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A Family with a Balanced C/C Translocation Carrier and an Unbalanced 47,XY,(Cq—)+ Son[1]

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SUMMARY

An account is given of a family identified by a newborn malformed male. The chromosome anomalies described are interpreted as indicating that the father has a balanced translocation with a reciprocal exchange between no. 9 and no. 12. The supernumerary chromosome resembling a group F element, which is found in the propositus, is in fact one of the two rearranged chromosomes present in the father. The propositus therefore is trisomic for part of no. 9 and no. 12. His brother has a normal karyotype. Possible meiotic situations leading to the formation of the observed karyotypes are discussed.

Reciprocal translocations in man are generally ascertained through phenotypically abnormal individuals who usually carry one of the possible unbalanced states. Such individuals are often found to be offspring of translocation heterozygotes who are phenotypically normal.

In the present paper we are reporting clinical and cytogenetic findings of a patient with an additional metacentric chromosome of the same size of group F (19-20), that resulted in a rearranged chromosome (12^9) inherited from the father, who was the carrier of a balanced reciprocal translocation 9/12.

Case Report

The patient, a newborn male, was the second child of healthy, unrelated parents, both aged 26. The mother has had no abortions; another preceeding offspring, also male, is normal. Pregnancy, delivery and birth weight (4300 g) were also normal. A few hours after birth the propositus was hospitalized with symptoms of severe anoxia and amniotic fluid ingestion; he was discharged with a diagnosis of cerebropathia, caused by anoxic-haemorrhagic syndrome. Fifty days after birth, he was again admitted to hospital with a diagnosis of cardiovascular failure associated with external cephalhematoma. A few days after admission, he was carried out by his parents, against the paediatrician's advice, and he died at home.

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Physical Examination

Patient fed poorly, failing to thrive; paleness of cutis and mucosae; perioral cyanosis; skin shedding; marked hypotonia; superficial reflexes present; no seizures; generalized dystrophia; no external malformations; no clinodactily; no epicanthal folds.

Head: external right parieto-occipital cephalhematoma; large fontanelles (4 × 4).

Chest: symmetric; shield-shaped; respiration 30/m.

Heart: enlarged cardiac area; presystolic murmur with accentuation of the 1st heart sound in mesocardial region; no thrills; heart rate 140/m; gallop rhythm.

Abdomen: globular; no umbilical hernia; liver parenchymatous, palpable 2 cm below the right costal margin; spleen palpable 1 cm below the left costal margin.

External genitalia: normal; both testes descended.

Clinical Findings

Radiological examination of cranium: no osseous lesions.

Radiological examination of chest: areas of parenchymal thickening with homogeneous opacity in the right cardio-phrenic region, degrading from hilum to right costo-diaphragmatic region; cardiomegaly.

Radiological examination of digestive apparatus: normal; abnormal insertion of right hemodiaphragm.

ECG: bundle right branch block; generalized myocardic ailment.

Laboratory Data

Haemoglobin: 8.75 g; R.B.C. 3,442,000; W.B.C. 16,000; differential W.C.C.: N = 44%, E = 3%; L = 50%, M = 3%.

Blood chemical determinations: nonprotein nitrogen 0.28 g%; sugar 0.90 g%; sodium 157 mEq/l; potassium 4 mEq/l; chloride 101 mEq/l; alkaline reserve 28 mEq/l.

Urinalysis: normal.

Blood groups transmission, controlled in all family members, revealed no abnormalities.

Cytogenetic Investigations

Karyotype of the Propositus

The chromosome examination of the propositus was carried out on peripheral blood by Hungerford method modified. As many as 100 mitoses were counted and analyzed and all revealed a modal number of 47. The extra chrosomosome was a small metacentric indistinguishable from the two pairs of group F (Figs. 1 and 4).

Sex chromatin was negative.

