D group. On the long arm of this abnormal chromosome a secondary constriction was demonstrated. Heat treatment and Giemsa staining (Dutrillaux and Lejeune, 1971) revealed that this chromosome was formed from a No. 15 chromosome and by the short arm of a No. 9 chromosome; the other chromosomes were normal (Figs. 2a and b). Therefore there was a trisomy for the short arm of the No. 9 chromosome. The chromosome pattern after heat treatment and Giemsa staining was normal in the parents and the brother.

Discussion

As far as we know only 10 cases of this trisomy have been described (Rethoré *et al*, 1970; Cantu, Buentello, and Armendares, 1971; Hoehn, Engel, and Reinwein, 1971; Rott, Schwanitz, and Grosse, 1971) and a complete review is given by Rethoré *et al* (1973).

The malformations and the dermatoglyphics of our case are quite similar to those previously described but the mental retardation is not so severe.

In our case the trisomy for the short arm of the No. 9 chromosome can be considered 'pure', since deletion of the short arm of the No. 15 chromosome is not usually associated with phenotypic anomalies.

However it is noticeable that in Rethoré's series one case (case 10) had the same cytogenetic findings but with very severe mental retardation (QD = 45).

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Developmental Abnormalities Associated with a Ring Chromosome 6*

Summary. A clinical and cytogenetic report is made of a patient with microcephaly, peculiar facies, and retardation of physical and mental development, who possesses a karyotype containing a ring chromosome No. 6 identified by Q-staining with quinacrine mustard. This is the first report of a ring autosome in the C group to be identified. Comparison with other patients reported as having C-group autosomal rings failed to reveal many common phenotypic characteristics.

While ring chromosomes are rare, they have been observed in each of the seven chromosomal groups, including at least 10 cases in the C group (Turner *et al*, 1962; Smith-White *et al*, 1963; Atkins *et al*, 1966/67; Butler, France, and Jacoby, 1967; Bueno, del Amo, and Hermida, 1969; Wurster *et al*, 1969; Gacs, Schuler, and Sellyei, 1970; Kistenmacher and Punnett, 1970; Therkelsen, Møller, and Henningsen, 1971; de Chieri *et al*, 1972). None of the C-group chromosomes involved in the ring formation was identified. We report here another C-group ring chromosome shown to involve a No. 6 chromosome.

Case Report

The proposita (SH 512 463) was the product of an uncomplicated pregnancy, labour, and delivery. At birth the patient weighed 2910 g, measured 48·2 cm in length, and had a head circumference of 32·2 cm. The patient's mother and father were 26 and 27 years of age, respectively, at the patient's birth. Two older sibs, a brother and sister, are described as being in excellent health. There are no known instances of birth defects, mental retardation, or recurring abortion on either side of the family.

The patient's developmental milestones have been delayed with spontaneous sitting, standing, and walking occurring at 11, 22, and 26 months, respectively. Intelligible speech was still lacking at 24 months of age. Throughout the first 2½ years of development, the patient's length, weight, and head circumference have consistently been below the third centile.

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During a severe infection with *Staphylococcus aureus* tracheobronchitis, which responded only after aggressive antimicrobial treatment, studies of the patient's cellular and humoral immune mechanisms were found to be normal. Transient leucopenia occurred during a subsequent infection, but this resolved spontaneously. The bone marrow during this time appeared normal.

Abnormal physical findings at 2½ years included microcephaly; microphthalmia; micrognathia; microstomia; bilateral epicanthal folds; large, low-set ears; depressed nasal bridge; mildly high-arched palate; delayed dentition; stiff ankles and mild pes equinus; and mild hyperkeratosis of the soles (Fig. 1).

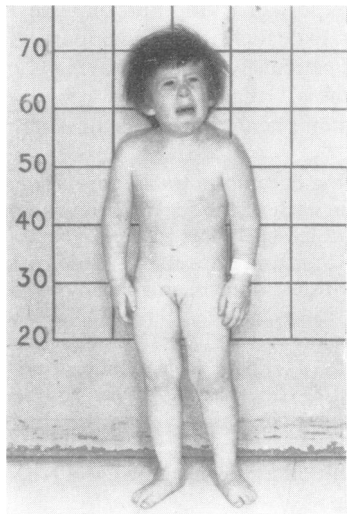

FIG. 1. Physical appearance of the patient at 28 months of age.

