Familial 21-Trisomic Mongolism Coexistent with Leukemia

MARGARET W. THOMPSON, Ph.D.,* R. EDWARD BELL, M.D.†
and A. S. LITTLE, M.D.,‡ *Edmonton, Alta.*

LEUKEMIA is known to occur much more frequently in subjects with mongolism (Down's syndrome) than in the general population.[1, 2] Cytogenetic studies of leukemic mongols have shown that they may be either of the standard trisomy-21 type[3, 4] or of the translocation type.[5] No leukemic mongol previously reported has had familial mongolism, although the patient described by German, DeMayo and Bearn[5] carried a familial translocation.

We have recently encountered a family in which there are two 21-trisomic mongols, one of whom has acute leukemia.

GENETIC DATA

The index patient, the leukemic mongol, is a 28-year-old woman, the fifth-born of 16 children. A younger brother, now 17, is also a mongol. The mother was 26 at the time of the birth of the index patient and 37 at the birth of the affected sib. The parents, the 14 other sibs (eight males and six females, ranging in age from 36 to nine years) and the six nephews and 14 nieces are phenotypically normal. No consanguinity is present in either the paternal or the maternal grandparents, or in the parents. Neither parent had any x-irradiation whatsoever up to the time of the conception of the second mongol.

TABLE I.—CYTOGENETIC DATA

	Total No. of cells counted	*Chromosome counts*					*Photographic karyotypes*
		<45	*45*	*46*	*47*	*>47*	
Patient.....	51	—	—	—	51	—	47/XX (trisomy-21)
Mongol brother..	50	2	—	—	48	—	47/XY (trisomy-21)
Father.....	25	—	—	25	—	—	46/XY (normal)
Mother.....	25	1	—	24	—	—	46/XX (normal)
Normal sib.....	25	2	1	22	—	—	46/XX (normal)
Normal sib.....	25	2	—	23	—	—	46/XX (normal)
Normal sib.....	26	2	—	24	—	—	46/XX (normal)

Chromosome analyses by the Moorhead technique[6] have been performed for the index patient, her mongol brother, her parents, and three sisters. The results are summarized in Table I. Both mongols have modal chromosome numbers of 47 and karyotypes compatible with trisomy-21. All the other family members tested have apparently normal karyotypes. The karyotype of the index patient is shown in Fig. 1.

From the Departments of Pediatrics, Pathology and Medicine, University of Alberta Faculty of Medicine.

Supported by National Health Grants 608-7-33 and 608-13-12, and by a Special Services Grant of the University of Alberta Hospital.

*Assistant Professor of Human Genetics, Department of Pediatrics; Scientific Associate (Genetics), University of Alberta Hospital. Temporary address: Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, U.S.A.

†Associate Professor of Pathology; Director of Clinical Laboratories, University of Alberta Hospital.

‡Assistant Professor of Medicine; Director of Out-Patient Services, University of Alberta Hospital.

CLINICAL DATA

The index patient, a 28-year-old woman, was referred to us in March 1962 because of anemia. Her illness appears to have begun in January 1962 when she consulted her family physician because of profuse menstrual bleeding. Her hemoglobin is reported to have been 30%. She was treated with various "shotgun" hematinics. Her menstrual bleeding subsided but her anemia did not improve and she was referred for further investigation. The history was sparse because of the patient's mental status, but her parents knew of no exposure to drugs or chemicals prior to her illness.

Physical examination revealed a young woman with typical mongoloid features and dermal patterns, who occupied herself with crayons and cut-out dolls. She was pale but not dyspneic. There was no lymphadenopathy; the liver edge was palpable one fingerbreadth below the right costal margin; the spleen was palpable and moderately firm and extended four fingerbreadths below the left costal margin. There were no ecchymoses or purpura.

Peripheral blood studies revealed the following: the hemoglobin was 6.6 g. % and the white blood count was 2300 per c.mm. In the blood smears the erythrocytes were orthochromic and showed moderate anisocytosis, poikilocytosis and increased rouleaux. Rare normoblasts were present. The differential leukocyte count showed 62% neutrophils, 32% lymphocytes, and 6% monocytes. No primitive cells were seen. The platelets were greatly reduced. Bone marrow obtained by aspiration from the iliac crest showed a predominance of blast cells (68%) with only small numbers of erythroid precursors, granulocytes, and lymphocytes. The blast cells showed irregular nuclei with up to three nucleoli, a fine chromatin structure, and very sparse cytoplasm. A few cells in mitosis and moderate numbers of small, deeply stained blast cells were present. No Auer rods were found, but rare cells with heavy basophilic granulation were seen. No clear differentiation towards identifiable blood-cell lines could be made out. The findings were considered to be those of an acute leukemia.