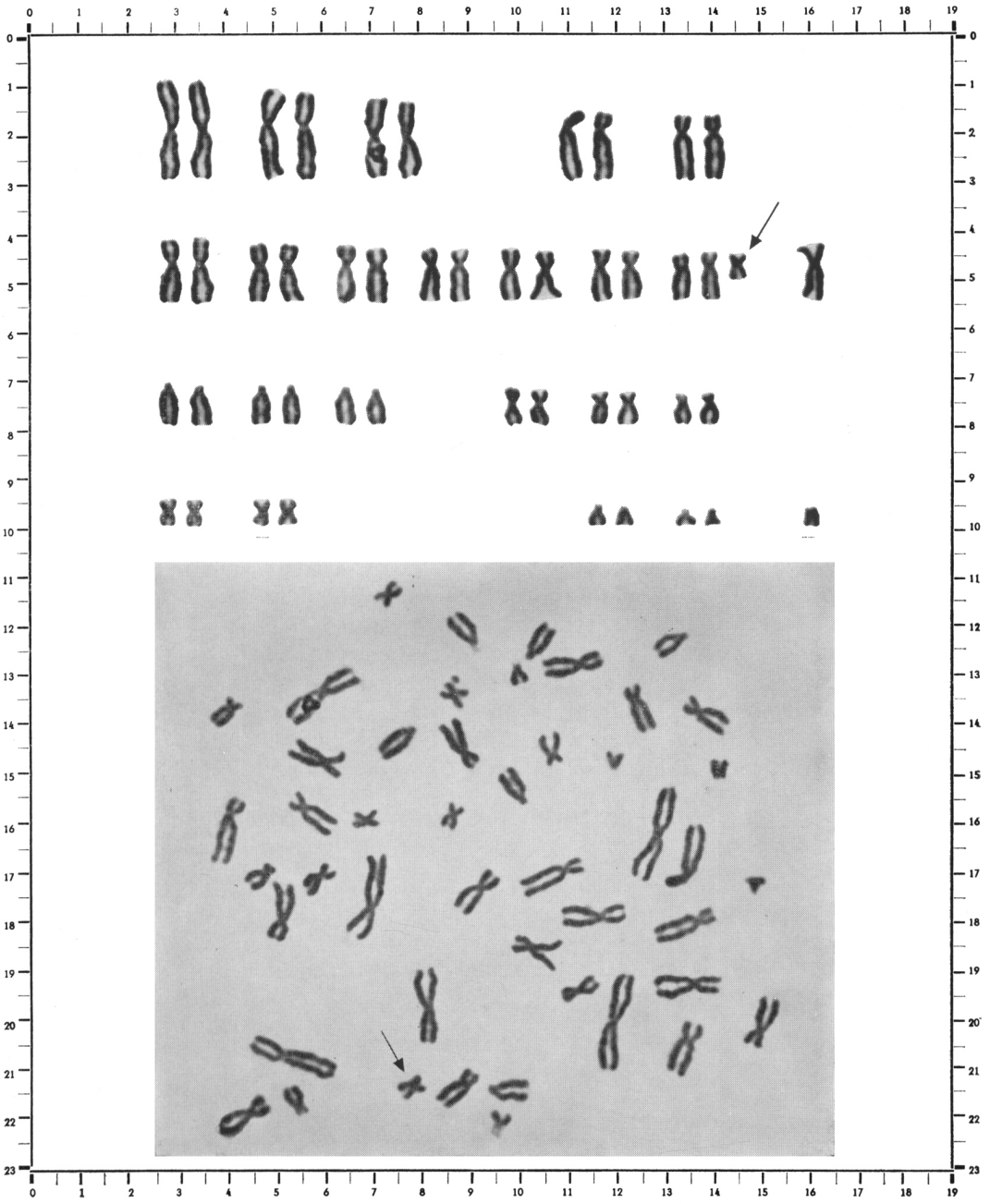

Fig. 1. Karyotype of the propositus: 47,XY,(12 q—)+. [2400 ×]

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Karyotype of the Parents

Karyotype analysis was performed also on blood cultures from the phenotypically normal parents. The karyotype of the mother resulted normal. In the father the modal number of 46 chromosomes was observed, but a structural alteration was established by reconstructing and studying 25 metaphases. In all cells two group C chromosomes were missing (tentatively identified as nos. 9 and 12); two new chromosomes were present: one was apparently identical to the additional chromosome found in the propositus (Figs. 2 and 3: T^2) and the other was an almost mediocentric chromosome about the size of a no. 3, from which, however, it could be differentiated, since in most instances it was somewhat larger and presented a secondary constriction near the centromere (Figs. 2 and 3: T^1).

Interpretation of the Karyotype of the Father

The two abnormal chromosomes (T^1 and T^2) can be interpreted as the product of a balanced reciprocal translocation between a chromosome no. 9 and a chromosome no. 12. To simplify, we shall call T^1 the larger (9^{12}) and T^2 the shorter (12^9) of the two rearranged chromosomes.

