Down's Syndrome and Acute Leukaemia: A Cytogenetic Study

J. G. BUCHANAN and D. M. O. BECROFT

From the Central Laboratory, Auckland Hospital, and Princess Mary Hospital for Children, Auckland, New Zealand

The incidence of acute leukaemia in children with Down's syndrome is substantially greater than it is in normal children (Stewart, Webb, and Hewitt, 1958; Holland, Doll, and Carter, 1962), and the leukaemia complicating Down's syndrome is more often of myeloblastic type than is the case in childhood leukaemia generally (Boggs, Wintrobe, and Cartwright, 1962; Warkany, Schubert, and Thompson, 1963; Conen and Erkman, 1966). These indications that there may be fundamental differences between the leukaemias arising in association with trisomy 21 and those found in normal children have not been reflected in differences in the acquired cytogenetic abnormalities reported to date (Conen and Erkman, 1966). However, the combination of the two diseases is still rare and chromosome studies on further cases are required to evaluate fully the pattern of karyotypic abnormalities which may be present.

This report describes studies performed on a 3-year-old girl with acute leukaemia complicating Down's syndrome.

Case Report

A female child, aged 3 years, was admitted to hospital with a history of upper respiratory tract infections for several weeks and a recurrent rash on the legs and trunk for one month. Her birthweight had been 3060 g. after a normal pregnancy and delivery. At the time of her birth her mother was 21 years old and her father 24 years old. The parents and two younger sibs were in good health; there was no family history of Down's syndrome nor of leukaemia.

On examination the patient showed features typical of Down's syndrome. In addition, there was moderate skin and conjunctival pallor and a purpuric rash on the trunk. The liver was palpable 4 cm. below the right costal margin; the spleen was not palpable. There was no enlargement of the superficial lymph nodes. The haemoglobin value was 6.5 g./100 ml. and the white blood cell count was 10,200/cu. mm., with 38% myeloblasts, 3% myelocytes, 25% neutrophils, 7% mature

basophils, and 27% lymphocytes. The platelet count was 23,000/cu. mm. A diagnosis of acute myeloblastic leukaemia was established by bone-marrow aspiration before treatment. Numerous myeloblasts and abnormal promyelocytes with basophilic granulation were present. The differential cell count showed 34% myeloblasts, 8% promyelocytes, 3% myelocytes, 3.5% metamyelocytes, 7.5% band forms, 4.5% segmented neutrophils, 2% basophils, 17% lymphocytes, 0.5% plasma cells, and 20% normoblasts.

The patient was transfused and given 6-mercaptopurine and prednisone, but remission of the leukaemia was not induced and she died four weeks later.

Chromosome Studies. Chromosome preparations were obtained from the bone-marrow aspirate by a modification of the method of Tjio and Whang (1962). Two aneuploid cell lines were present and only one cell with a normal chromosome number was counted (Table). The major line had 49 chromosomes (Fig.) with 6 small acrocentric chromosomes and 17 chromosomes in group C (49,XX,C+,G+,G+). The minor line had 47 chromosomes with one small acrocentric chromosome in addition to the female chromosome complement (47,XX,G+).

Discussion

The leukaemia in our patient was of myeloblastic cell type with basophilic granulation unusually prominent in the leukaemic cells. The cytogenetic studies revealed a minor cell line with 47 chromosomes interpreted as being non-leukaemic and showing constitutional trisomy 21, while the cells with 49 chromosomes presumably represent a clone of leukaemic cells. The additional chromosomes in the C and G groups have presumably arisen by non-disjunction during division of a precursor cell.

TABLE
CHROMOSOME COUNTS ON BONE-MARROW

Chromosome Counts	45	46	47	48	49	Polyploid	Total
No. of cells	—	1	11	—	41	3	56

Received 21 July 1969.

FIG. Karyotype of bone-marrow cell with 49 chromosomes.

The earlier cytogenetic studies of acute leukaemia in children with Down's syndrome did not reveal any chromosome abnormalities other than those known to be associated with the primary condition (Sandberg *et al.*, 1961; Tough *et al.*, 1961; Wald *et al.*, 1961; German, DeMayo, and Bearn, 1962; Thompson, Bell, and Little, 1963). Methods of preparation involving preliminary culture were used in most of these studies so that the leukaemic cells may not have been represented in the final metaphase preparations. More recent investigations using direct marrow methods suggest that acquired chromosome abnormalities are common in the acute leukaemia accompanying Down's syndrome (Ross and Atkins, 1962; Lejeune *et al.*, 1963; Mercer, Keller, and Lonsdale, 1963; Warkany *et al.*, 1963; Honda *et al.*, 1964; Kiosoglou *et al.*, 1964; Reisman, Mitani, and Zuelzer, 1964; Conen and Erkman, 1966). The abnormal cell lines shown have usually possessed 48 or 49 chromosomes with trisomy 21 and additional chromosomes most commonly of either group C or G, and occasionally of other groups. Similar varied and apparently non-specific abnormalities have been described in the

largely lymphoblastic acute leukaemias occurring in children without Down's syndrome, again with frequent occurrence in groups C and G. The C group is numerically large, but the frequent occurrence of abnormalities in this group is said to be more than would be expected if these arose at random (Sandberg, 1968).