Blood and urine chemistry, haematological indices, serological tests, toxoplasmosis titre, sweat test, bone age, immunoelectrophoretic pattern and radiology of the chest, skull, and skeleton were all within normal limits. Electroencephalography performed at 26 months of age and intravenous pyelography were both within normal limits. Psychometric testing performed at 21 months of age using a Cattell Infant Intelligence Scale revealed a mental age of 14·4 months with a CQ of 69. On a Vineland Social Maturity Scale she had an SQ of 66.

Dermatoglyphics

Dermatoglyphic analysis of the fingers revealed the following pattern. Left: I ulnar loop, II whorl, III whorl, IV whorl, V ulnar loop; right: I whorl, II whorl, III ulnar loop, IV whorl, V ulnar loop. The *atd* angle was distal on both palms, and a radial loop was noted in the hypothenar area of the right palm. The flexion creases of the palms and fingers were normal.

Sex Chromatin Studies

An examination of a buccal smear from the patient indicated that 19% of the cells had a single Barr body, which is within the normal range for females for this laboratory.

Chromosome Studies

Chromosomal analyses were performed on leucocytes cultured from peripheral blood and on cultured skin fibroblasts. A detailed analysis of the Q-bands was carried out using quinacrine mustard staining.

The patient's leucocytes had a modal number of 46 chromosomes including two X chromosomes (Table I). In the majority of cells, one of the C-group (6–12 + X) chromosomes was found to have a ring configuration. With the exception of the ring, the rest of the karyotype appeared normal.

In most of the cells the abnormal chromosome appeared to be a single monocentric ring. In a small number (12%) of the cells the ring differed from this form in either number, size, morphology or a combination of these. As is shown in Fig. 2, these atypical cells included those with a single large dicentric ring, those with two 'typical' rings, those with both a large and a small ring and, finally, those with small interlocking rings.

Leucocyte cultures of the parents and sibs of the patient revealed normal karyotypes.

In a chromosomal analysis of 98 fibroblasts from the patient, 72 lacked one or more chromosomes, including 56 which lacked the ring. Also the ring varied more morphologically in the fibroblast culture than in the leucocyte culture (see Table I).

TABLE I

CHROMOSOMAL COUNTS

	≤44	≤44,r	≤44,rr	45	45,r	45,rr	46	46,r	47	47,r	47,rr	Tetraploid	Tetraploid, r	Tetraploid, rr	Total
Leucocytes	1	14	1	1	7	0	0	38	0	0	1	1	1	1	66
Fibroblasts*	25	9	0	29	5	2	2	21	1	2	1	0	1	0	98

r = one ring, rr = two rings.
* Cells were taken from a second subculture. Total 'culture age' was 28 days.

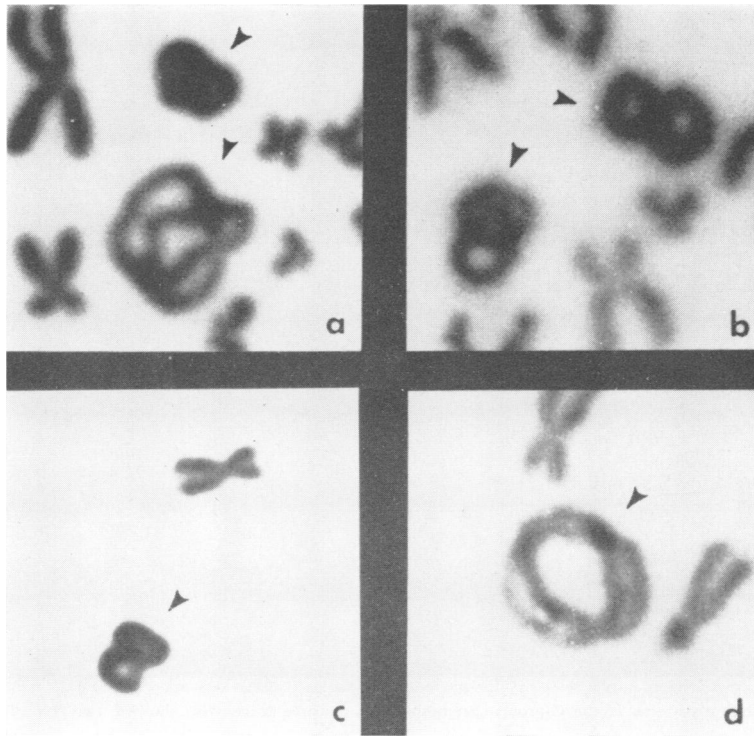

FIG. 2. Portions of four leucocytes, indicating the variations in size and number of the ring.