The exact identification of the chromosomes involved in the translocation was discovered by measuring the chromosomes of groups A, C and F. Chromosome measurements were made on photographic enlargements (6000 ×) of 20 metaphases and the relative chromosome lengths were expressed as percentages of the haploid autosomal complement. The data are presented as a mean ± one standard error. Differences of means were tested for statistical significance by the *t*-test.

The following relationships can be seen from the data:

(1) The sum of the total length of the two translocated chromosomes is equal to the sum of the length of the two normal chromosomes nos. 9 and 12:

$$9\ (4.72 \pm 0.055) + 12\ (4.25 \pm 0.066) = 8.97$$
$$9^{12}(6.12 \pm 0.064) + 12^{9}(2.82 \pm 0.046) = 8.94$$

(2) No significant differences were found between the long arm of 9^{12} and the long arm of no. 9, or between the short arm of 12^9 and the short arm of no. 12:

$$9^{12}\ \text{l.a.}\ (2.27 \pm 0.046) = 9\ \text{l.a.}\ (2.23 \pm 0.032)$$
$$12^{9}\ \text{s.a.}\ (1.38 \pm 0.035) = 12\ \text{s.a.}\ (1.45 \pm 0.031)$$

(3) No significant differences were found between the short arm of 9^{12} and the long arm of no. 12, or between the long arm of 12^9 and the short arm of no. 9:

$$9^{12}\ \text{s.a.}\ (2.83 \pm 0.055) = 12\ \text{l.a.}\ (2.80 \pm 0.055)$$
$$12^{9}\ \text{l.a.}\ (1.46 \pm 0.025) = 9\ \text{s.a.}\ (1.50 \pm 0.038)$$

