sulted in 2 normal living children. The 3rd pregnancy resulted in a spontaneous abortion. Her last pregnancy at the age of 29 years resulted in a child with Down's syndrome. The child had 47 chromosomes with trisomy 21. The patient also has 47 chromosomes with a triple X karyotype. About 20% of her buccal cells contain 2 chromatin bodies. The patient's husband is physically and mentally normal. He has 46 chromosomes with a normal XY karyotype.

Discussion

Triple X females have shown a marked phenotypic variability. It is this variability of the physical findings that has made screening for these females difficult without examining their buccal cells for 2 chromatin bodies or doing a chromosome evaluation. The present triple X female was drawn to our attention after she gave birth to a child with Down's syndrome. There was nothing about this woman's physical appearance that would have indicated that she possessed an extra X chromosome.

While many of the reported patients with the triple X syndrome have had reduced intelligence, this finding is probably due to a biased selection of patients (Day *et al*, 1964). Many of the initial reports about these females came from institutions for the mentally retarded where mass screening was performed. Our patient is one of the few observed with normal intelligence; however, it is suspected that there are many more like her in the general population. Incidence at birth of this trisomic state is between 1·4 and 1·8 per 1000 live births (Maclean, Harnden, and Court Brown, 1961). Such a high frequency of this trisomic condition would indicate that there are many more triple X females in the general population than can be accounted for in institutions for the mentally retarded.

To our knowledge this is the first example of a triple X female giving birth to a child with a chromosomal abnormality. While a number of triple X females have given birth, the offspring have been chromosomally normal. It is not possible to determine if this triple X mother was at an increased risk of giving birth to a child with Down's syndrome. Examples of 2 chromosomal abnormalities in the same individual are well documented (Smith, 1970). There is, however, a lack of information about females with chromosomal abnormalities being at risk to produce an entirely different chromosome abnormality since most of these individuals are physically or mentally handicapped or fail to procreate.

It would be of interest to speculate that there is a causal relationship in the fact that this triple X mother produced a trisomy 21 child. By now many mothers of patients with Down's syndrome have had chromosomal studies done and this is the first instance where a triple X mother has been identified. If there is a cause and effect relationship between this triple X mother and the trisomic 21 offspring, it is difficult to propose a mechanism at this time. Whether or not this was a chance occurrence will be determined as more children of triple X females are examined.

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It is with great regret that I have to report the death of Professor Hsia on 27 January 1972—Ed.

A Human Ring C Chromosome Associated with Multiple Congenital Abnormalities

Studies over the past several years have demonstrated a number of different chromosome abnormalities in patients with retardation and congenital defects. One of the less common structural abnormalities is a ring chromosome, and we have found only 5 instances of a ring C chromosome recorded in the literature. We have recently evaluated another patient with this chromosome abnormality and report the cytogenetic and phenotypic changes in this patient.

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Case Report

The proposita (Fig. 1), a 3-month-old girl, was born at term to a 25-year-old woman who previously had a normal boy and girl (5 and 9 years old, respectively) and one stillborn child who appeared to be grossly normal. The mother had only a non-specific virus infection during the first 3 months of the present pregnancy. The father, aged 37, is an alcoholic. The parents have no history of unusual radiation exposure and there is no parental consanguinity.

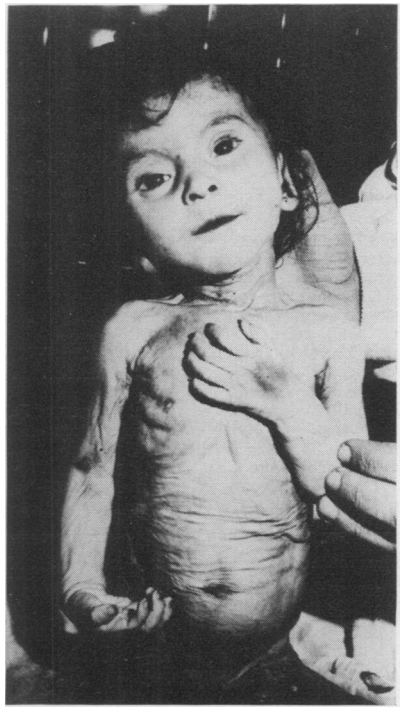

FIG. 1. The proposita.

The birth weight was 3100 g. At birth the proposita failed to breathe spontaneously and was resuscitated only after 15 minutes of treatment. Bilateral epicanthal folds, small head circumference (34 cm), bird-like facies, big ears, long and thin fingers, adduction of 5th toe, and a prominent heel were present. Ocular fundi were normal. She had angiomata plana in the frontonasal region and over her back; a 'cafe au lait' spot was present in the external region of the left leg.

Death at 4 months of age was attributed to renal failure and terminal bronchopneumonia.

Necropsy

Bronchopneumonia and extensive congestion were seen in the lungs, there was atrophy of the thymus, microcephaly; fatty degeneration of the adrenal-cortex, and nephrosis. The brain was small but did not show any gross or histological lesion. No internal malformations were found.