A detailed analysis of the banding patterns of the chromosomes of six of the patient's leucocytes showed that all of the chromosomes had normal Q-bands and could be paired with the exception of the No. 6 chromosomes. The single No. 6 chromosome also had normal Q-bands, and the pattern of the ring chromosome was virtually the same as that of the No. 6. It was concluded that the ring chromosome in this patient was derived from a No. 6 chromosome (Fig. 3).

Measurement of the ring and the banding pattern both indicated that only a small proportion of the total chromosome was lost in the formation of the ring. Since both the parents and sibs lack this chromosome, it is assumed that the ring was formed in one of the parent's germ cells or in the zygote.

Discussion

The patient presented here has comparatively mild physical and mental abnormalities when compared with the other patients with ring C autosomes. This is probably due in part to the very small amount of genetic material lost when the ring was formed. Another factor affecting the phenotypic manifestations of this chromosomal abnormality may be the ability of the ring to maintain a stable structure in the many tissues of the body. The relatively constant structure of the ring in the leucocytes may reflect stability in other tissues. The ring appeared less stable in the fibroblast culture, but the large amount of random chromosomal loss in the culture may indicate that the apparent instability was to some degree artefactual.

In comparing the phenotypes of the 11 patients reported in the literature with C-group ring chromosomes, excluding the X, few common phenotypic characteristics were noted. The only findings in common are microcephaly and physical and mental retardation. Even the degree of these characteristics varies widely among the patients. This is not unexpected, since the rings could be formed from different members of the C group and, even if formed from the same chromosome, could lack different amounts of genetic material, depending upon the position of the break points. The stability

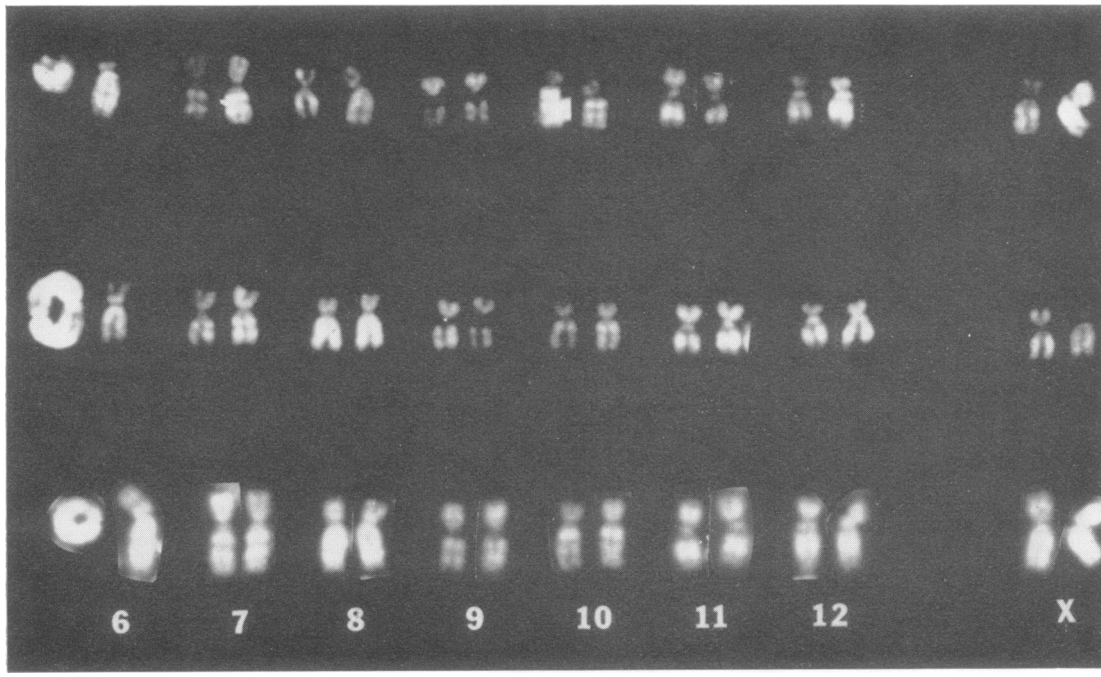

FIG. 3. Fluorescent banding patterns of the C-group chromosomes from three leucocytes, showing two 'typical' rings and one large dicentric ring.

of the different rings may also vary, resulting in a variation in phenotypic effect, especially if the rings are unstable during embryogenesis.

