Summary

In a young male with Fanconi’s anaemia, 10% of cells in a direct bone marrow preparation had chromosome abnormalities. Breaks involving primarily groups B and C members constituted the most frequent changes encountered, while 2 cells had either a dicentric or a ring chromosome. Smears from the same aspirate showed anaphase bridges in 3% of mitoses. It is suggested that in this disease chromosome breakage is a process in vivo, and that its occurrence in bone marrow cells possibly contributes to their progressive elimination and ultimate depletion.

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Case Report

Down’s Syndrome with an Atypical G/G Translocation Derived from Familial Pericentric Inversion in One Chromosome of the G Group

The propositus was born on 28 September 1956, the 2nd child of a mother of 30, and a father of 45 years of age (Fig. 1).

The pregnancy and confinement were normal. Birth weight was 4500 g. Psychomotor development was retarded; he sat at 9 months, walked at 18 months, and spoke his first words at 4 years of age. At the first examination, in 1961, Down’s syndrome was diagnosed.
In June 1969, when he was 12 years 8 months, he was 131 cm tall and weighed 30·5 kg. Head circumference was 50·5 cm with a cephalic index equal to 0·94, the eyes and the eyebrows were oblique, epicantthic folds were present, and the nasal bridge was flat. There were fissures on the lips and a furrowed tongue. The occiput was typical. The hands were short and the little finger showed clinodactyly. He was tested with the Bühler-Hetzer developmental test, and with the Vineland-
Fig. 2. Karyotype of the propositus.
Doll scale for social maturity; his IQ was equivalent to that of a child of 2-5 years of age. The social development (maturity) SQ was equal to 36, showing that this is a case of serious mental retardation at the level of imbecility.

**Chromosome Analysis**

Analysis of the chromosomes of lymphocytes of the peripheral blood was made using a modification of the method of Moorhead *et al* (1960) and from the first passage of a culture of skin fibroblasts.

Thirty-seven cells of 2 independent cultures of peripheral blood and 20 cells of the culture of fibroblasts were analysed. In all the analysed cells the chromosomal complement was 46,XY, but with an atypical chromosome in the G group. This G chromosome differs from others in having an apparently elongated short arm (Fig. 2).

Clinical examination of the propositus’ family showed that they were all phenotypically normal. Cytogenetic analysis showed one chromosome in the G group with an unusual appearance, in the propositus’ mother and in her 2 sisters (Fig. 3). This marker chromosome differs from the other G group chromosomes in having the long arm shortened, while the short arm is elongated in the same way as in the propositus (Fig. 4). In all the other family members the chromosome complement was normal.

**Discussion**

The marker chromosome found in the G group in all 3 sisters is assumed to represent a pericentric inversion. The mother’s parents were not available for analysis, and therefore it is not known which of

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**Fig. 3.** Family pedigree.

**Fig. 4 (on the right).** G group chromosomes in 6 cells from the propositus’ mother (a) and the propositus (b).
them transmitted the marker chromosome to their daughters. There is no detectable phenotypic expression at the clinical level caused as a result of the inversion (46,XX,G inv,p + q−). The abnormal chromosome in the propositus differs morphologically from that of his mother and her sisters, having a long arm of normal length. The most probable explanation for the phenotype of the propositus is an error during meiosis in the mother as a result of the pericentric inversion of her G chromosome.

resulting from a duplication deficiency following crossing-over. This assumption is supported by the morphology of the marker chromosome in the mother and in her 2 sisters, as well as by the morphology of the propositus’ chromosome.

It could be assumed that the mother’s marker chromosome is translocated with one of the normal G chromosomes. Such a gamete with partial translocation of G/G marker could also lead to Down’s syndrome. This last suggestion is less probable.

![Fig. 5. Probable origin of marker chromosome in the mother's and the propositus' G chromosome derived by the duplication-deficiency effect. A. The marker chromosome arises by the pericentric inversion (mother and her 2 sisters). B. The marker chromosome in meiosis (the inside chromatides). C. Recombinates. D. The G chromosome of the propositus with duplication of genetic material on the long arm (d and e).](image-url)

It is well known that crossing-over normally occurs during the pachytene stage of prophase of meiosis, and during this period the reduplicated and paired chromosomes form a tetrad or 4-strand structure. The chromosome with the pericentric inversion and its homologue theoretically could give rise in meiosis (as a result of one crossing-over) to one normal G and one recombined G with balanced genetic material as in the mother, and also 2 more chromosomes which during meiosis produce recombined gametes with deletion or duplication. In this case it is possible to presume that the propositus’ unusual G group chromosome (Fig. 5) possesses a surplus of genetic material of the long arm of a G chromosome, behaving as a double G(46, XY,G inv,p +). Fertilized by a normal gamete it produces Down’s syndrome with a masked trisomy

Analysis of this family suggests that there may be a greater risk of mongoloid children being born to persons with a G marker which consists of altered genes sequences as the result of a pericentric inversion. This high risk of having a child with Down’s syndrome may be similar to that of parents who are carriers of a balanced translocation of 2 acrocentric chromosomes.

