Evidence of Selection in Mosaicism

IAN H. PORTER, CHARLES D. BROWN, LORAINA A. GERGOSIAN, and
BETTY A. PAUL

From Birth Defects Institute, New York State Department of Health, and Department of Pediatrics, Albany Medical College, Albany, New York, U.S.A.

The chromosomes of normal somatic cells appear to be remarkably stable. But whether this stability is the result of a high rate of elimination or of a low rate of production of cells with abnormal chromosomes is not known. If the former were the case it would imply a proliferative differential between cells with normal and abnormal chromosomes. Ford (1964) suggested that evidence for such proliferative differential should be looked for in patients with chromosome mosaicism. This could be done by comparing the ratios observed in cultures of blood and other tissues taken from the same patient at different ages to see if the proportion of cells with a given karyotype increased in relation to the other components of the mosaic.

The following is a report of a boy with a complicated mosaic pattern, whom we followed from birth to death with repeated chromosome studies, and in whom we believe there was evidence of selection of one stem-line in favour of others.

Case Report

The patient was born on December 12, 1965, the fifth child of 27-year-old unrelated Caucasian parents who were both in good health. The pregnancy was uncomplicated. The mother had had no miscarriages, no viral illness around the time of conception or during pregnancy, and had not received any x-irradiation. There was no family history of congenital abnormalities, mental retardation, leukaemia, auto-immune diseases, or diabetes.

The patient was the product of a full-term normal delivery and his birthweight was 2012 g. (4 lb. 7 oz.).

On December 21, he was transferred to the Albany Medical Center Hospital for repair of cleft lip and palate. He had prominent occiput, a cleft lip, and an incomplete cleft palate, dysplastic ears, micrognathia, and a coloboma of the left iris. He was hypertonic. There were 6 fingers on the left hand, and the second and fifth fingers overlapped the third and fourth fingers of both hands. He had 'rockerbottom' feet. Examination of the cardiovascular system showed right ventricular hyper-

trophy and a loud pansystolic murmur heard maximally in the fourth left intercostal space. There was, in addition, umbilical and bilateral inguinal hernias, and bilateral cryptorchidism (Fig. 1).

He had normal Hb A and F, and the level of foetal Hb was 72%. The galactose-1-uridyl phosphate transferase activity was 0.8 corrected for a haematocrit of 32, and the leucocyte alkaline phosphatase index was 373 (normal range: 2-76, with a mean of 22). An electrocardiogram and chest x-ray showed right ventricular hypertrophy. The blood groups were consistent with those of the parents. The child died suddenly at home at the age of 10 months. Permission for necropsy was not granted.

Cytogenetics. Chromosomal analyses were made from preparations obtained from cultures of peripheral blood lymphocytes and of fibroblasts obtained from skin biopsy.

Chromosomes were examined from peripheral blood cultures on four occasions (Table I). (1) At 2 weeks of

TABLE I
CHROMOSOME COUNTS IN
LYMPHOCYTES

Age	Counts				Total
	< 45	45	46	47	
2 wk.	1	6	82	4	93
3 mth.		1	106		107
6 mth.	2	11	156		169
8 mth.	1	1	147		149

age, 93 cells were analysed from the first peripheral blood culture of the patient, and 4 stem-lines were present (Table II; Fig. 2 and 3); (2) at 3 months of age 107 cells were examined and 3 stem-lines were present (Table II); (3) at 6 months of age 169 cells were examined and 2 stem-lines were present (Table II); (4) at 8 months of age 149 cells were examined and only 1 stem-line was present (Table II). In addition, 1 cell had 44 chromosomes with 2 chromosomes missing from Group D. These were taken to be artefacts produced during preparation.

Chromosome analysis of fibroblasts from skin biopsies taken at the age of 2 weeks and at 3 months showed

Received October 14, 1968.

FIG. 1. Note the cleft lip before operation, low-set and pointed ears, prominent occiput, micrognathia, the 6 fingers on the left hand, flexion of the fingers, and index fingers overlying the third ones. Note also the hernias, rockerbottom feet, and hammer toe.

TABLE II
PERCENTAGE OF CELLS WITH DIFFERENT CHROMOSOME COMPLEMENTS

Age	45,XY,D-,G-,t(DqGq)+	46,XY	46,XY,D-,t(DqGq)+	46,XY,D-E+,G-,t(DqGq)+	47,XY,D-,E+,t(DqGq)+
2 wk.	7		58	30	4
3 mth.	22	4	92		
6 mth.	8		92		
8 mth.			98		

that all the cells had a 46,XY,D-,t(DqGq)+ chromosome complement (Table III).