The comparison of cytogenetic findings in leukaemias arising in children with or without Down's syndrome is at present limited by the variable incidence of the chromosome abnormalities reported in different series as well as by the rarity of the combination of leukaemia and Down's syndrome and consequent lack of studies in this group.

Summary

Cytogenetic studies on bone-marrow cells from a 3-year-old girl with acute myeloblastic leukaemia complicating Down's syndrome showed two cell lines. One cell line showed trisomy 21 only, while the other, assumed to represent a clone of leukaemic cells, had a consistent chromosome number of 49 and a karyotype 49,XX,C+G+G+.

REFERENCES

- Boggs, D. R., Wintrobe, M. M., and Cartwright, G. E. (1962). The acute leukemias. Analysis of 322 cases and review of the literature. *Medicine*, **41**, 163-225.
- Conen, P. E., and Erkman, B. (1966). Combined mongolism and leukemia. Report of eight cases with chromosome studies. *American Journal of Diseases of Children*, **112**, 429-443.
- German, J. L., DeMayo, A. P., and Bearn, A. G. (1962). Inheritance of an abnormal chromosome in Down's syndrome (mongolism) with leukemia. *American Journal of Human Genetics*, **14**, 31-43.
- Holland, W. W., Doll, R., and Carter, C. O. (1962). The mortality from leukaemia and other cancers among patients with Down's syndrome (mongols) and among their parents. *British Journal of Cancer*, **16**, 177-186.
- Honda, F., Punnett, H. H., Charney, E., Miller, G., and Thiede, H. A. (1964). Serial cytogenetic and hematologic studies on a mongol with trisomy-21 and acute congenital leukemia. *Journal of Pediatrics*, **65**, 880-887.
- Kiossoglou, K. A., Rosenbaum, E. H., Mitus, W. J., and Dameshek, W. (1964). Multiple chromosomal aberrations in a patient with acute granulocytic leukemia associated with Down's syndrome and twinning. Study of a family with a possible tendency to nondisjunction. *Blood*, **24**, 134-159.
- Lejeune, J., Berger, R., Haines, M., Lafourcade, J., Vialatte, J., Satge, P., and Turpin, R. (1963). Constitution d'un clone à 54 chromosomes au cours d'une leucoblastose congénitale chez une enfant mongolienne. *Comptes Rendus Hebdomadaires de Séances de l'Académie des Sciences*, **256**, 1195-1198.
- Mercer, R. D., Keller, M. K., and Lonsdale, D. (1963). An extra abnormal chromosome in a child with mongolism and acute myeloblastic leukemia. Report of a case. *Cleveland Clinic Quarterly*, **30**, 215-240.
- Reisman, L. E., Mitani, M., and Zuelzer, W. W. (1964). Chromosome studies in leukemia. I. Evidence for the origin of leukemic stem lines from aneuploid mutants. *New England Journal of Medicine*, **270**, 591-597.
- Ross, J. D., and Atkins, L. (1962). Chromosomal anomaly in a mongol with leukaemia. *Lancet*, **2**, 612-613.
- Sandberg, A. A. (1968). Chromosome abnormalities in human leukemia. *Geriatrics*, **23**, 124-136.
- , Ishihara, T., Miwa, T., and Hauschka, T. S. (1961). The *in vivo* chromosome constitution of marrow from 34 human leukemias and 60 nonleukemic controls. *Cancer Research*, **21**, 678-689.
- Stewart, A., Webb, J., and Hewitt, D. (1958). A survey of childhood malignancies. *British Medical Journal*, **1**, 1495-1508.
- Thompson, M. W., Bell, R. E., and Little, A. S. (1963). Familial 21-trisomic mongolism coexistent with leukemia. *Canadian Medical Association Journal*, **88**, 893-894.
- Tjio, J. H., and Whang, J. (1962). Chromosome preparations of bone marrow cells without prior *in vitro* or *in vivo* colchicine administration. *Stain Technology*, **37**, 17-20.
- Tough, I. M., Court Brown, W. M., Baikie, A. G., Buckton, K. E., Harnden, D. G., Jacobs, P. A., King, M. J., and McBride, J. A. (1961). Cytogenetic studies in chronic myeloid leukaemia and acute leukaemia associated with mongolism. *Lancet*, **1**, 411-417.
- Wald, N., Borges, W. H., Li, C. C., Turner, J. H., and Harnois, M. C. (1961). Leukaemia associated with mongolism. *ibid.*, **1**, 1228.
- Warkany, J., Schubert, W. K., and Thompson, J. N. (1963). Chromosome analyses in mongolism (Langdon-Down syndrome) associated with leukemia. *New England Journal of Medicine*, **268**, 1-4.