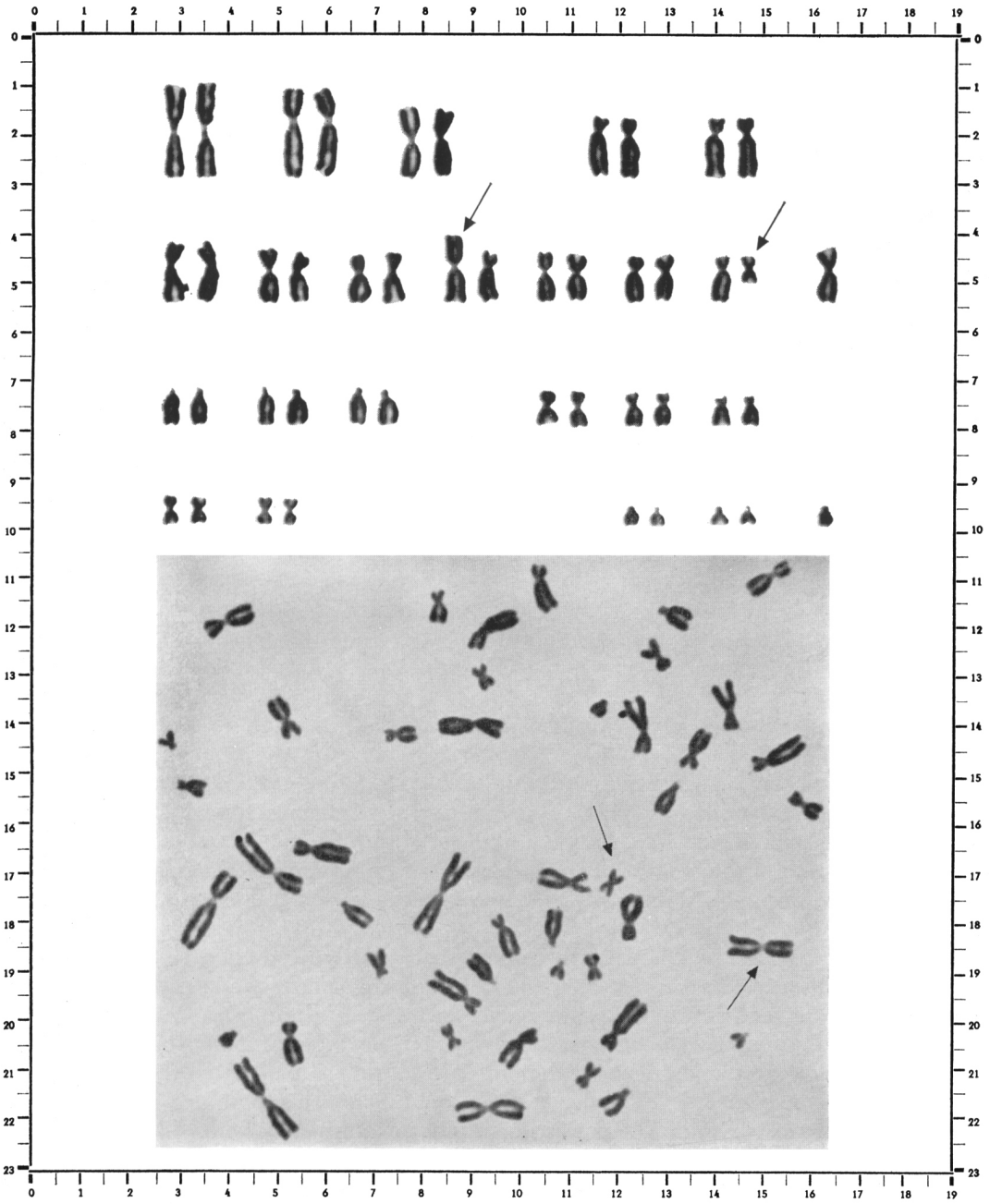

Fig. 2. Karyotype of the father: 46,XY,t(9p+; 12q—). [2400 ×]

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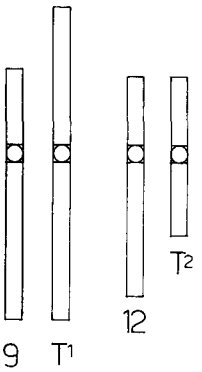

Fig. 3. Chromosomes nos 9, 12, T^1, T^2 of the father

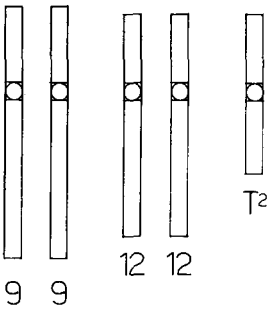

Fig. 4. Chromosome pairs nos. 9, 12 and the supernumerary T^2 of the propositus

(4) The short arm of the 9^{12} is about equal to the sum of the short arm of no. 9 plus the long arm of no. 12, less the long arm of the 12^9:

9 s.a. $(1.50 \pm 0.038) + 12$ l.a. $(2.80 \pm 0.055) - 12^9$ l.a. $(1.46 \pm 0.025) =$
$= 2.84$

9^{12} s.a. $= 2.83 \pm 0.055$

Karyotype of the Normal Brother

Karyotype analysis of the normal brother revealed no abnormalities.

Discussion

The chromosome anomaly present in the paternal karyotype is evidently the result of a rearrangement which occurred during the gametogenesis of a grandparent of the propositus.

Since the sum of the lengths of the two new chromosomes is equal to the combined lengths of the normal chromosomes nos. 9 and 12, we postulated that a balanced translocation had occurred.

Figs. 5-7 illustrate the following three possible cases of reciprocal 9/12 translocation:

(1) Translocation at the level of the centromeres (Figs. 5*a*, *b*, *c*, *d*), leading to chromosomes T^1 (consisting of the long arms of no. 9 and no. 12) and T^2 (consisting of the short arms of no. 9 and no. 12);

(2) Translocation at the level of the long arm of no. 12 and of the terminal region of the short arm of no. 9 (Figs. 6*a*, *b*, *c*, *d*), leading to chromosomes T^1 (consisting prevalently of no. 9) and T^2 (consisting almost exclusively of no. 12);

(3) Translocation at the level of the long arm of no. 9 and of the terminal region of the short arm of no. 12 (Figs. 7*a*, *b*, *c*, *d*), leading to chromosomes T^1 (consisting prevalently of no. 12) and T^2 (consisting almost exclusively of no. 9).

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The presence of a secondary constriction (typical of the long arm of no. 9 near the centromere), which we have always observed on T^1, clearly excludes the third mechanism which is based on its presence on T^2 (consisting almost exclusively of no. 9).

The genetic constitution in the progeny of a balanced translocation heterozygote depends on the meiotic segregation of four chromosomes, the two rearranged chromosomes and their corresponding unaltered normal homologues. These chromosomes form an assumed cross-shaped tetravalent configuration at pachytene (see Figs. 5*e*, 6*e*, 7*e*). Figs. $5f^{bis}$, $6f^{bis}$ and $7f^{bis}$ illustrate some tetravalent configurations just before the onset of anaphase I with a centromeric orientation giving rise to a distribution 3 : 1 (see Figs. 5*g*, 6*g*, 7*g*).