The chromosome studies of the peripheral blood leucocytes of the parents and 4 brothers did not show any numerical or structural abnormalities, nor did the chromosome studies of fibroblasts from a skin biopsy taken from the mother.

Discussion

Even though structural abnormalities may predispose to abnormal segregation of chromosomes, this case represents a most unusual combination of structural and numerical chromosomal abnormalities. The most interesting, and we believe the

FIG. 2. The relevant portions of the karyotypes from cells with: I: 45,XY,D-,G-,t(DqGq) chromosome constitution; II: 46,XY,D-,t(DqGq)+ chromosome constitution; III: 46,XY,D-,E+,G-,t(DqGq)+ chromosome constitution; IV: 47XY,D-,E+,t(DqGq)+ chromosome constitution.

TABLE III
CHROMOSOME COUNTS IN
FIBROBLASTS

Age	Counts				Total
	< 45	45	46	47	
2 wk.		1	13		14
3 mth.	4	1	35		40

most important, finding is that which appears to be an example of a proliferative differential between various stem-lines.

Selection of stem-lines may take place *in vitro* or *in vivo*. Patau refers to a case of D₁ isochromosome mosaicism, in which the mosaicism was initially demonstrable in tissue culture from skin, but after three months cells from the same culture were normal (Patau, 1964): this suggests selection *in vitro*.

I. A. Uchida (1966, personal communication) examined a patient with D₁ trisomy mosaicism, in whom repeated bone-marrow studies showed that the normal stem-line was being favoured: this suggests selection *in vivo*.

LaMarche, Heisler, and Kronemer (1966) presented a girl with the typical signs of trisomy-18 syndrome. Chromosome studies showed that she was a mosaic; 90% of the cells were trisomic for chromosome No. 18, and 10% of the cells had a normal chromosome complement. As she fared better than expected, she was reinvestigated at the age of 10 months and no chromosomal abnormalities

were found in cells from the peripheral blood, bone-marrow, or skin fibroblasts. This again suggests a proliferative advantage of one stem-line *in vivo*.

Hecht *et al.* (1966) reported a boy with cells which contained predominantly XX sex chromosomes and no Y. However, on careful examination a small proportion (3/270) of XXY cells were found in cultures of blood and testes. They suggest that selection may have worked against the clone of cells with the XXY sex chromosome constitution.

Selection favouring one stem-line at the expense of another may explain why some patients with the cardinal signs of a particular syndrome usually associated with a specific chromosomal anomaly have normal karyotypes (Burks and Sinkford, 1964; S. Armendarces, S. Frenk, and J. Sanchez, 1966, personal communication).

We do not know how often differential survival rate of cells with chromosomes occurs, because chromosome studies usually are not repeated once a diagnosis has been made. It would, therefore, be informative if infants with mosaic chromosome patterns had repeated chromosome studies.

Summary

A boy with multiple congenital malformations and a four stem-line chromosomal mosaic is presented, in whom *in vivo* differential proliferation of one stem-line appears to have occurred.

It is suggested that: (1) patients in whom the karyotype does not match the phenotype may in

FIG. 3. Autoradiography of a karyotype with a 46,XY,D-,t(DqGq)+ chromosome constitution shows the labelling characteristics of the translocation chromosome.

some instances be mosaics in whom differential survival of one stem-line has proliferated at the expense of another stem-line after the latter has determined the course of embryonic development and hence the phenotype of the patient; and (2) infants with mosaic chromosome patterns should be followed with repeated chromosome studies.

REFERENCES

- Burks, J. L., and Sinkford, S. (1964). Clinical trisomy E syndrome (16-18): A cytogenetic enigma. *Clin. Pediat. (Phila.)*, **3**, 233.
- Ford, C. E. (1964). Selection pressure in mammalian cell populations. In *Cytogenetics in Cells in Culture*, pp. 27-45. Ed. by R. J. C. Harris. Academic Press, New York.
- Hecht, F., Antonius, J. I., McGuire, P., and Hale, C. G. (1966). XXY cells in a predominantly XX human male: Evidence for cell selection. *Pediatrics*, **38**, 982.
- LaMarche, P. H., Heisler, A. B., and Kronemer, N. (1966). Disappearing mosaicism. In *Fifth Conference of Mammalian Cytology and Somatic Cell Genetics*, November, 1966.
- Patau, K. (1964). *Somatic Cell Genetics, Fourth Macy Conference on Genetics*, p. 78. Ed. by R. S. Krooth. The University of Michigan Press, Ann Arbor.