Electrophoresis of serum proteins showed increased α globulins and γM globulins.

The blood groups of the proposita were:

$$O, Rh, \frac{cDE}{c-e}, K-, FyA+, M+.$$

Haptoglobin electrophoresis showed 2–2 pattern.

The mother's blood groups are O and Rh $\frac{cDE}{c-e}$.

Dermatoglyphs

Palmar prints show a t' triradius bilaterally. Ulnar loops were found on all digits except the second digit of the right hand which had a whorl. Hallucal areas show whorls bilaterally.

Cytogenetic Studies

During life, chromosomes were studied on 3 different occasions from peripheral blood culture by the microtechnique of Arakaki and Sparkes (1963). A total of 120 mitoses were examined and all cells with 46 chromosomes showed a ring chromosome which was variable in shape and size (Fig. 2).

In 3 metaphases with 45 chromosomes the ring was missing. Based on its size and because a chromosome was missing from the C group, the ring chromosome was thought to be a large member of the C group. Autoradiographic studies were performed with tritiated thymidine in an attempt to identify better the ring chromosome. For analysis, 10 cells with 46 chromosomes were selected; the ring chromosome could be easily identified, and it had a relatively early labelling pattern. Autoradiography also showed a late replicating X chromosome (Fig. 3).

A bone-marrow sample was obtained 12 hours after death and we were able to select 15 good metaphases, all with the ring chromosome. Buccal smears were positive for sex chromatin.

The chromosomes of the mother were normal. No other members of the family would permit study.

Discussion

A female infant with multiple congenital anomalies was found to have a ring C chromosome in peripheral blood lymphocytes and bone marrow cells. Her clinical phenotype was not suggestive of a specific known chromosome abnormality, but the occurrence of a number of congenital defects raised the question of a chromosome change.

The finding of a ring chromosome in the C group in both lymphocytes and bone marrow cells suggests that the chromosome change was widespread in the body and probably came from one of the parental gametes. The routine karyotype indicated that there was a chromosome missing from the C group

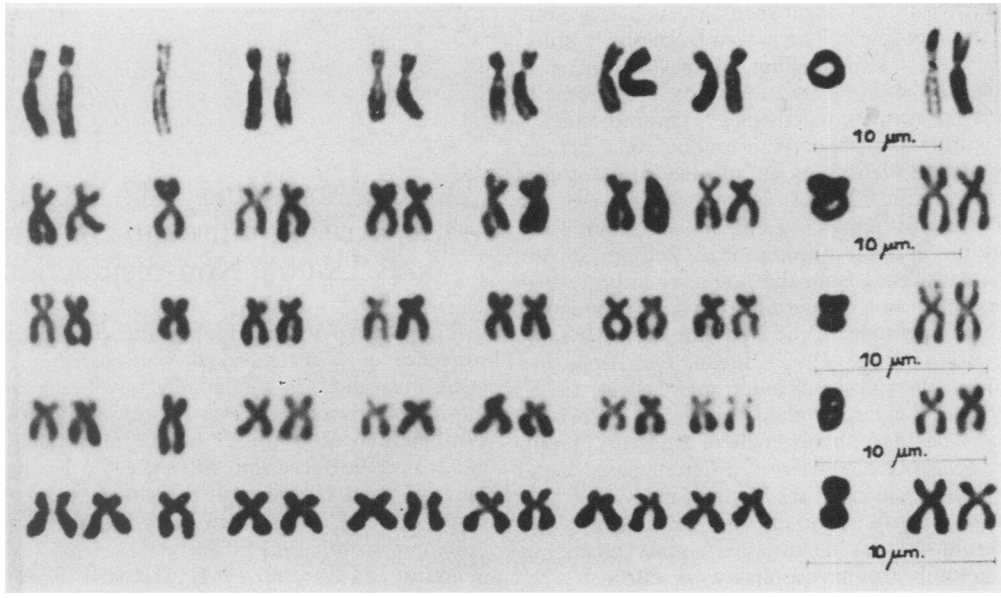

FIG. 2. A C group chromosome and the ring chromosome from each of 5 karyotypes of the proposita.