Figs. 5*f*, 6*f*, 7*f* illustrate less probable alternative configurations. The combination of a paternal gamete containing the normal no. 12, the normal no. 9, and T^2 with a normal maternal gamete may have given rise to the karyotype $47,XY,(12^9)+$ found in the propositus.

Fig. 8 illustrates a tetravalent configuration with a centromeric orientation giving rise to a distribution 2 : 2, and therefore producing gametes containing either the two rearranged chromosomes (T^1, T^2) or the two normal chromosomes (9, 12). The presence of the normal son clearly indicates that regular gametes may be produced.

A few reciprocal translocations involving only group C have been described (Rohde and Catz, 1964; Lejeune and Berger, 1965; Lindsten et al, 1965; Stahl et al, 1966; McDermott et al, 1968; Lejeune et al, 1968; Bargman et al, 1970). None of them, however, is comparable to the translocation found in the father of our patient.

The clinical findings in the propositus, trisomic for a variable part of chromosomes nos. 9 and 12, according to the point of translocation are considered to be the result of the genetic unbalance.

Several cases of partial trisomy C, none with 47 chromosomes, have been described (Edwards et al, 1962; Rohde and Catz, 1964; De Grouchy and Canet, 1965; Lindsten et al, 1965; Gray et al, 1966a, 1966b; Lejeune et al, 1966; Punnett et al, 1966; Stahl et al, 1966; Bühler et al, 1967; De Grouchy et al, 1967a, 1967b; Jensen and Melchior, 1967; Lord et al, 1967; Pitt et al, 1967; Lejeune et al, 1968; McDermott et al, 1968; Mikkelsen et al, 1968; Butler et al, 1969; Deminatti et al, 1969; Lozzio and Kattine, 1969; Thorburn et al, 1969), all of them with a different clinical picture. This phenotypical variability might be explained taking into account that in all described cases, including ours, different regions of different chromosomes are involved in the rearrangement.