**Summary**

The mother of a boy with Down’s syndrome and her 2 sisters have one G chromosome with a pericentric inversion (46,XX,G inv,p + q−). In cultures of peripheral blood and fibroblasts of the propositus the normal number of 46 chromosomes was found, but one of the G chromosome showed a duplication deficiency 46,XX,G inv,p +.
A greater risk of Down’s syndrome in the offspring of persons who are carriers of a pericentric inversion of a G chromosome, is suggested.

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A New HGPRT-deficient Phenotype?

Seizures were a retrospective neurological finding in one of 18 patients with gout, hyperuricaemia, and partial deficiencies of hypoxanthineguanine phosphoribosyltransferase (HGPRT) (Kelley et al, 1969). Seizures also accompany the clinical expression of hyperuricaemia associated with the complete enzyme deficiency, ie, the Lesch–Nyhan syndrome of mental retardation, spasticity, choreoathetosis, and self-mutilation (Michener, 1967; Dreifuss et al, 1968), but are not especially common. We describe a non-gouty, retarded, 14-year-old negro boy with hyperuricaemia and HGPRT deficiency, in whom seizures were not only the presenting sign, but were the main clinical feature of his disorder.

Case Report

The propositus was the product of a full-term, uncomplicated pregnancy, and normal delivery. Birth weight was 2636 g. His early developmental milestones were somewhat delayed; he sat at 1 year, walked at 16 months, and spoke single words only at 15 months. Speech developed slowly thereafter and was 'dysarthric' at age 5½ years when evaluated.

Seizures, which began at 5 years, were a mixture of generalized major motor, psychomotor, minor motor, and akinetic spells, almost from the onset; the latter 2 types occurring 15 times or more a day. At 5½ years, his height and weight were normal, 117 cm and 22 kg, respectively. Hyperactive and distractible, he was slightly unsteady on tandem gait and displayed mild dysmetria and dysdiadochokinesia. Cranial and sensory nerve examinations and deep tendon reflexes were normal. Spasticity and choreoathetosis were absent. His IQ was 86 on the Stanford-Binet Test, which revealed deficiencies in verbal and perceptual-motor skills. Electroencephalograms (EEG) consisted of diffuse 2–4 cps spike-and-wave, almost continuous, activity.

Treatment with phenobarbital, dilantin, tridione, myoline, triple bromides, zarontin, peganone, and valium in appropriate combinations and full therapeutic doses throughout the years failed to alter the frequency of his seizures appreciably, and the EEGs remained virtually unchanged.

At 14 years, his dysarthric, slurred speech persists. He may have deteriorated mentally, as his full scale IQ on the Wechsler Intelligence Scale for Children (which is not directly comparable to the Stanford-Binet scale) was 48 (verbal IQ 63 and performance IQ below 44) at the age of 11½ years. The main deficit, as before, was in perceptual-motor functioning.

Finger-nose-finger testing reveals mild cerebellar incoordination, and attempts at posture-holding during the last year or two provoke very minimal choreiform jerks of the outstretched fingers.

He weighs 41·6 kg and is 155 cm tall (25th centile). His head circumference is 53 cm (20th centile).

Uraciluric acidemia of 10–13 mg/100 ml was discovered recently as a chance finding on routine screening. Subsequent laboratory studies revealed 24-hour uric acid excretion averaging 20 mg/kg body weight, a rate in excess of normal, but less than that of the Lesch–Nyhan syndrome (Kelley, 1968). The following blood values were normal: calcium, phosphorus, glucose, urea nitrogen, cholesterol, total protein, lactic dehydrogenase, and glutamic-oxalic transaminase. A sickle-cell preparation was negative. Electromyogram and nerve conduction studies were normal. Urinalysis and urinary aminoacid screening were normal. Radiology showed a thickened calvarium, a finding not present on initial x-rays at age 5½ years, and a consequence, perhaps, of chronic dilantin administration (Kattan, 1970). Haemoglobin was 13–14 g/100 ml, and reticulocyte counts were 1·5–3%. Glucose-6-phosphate dehydrogenase (G6PD) was deficient in the fluorescent spot test (Beutler, 1966).

His negro parents, who are in their late 30s, and a 9-year-old sister are healthy. The father’s serum uric acid was 5·0 mg/100 ml, 3·7 mg/100 ml in the mother, and 3·9 mg/100 ml in the sister. A paternal uncle has renal disease not related to hyperuricaemia, gout, or arthritis. Other family history is not pertinent. The mother’s erythrocyte G6PD was also deficient; those of the father and sister were normal.

Treatment with allopurinol has reduced the uric acid concentration in his serum to 5–6 mg/100 ml and his uric