With the introduction of the new banding techniques, it should now be possible to compare patients having rings not only formed from the same chromosome but also having similar break points. In this manner, a number of well-defined syndromes associated with specific ring chromosomes may emerge. This is particularly true if, as has been suggested (Gripenberg, 1967), certain areas of the chromosomes are more prone to breakage than other areas. Similar studies of this type should yield information regarding these possibilities.

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Familial Occurrence of Ivemark Syndrome with Splenic Hypoplasia and Asplenia in Sibs*

Summary. Two sibs with Ivemark syndrome are described. This is the fourth observation of familial Ivemark syndrome, while over 200 cases reported in the literature have been sporadic.

One of the affected sibs reported here had total absence of the spleen, while a hypoplastic spleen was found in the other sib. The occurrence of splenic aplasia and splenic hypoplasia in the same family would be in support of the unitary concept of Ivemark syndrome. Contrary to previous concepts, Ivemark syndrome with splenic hypoplasia and Ivemark syndrome with splenic aplasia represent variants of one and the same disease entity.

The Ivemark syndrome, named after a contemporary Swedish pediatrician, has been known for more than a century. It consists of agenesis of the spleen or—according to some investigators—of dextroposed or hypoplastic or lobulated spleen, or multiple spleens, and various cardiovascular anomalies such as common atrioventricular canal, common ventricle, isomerism of atria with absent or rudimentary atrial septum, dextrocardia, transposition of the great vessels, stenosis or atresia of pulmonary artery or common truncus arteriosus, bilateral superior vena cava, bilateral persistence of the proximal portions of the vitelline veins (right inferior vena cava, left hepatic vein), and anomalous venous return. It is associated frequently with trilobulated left lung, isomerism of liver with median position of gallbladder, malrotation of the gut, and Howell-Jolly and Heinz bodies in the erythrocytes. Life expectancy is reduced: 10% of cases are stillborn or die within the first 24 hours, 80% die in the first year of life, and very few reach school age. Death is due to cardiovascular malformation and, less frequently, to overwhelming bacterial infections.

Over 200 cases have been reported, yet aetiology and pathogenesis are still unknown. A teratogen exerting its effect between the 31st and 38th day of gestation has been considered, yet its nature has not been elucidated. While previous observations suggested that males are more often affected than females, larger experience showed that both sexes are affected with equal frequency. Cytogenetic and genetic aetiologies have been discussed, yet chromosome studies have yielded normal results and familial occurrence of the syndrome is rare, with most cases being sporadic.

It is the purpose of this presentation to report two sibs with Ivemark syndrome and to discuss their significance for a better understanding of the syndrome.

Case Reports

Case 1. This 3225 g female infant was the product of a normal full-term pregnancy during which the mother had no infections, bleeding, or medications. This was the second pregnancy of a 24-year-old mother whose first child is a normal 4-year-old male. There is no family history of congenital heart disease or other known abnormalities. There is no consanguinity and both parents possess normal karyotypes. The maternal serology was negative for rubella, toxoplasmosis, cystomegalic inclusion disease, and syphilis.

On examination after birth, the infant appeared normal and healthy; Apgar scores at both one and five minutes were 10. The baby's colour was good for two days. On the third day, she became cyanotic when crying, and a heart murmur was noted. She was admitted to the Iowa University Hospitals. Cardiac catheterization revealed dextrocardia, transposition of the great vessels, probable single ventricle, subpulmonic stenosis, and a patent ductus arteriosus. A Waterston's shunt was performed, but the child expired (aged 17 days) on the fifth postoperative day from anoxia.

The necropsy examination confirmed the above cardiovascular anomalies, and revealed in addition a total anomalous pulmonary venous return to the left superior vena cava, trilobulated left lung, malrotation of gut, and hypoplastic spleen.

Case 2. This male sib was born a year after case 1. He was the product of a 7-month pregnancy. The mother was well during the first 3 months, then followed

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