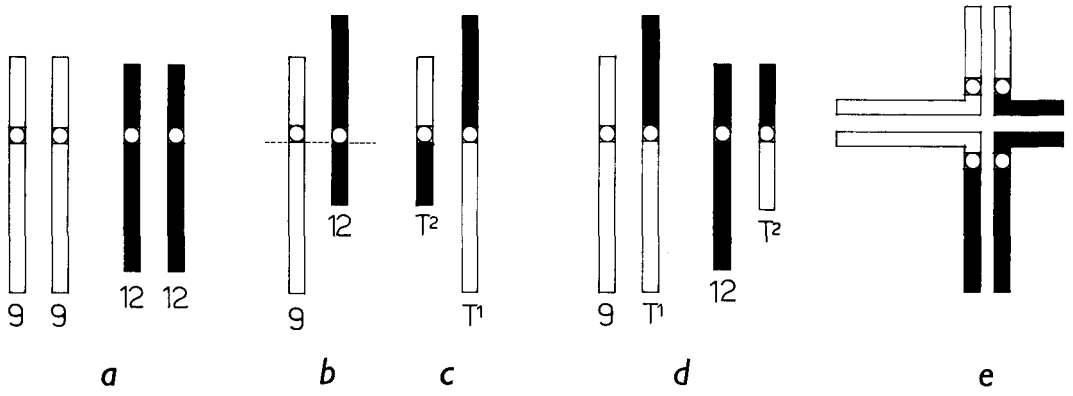

Fig. 5

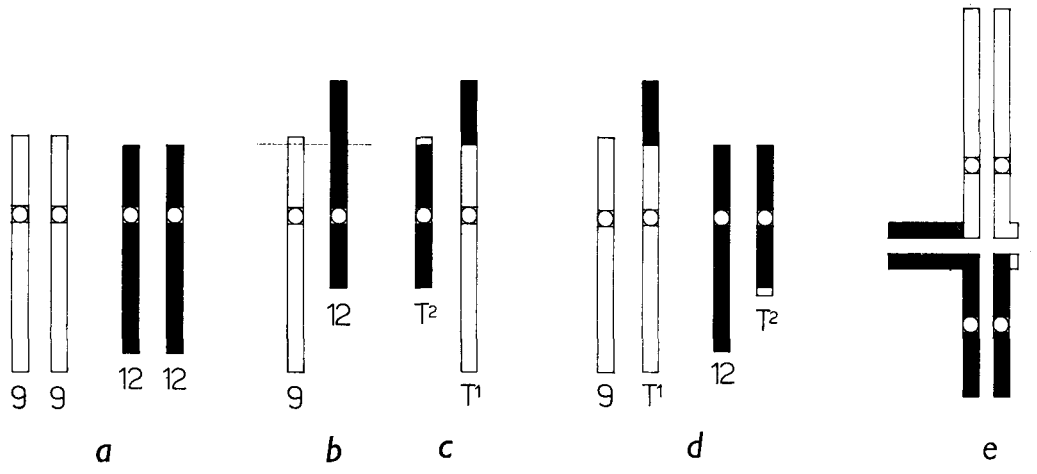

Fig. 6

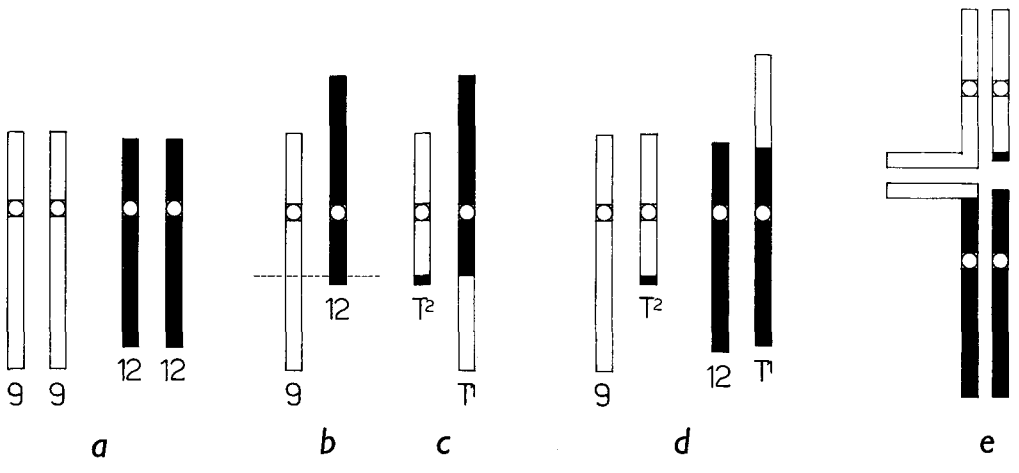

Fig. 7

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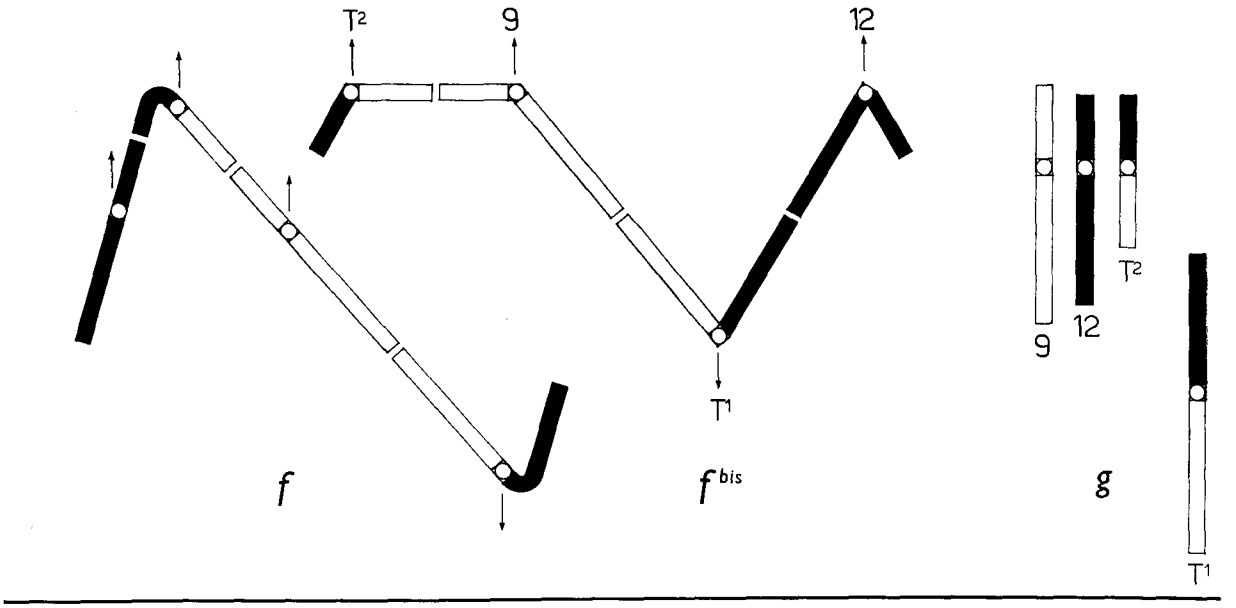

