns. It is, therefore, practically impossible to exclude the possibility of mosaicism with absolute certainty, since every organ and tissue cannot be examined for the chromosomal constitution of its cells.

Chromosomal examination being complicated, it may happen that more than the normal number is counted in some and less in other cells. TURNER and WALD [37] examined 8486 cells from the blood culture of healthy individuals: there were 46 chromosomes in 89.2 per cent, less than 46 in 8.5 and 47 in 1.33 per cent. Chro-

mosomal aberrations may arise *in vitro* as well [9]. Therefore, chromosome counting should be carried out and evaluated with much circumspection so as to avoid an erroneous diagnosis of mosaicism.

The clinical picture of mosaicism depends on the quality of the different chromosomal patterns, the proportion of the affected cells and the organs composed of pathologic and normal cells. In cases of super-numerary X chromosome the phenomenon called lyonisation has also to be taken into account [30]. It is possible that not all organs contain both abnormal and normal cells but that some are built up by cells of one type, others by cells of a different type [29]. Cell division is influenced, among others, by the time at which the mosaicism has developed; the earlier it arose, the greater the number of affected tissues. For instance, mosaicism in which the cells contain different sex chromosomes (e.g. XO/XY or XX/XY) may give rise to hermaphroditism; whether or not it does so also depends on the chromosomal pattern in the gonads [32]. The clinical patterns brought about by abnormal sex and autosomal chromosomes are less pronounced in the case of mosaicism, but extremely variable nevertheless. The above case No. 4, for instance, displayed most symptoms of Down's syndrome, and by mere clinical examination it was hardly possible to distinguish the observed disorder

from Down's syndrome. The boy in Case No. 5 was, on the other hand, normal both physically and mentally, and only a few symptoms were suggestive of Down's syndrome. Trisomy mosaicism induced grave developmental abnormalities in patient No. 2 while the same form of mosaicism caused no symptoms in her daughter.

Detection of mosaicism is important for the offspring also. If mosaicism extends to the gonads, some of the gametes will contain an abnormal chromosomal set, and bring about a correspondingly pathological clinical pattern in the offspring. Several cases are known in which a phenotypically normal mother with 21-trisomy gave birth to children suffering from Down's syndrome [34, 40, 44]. Several cases of mosaicism among members of the same family point to a hereditary susceptibility to non-disjunction.

Mosaicism is, thus, not merely of scientific interest but also significant for the correct diagnosis of certain atypical clinical manifestations, and most important in genetic clinics.

SUMMARY

Seven cases of chromosomal mosaicism have been reported, and the development, clinical symptoms and significance of mosaicism have been discussed.

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