- Kiossoglou, K. A., Mitus, W. J., and Dameshek, W. (1965). Chromosomal aberrations in acute leukemia. *Blood. The Journal of Hematology*, **26**, 610-641.
- Loiodice, G., Rovetta, D. G., Bellicini, G., Callura, G., and Bergamo, F. (1970). Malformazioni multiple congenite in un bambino portatore di una anomalia cromosomica del gruppo F(46/XY,20 - p), figlio di un soggetto, clinicamente sano, affetto da analoga malformazione cromosomica. *Minerva Pediatrica*, **22**, 1084-1088.
- Lucas, M., Kemp, N. H., Ellis, J. R., and Marshall, R. (1963/1964). A small autosomal ring chromosome in a female infant with congenital malformations. *Annals of Human Genetics*, **27**, 189-195.
- Millard, R. E., Lawler, S. D., Kay, H. E. M., and Cameron, C. B. (1968). Further observations on patients with a chromosomal abnormality associated with polycythaemia vera. *British Journal of Haematology*, **14**, 363-374.
- Reeves, B. R., Lobb, D. S., and Lawler, S. D. (1972). Identity of the abnormal F-group chromosome associated with polycythaemia vera. *Humangenetik*, **14**, 159-161.
- Sparkes, R. S., Carrel, R. E., and Wright, S. W. (1968). Partial F trisomy and parental chromosomes. *Lancet*, **2**, 404-405.
- Steele, M. W., Breg, W. R., Eidelman, A. I., Lion, D. T., and Terzakis, T. A. (1966). A B-group ring chromosome with mosaicism in a newborn with Cri du Chat syndrome. *Cytogenetics*, **5**, 419-429.

Bone Marrow Chromosomes in Fanconi's Anaemia

Patients with the autosomal recessive syndrome, Fanconi's anaemia (FA), exhibit a high frequency of chromosome breakage and rearrangement in their cultured lymphocytes and skin fibroblasts (Swift and Hirschhorn, 1966). However, there is little published data on the aberration frequency in direct bone marrow preparations: in a recent review, bone marrow from 3 FA patients were reported to show no chromosome breaks while in 4 other cases 10% aberrant metaphases were found (Schroeder and Kurth, 1971). Bone marrow chromosome preparations differ significantly from those of lymphocytes in that the relatively short incubation time of marrow cells *in vitro* (approximately 2 hours) includes only a small fraction of a single cell cycle. Therefore findings in the marrow cells are important

because it is likely that these cells synthesized their DNA within the living patient. In contrast lymphocytes undergo one to two entire cell cycles *in vitro* (48-72 hr) before chromosome analysis.

Case Report

We have studied a patient with Fanconi's anaemia whose clinical course has been described previously (Pochedly *et al*, 1971).

The propositus, an 8-year-old Negro male, was of subnormal size and weight for his age with a normocytic, normochromic anaemia and pancytopenia. Skeletal anomalies included small head circumference, Sprengel's deformity, Klippel-Feil anomaly, and short thumbs with flat thenar eminences. There was renal ectopia with both kidneys on the right side. Unusual features included growth hormone deficiencies and a marked elevation of haemoglobin F.

Chromosome Studies

Chromosome studies were done on direct bone marrow preparations following incubation of 1½ hr with vincalucoblastine, on peripheral blood lymphocytes incubated with phytohaemagglutinin for 72 hr *in vitro*, and on skin fibroblasts cultivated *in vitro* for 7 weeks. The percentage of dividing cells (Table I) containing significant structural damage comprised 10% of the bone marrow cells, 26% of the fibroblasts, and 60% of the lymphocytes. There were, therefore, striking differences between populations of cells derived from a single individual.

Gaps, which were not recorded in the table of aberrations, were found in 4 marrow metaphases, 11 lymphocytes, and 7 of the cultured fibroblasts. Both gaps and breaks, chromatid and chromosomal, appeared to be distributed randomly within the chromosome groups with the exception that group A may have had slightly more than its share of breaks. No predilection for specific chromosomes or loci within chromosomes, such as points of secondary constriction, was apparent.

In this laboratory we have not obtained a series of marrow preparations from normal controls. Of 300 bone marrow cells from 15 patients, mainly suffering from leukaemia, 17 had chromatid or

Received 8 May 1972.