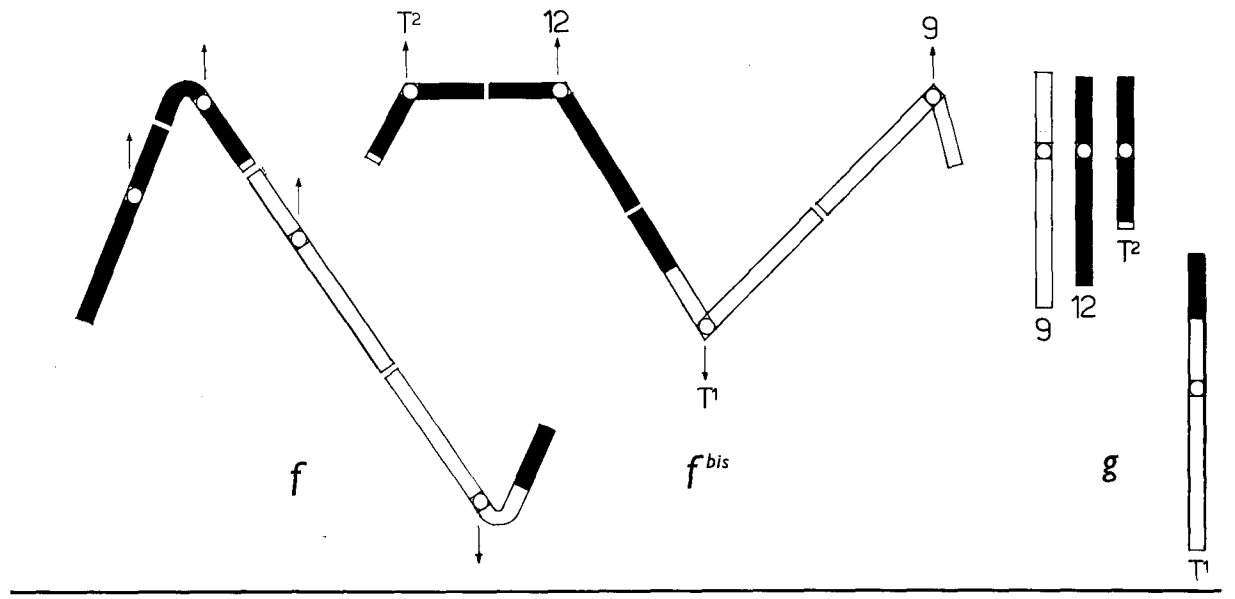

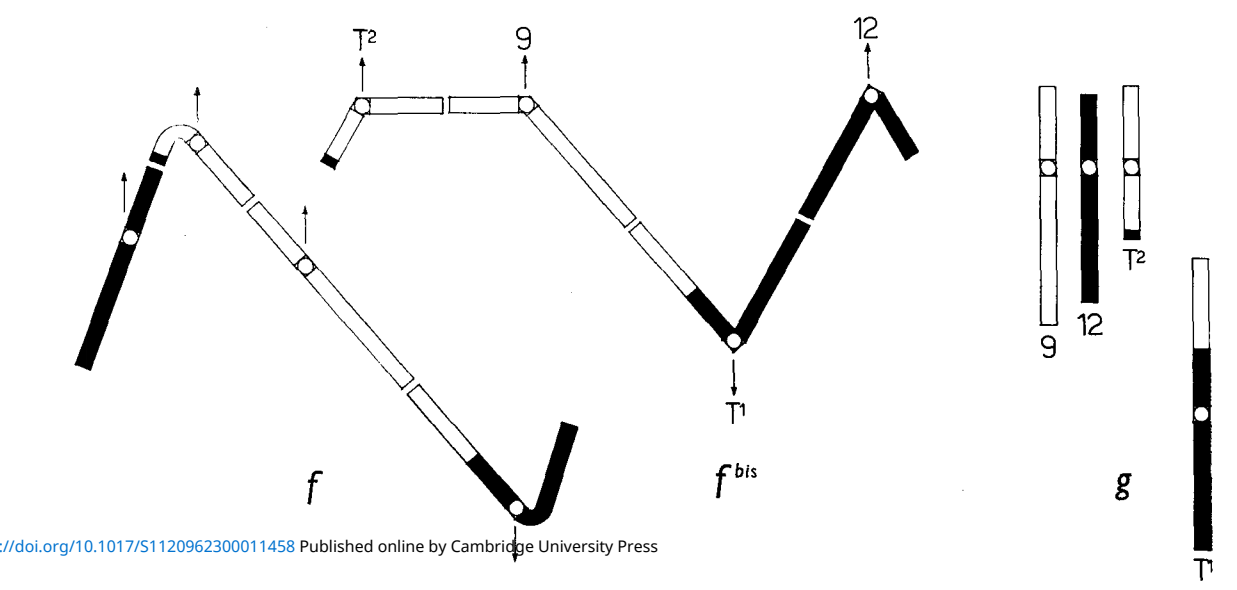

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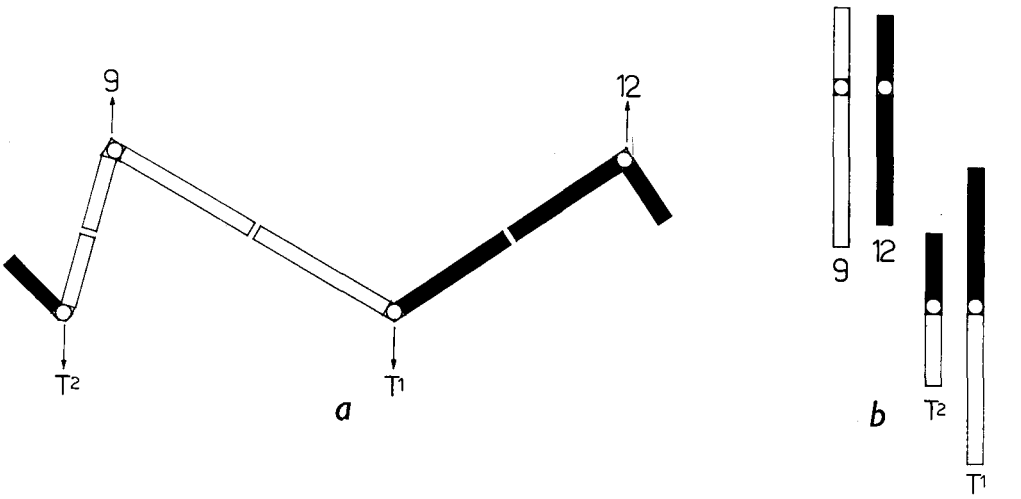

Fig. 8

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Riassunto

Si descrive una famiglia identificata mediante un neonato di sesso maschile portatore di malformazioni multiple. Il padre del paziente è risultato portatore di una traslocazione bilanciata coinvolgente i cromosomi n. 9 e 12. Il cromosoma soprannumerario, morfologicamente simile ad un membro del gruppo F, osservato nel proposito, è in effetti uno dei due cromosomi rimaneggiati presenti nel padre. Il paziente è quindi parzialmente trisomico per il 9 e il 12. Il fratello ha cariotipo normale.

Sono discussi i possibili meccanismi meiotici che conducono alla formazione dei cariotipi osservati.

Résumé

Les auteurs décrivent une famille identifiée à cause d'un nouveau-né atteint de malformations multiples. Le père du patient est résulté conducteur d'une translocation balancée concernant les chromosomes 9 et 12. Le chromosome surnuméraire, observé chez le patient, ressemble à un membre du groupe F du point de vue morphologique, et est en effet l'un des deux chromosomes altérés présents chez le père. Le patient est par conséquent partiellement trisomique pour les chromosomes 9 et 12. Son frère présente un caryotype normal.

Les possibles mécanismes méiotiques responsables de la formation des caryotypes observés sont discutés.

Zusammenfassung

Verf. untersuchten die Familie eines Neugeborenen männlichen Geschlechts mit multiplen Missbildungen. Dabei erwies sich der Vater als Träger einer bilancierten Translokation der Chromosomen 9 und 12. Beim Patient fand sich ein überschüssiges Chromosom, das morphologisch einem Glied der Gruppe F ähnelt und in Wirklichkeit eines der beiden « umgearbeiteten » Chromosome ist, die sich beim Vater fanden. Patient weist also eine partielle Trisomie für 9 und 12 auf. Der Bruder hingegen hat normalen Karyotyp.

Es werden die Mechanismen erwogen, die zur Bildung des beobachteten Karyotyps führen konnten.

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