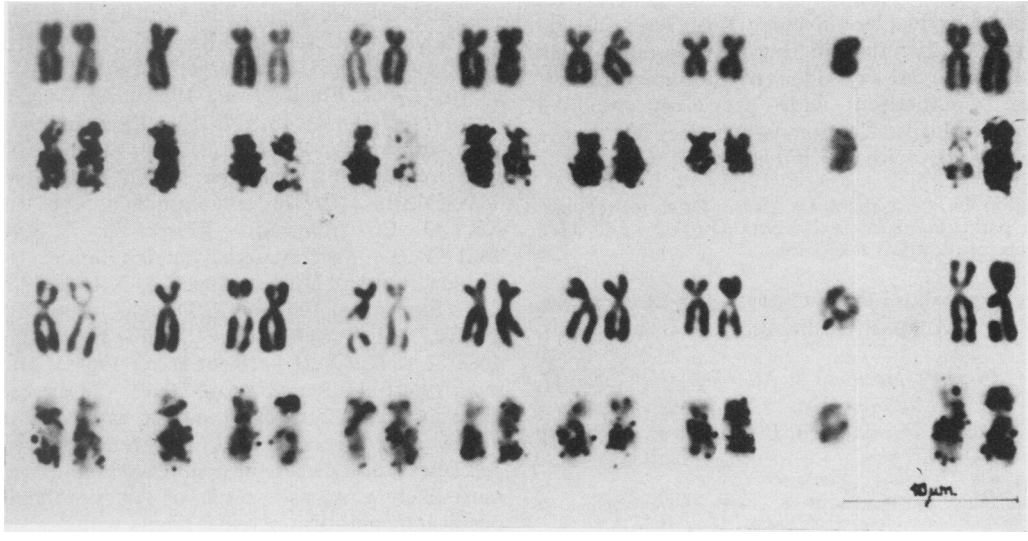

FIG. 3. Autoradiography of group C chromosome of 2 cells of the proposita.

and that the ring chromosome was most likely formed from it. Examination of the C group chromosomes suggested that the ring could have been formed from a larger member, such as a number 7 chromosome. The autoradiographic results, which show a late-labelling, normal appearing X chromosome, indicate that the ring chromosome is not derived from the inactivated X chromosome.

Sometimes the phenotypic findings in a patient are helpful in identifying an affected chromosome. The nonspecific findings in our patient are not helpful in this regard. Comparison of both the phenotypic and the chromosomal findings in our patient with those from the literature indicate that microcephaly and mental and physical retardation is a common pattern in these patients (Turner *et al*, 1962; Atkins *et al*, 1966; Bueno, Del Amo, and Hermida, 1969; Gacs, Schuler, and Sellyei, 1970). The lack of a common phenotype is not surprising and could be due to involvement of different C group chromosomes or alteration of different parts of the same chromosome in the formation of the ring structure. Further, the effect of instability of the ring chromosome as in our patient, is not known, but could possibly also have a phenotypic effect.

Summary

A 3-month-old mentally and physically retarded girl with multiple congenital defects was found to have a ring C chromosome in lymphocytes and bone marrow cells. Autoradiography of lymphocytes suggests a normal late-labelling X is present but do not further identify the ring chromosome which appears to be one of the longer autosomes of the C group. Comparison with previously reported patients with ring C chromosomes does not show a close similarity with any of these.

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Double Aneuploidy (47,XX,21+/45,X) Arising Through Simultaneous Double Non-disjunction

The occurrence of double aneuploidy, ie, the existence of 2 chromosomal abnormalities in the same individual, is a relatively rare phenomenon. Double autosomal trisomy has been reported in combinations of groups D and G (Gustavson *et al*, 1962; Becker, Burke, and Albert, 1963; Koch, Santamouris, and Ulbrich, 1967; Zellweger and Abbo, 1967; Porter, Petersen, and Brown, 1969); E and G (Gagnon *et al*, 1961; Hsu *et al*, 1965; Marks, Wiggins, and Spector, 1967); D and E (Schmidt *et al*, 1967; Garson *et al*, 1969); 17 and 18 (Korányi and László, 1969); and tetrasomy D (Dhadial, 1970). In addition, structural rearrangements of the autosomes coexisting with autosomal trisomy have been noted (Petit *et al*, 1968; Šubrt and Prchlikova, 1969; Miller *et al*, 1970). Mixed sex-chromosomal and autosomal double aneuploidy has been of the types 48,XXX,18+ (Uchida and Bowman, 1961; Uchida *et al*, 1962; Ricci and Borgatti, 1963; Haas and Lewis, 1966; Engel *et al*, 1967); 48,XXX,21+ (Day *et al*, 1963); 48,XXY,13+ (Pergament and Kadotani, 1965); 48,XXY,21+ (Ford *et al*, 1959; Hustinx *et al*, 1961/62; Punnet and DiGeorge, 1967); 48,XXY,18+ (Cohen and Bumbalo, 1967); 46,XXY,D−D−,t(Dq,Dq)+ (Tiepolo *et al*, 1967); 48,XYY,21+ (Verresen and van den Berghe, 1965; Uchida, Ray, and Duncan, 1966); 46,X,13+/47,XX,13+ (France *et al*, 1967); 44,X,D−D−,t(Dq,Dq)+/45,XX,D−D−,t(Dq,Dq)+ (Stahl *et al*, 1966); and 46,X,21+/47,XX,21+ (Root *et al*, 1964; Candela *et al*, 1966; Duillo and Serra, 1969). In almost all these instances, both chromosomal anomalies were observed in the same cell. The following report describes a unique case of double aneuploidy which most likely arose as a result of two simultaneous postzygotic non-disjunctional events within a single cell leading to two leucocyte stem lines: 47,XX,21+ and 45,X.

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