TABLE I
CHROMOSOME ANALYSIS

	Number of Cells		Number of Aberrations		
	Examined	With One or More Major Aberrations	Chromatid Breaks	Isochromatid Breaks	Rearrangements (rings, dicentric triradials, etc)
Bone marrow	50	5	4	1	—
Lymphocytes	50	30	16	24	9
Skin fibroblasts	100	26	13	15	—

isochromatid breaks. Thus, the proportion of marrow cells with breaks in our FA patient (10%) was greater than the average (5%) found in individuals many of whom had diseases known to predispose to chromosome aberrations (Sandberg, 1966). A recent study of bone marrow chromosomes in a male control population found incidences of 3.19% and 0.55% for chromatid and chromosome aberrations respectively and a slightly greater than expected proportion of non-modal (hypodiploid) cells (O'Riordan, Berry, and Tough, 1970). The incidence of chromosome breakage in FA bone marrows may therefore be greater than in normals, but we have not been able to establish this conclusively.

Conclusion

The FA gene is of great interest because of its association with cancer and leukaemia in homozygotes and heterozygotes (Swift, 1971). If the bone marrow chromosomes are representative, it is unlikely that the inherited metabolic defect of Fanconi's anaemia is expressed *in vivo* primarily through frequent chromosome breaks and rearrangements. The nature of this genetic defect might be elucidated if we could learn what factors are responsible for the increase in chromosome aberrations in cell cultures *in vitro* from patients with Fanconi's anaemia.

Summary

The chromosomes of bone marrow cells from a patient with Fanconi's anaemia showed a lower aberration frequency than that of either lymphocyte or fibroblast cultures from the same patient. This difference between the aberration frequency *in vivo* and *in vitro* may provide a clue to the nature of the inherited metabolic defect underlying Fanconi's anaemia.

We thank Thea Cohen for technical assistance.

SANDRA R. WOLMAN and MICHAEL SWIFT

*Departments of Pathology and Medicine,
New York University Medical Center,
New York, USA*

REFERENCES

- O'Riordan, M. L., Berry, E. W., and Tough, I. M. (1970). Chromosome studies on bone marrow from a male control population. *British Journal of Haematology*, **19**, 83-90.
Pochedly, C., Collipp, P. J., Wolman, S. R., Suwansirikul, S., and Rezvani, I. (1971). Fanconi's anemia with growth hormone deficiency. *Journal of Pediatrics*, **79**, 93-96.
Sandberg, A. A. (1966). The chromosomes and causation of human cancer and leukemia. *Cancer Research*, **26**, 2064-2081.

- Schroeder, T. M. and Kurth, R. (1971). Spontaneous chromosomal breakage and high incidence of leukemia in inherited disease. *Blood*, **37**, 96-112.
Swift, M. (1971). Fanconi's anaemia in the genetics of neoplasia. *Nature*, **230**, 370-373.
Swift, M. R. and Hirschhorn, K. (1966). Fanconi's anemia. Inherited susceptibility to chromosome breakage in various tissues. *Annals of Internal Medicine*, **65**, 496-503.

Fanconi's Anaemia: Report of a Patient with Significant Chromosomal Abnormalities in Bone Marrow Cells

In Fanconi's anaemia, the presence of frequent chromosomal aberrations in cultured peripheral lymphocytes is now an established phenomenon. In fact, a number of authors (Bloom *et al*, 1966; Swift and Hirschhorn, 1966; Hirschman *et al*, 1969), suggest its demonstration as a valuable aid in establishing diagnosis in doubtful cases. On the other hand, very few instances of the above disease have been encountered in which similar changes were seen in bone marrow cells. The following communication describes one such patient.

Methods

Routine haematological investigations were carried out on blood and bone marrow aspirates according to standard methods.

Chromosome studies were performed on a peripheral leucocyte culture following the method of Moorhead *et al* (1960). One hundred consecutive metaphases were examined in detail. In addition, a bone marrow specimen obtained by sternal puncture was prepared for karyotyping using a slight modification of the technique of Tjio and Whang (1962). Ninety suitable spreads were photomicrographed and analysed.

Case Report

The patient, an 11-year-old male, was first seen at the paediatric service at the American University Hospital in September, 1966. His symptoms dated back to the age of 4 years, when he started having repeated attacks of easy bruising and bleeding from various sites (nose, urinary tract, rectum, and retina). Meanwhile he was noticed to develop progressive pallor which was not commensurate with the amount of blood loss. There was no history of exposure to drugs or bone marrow toxins.

The family history disclosed consanguinity in the

Received 11 April 1972.