In May 1962 the patient's blood picture became frankly leukemic with a leukocyte count of 26,000 of which 60% were blast cells, probably lymphoblasts, and 26% lymphocytes. The final diagnosis of acute lymphatic leukemia was made. Shortly thereafter the patient moved to another province and we have had no further contact with her or her family.

Canad. Med. Ass. J.
April 27, 1963, vol. 88

DISCUSSION

Although it is well known that mongols are particularly susceptible to leukemia, the significance of the association is not clear. No chromosomal abnormality has been observed in leukemic mongols other than the ones known to be associated with mongolism, namely, trisomy-21 or a translocation involving chromosome No. 21. The observation that the chromosome found to be abnormal in the majority of patients with chronic myeloid leukemia, Ph[1] (the "Philadelphia" chromosome), is probably a No. 21 has prompted speculation that this chromosome may carry a locus concerned with leukopoiesis or leukocyte function.[3, 5] This hypothesis alone does not adequately explain all the genetic data which have accumulated. For example, there have been reports of leukemia in the apparently normal relatives of mongols, or in association with other aneuploid conditions. Buckton *et al.*[7] have described a sibship in which there were three mongols and one leukemic subject; in their family and that of the leukemic mongol described by German, DeMayo and Bearn[5] there was a familial translocation. Johnston[4] has reported a leukemic mongol with two leukemic relatives. Baikie *et al.*[8] have noted the association of a sex chromosome abnormality and leukemia within a single sibship. Instances of coexistent leukemia and Klinefelter's syndrome are known.[9, 10] Doubly trisomic patients have been seen,[11, 12] as have sibships in which trisomy and sex chromosome abnormalities were present in different members.[13] One family has been reported in which leukemia, trisomy-21, and a sex chromosome abnormality had all occurred.[14] Late maternal age is a common finding in cases of mongolism, but Stewart and Hewitt[1] have found an excess of mothers aged 40 or over among the mothers of a series of leukemics from which mongols had been excluded. Thus it appears that the frequent coexistence of leukemia and mongolism may be part of a more general association between leukemia and chromosome abnormalities, and that a common genetic predisposition may exist, as suggested by Baikie *et al.*[8]

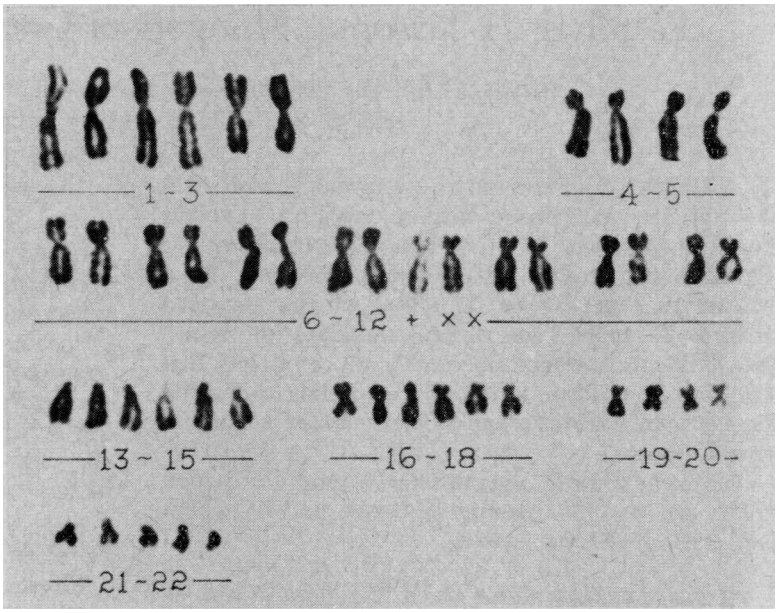

Fig. 1.—Karyotype of index patient, a female mongol with leukemia.

If this is so, the familial nature of our patient's mongolism may have special significance. The risk of occurrence of more than one mongol in a sibship is considered to depend mainly upon the presence of a familial translocation; however, it has been suggested that there is also some increased risk of recurrence when standard trisomy-21 is present, and that this increased risk may depend upon a genetic predisposition toward non-disjunction.[15-17] In view of the unusually large number of sibs of our index patient, the occurrence of a second mongol in the sibship may be fortuitous; but the relatively young age of the mother when the patient was born suggests that something more than the play of chance is involved. Additional data are required concerning both familial mongolism and the coexistence of leukemia and chromosomal aberrations.

SUMMARY

Chromosome studies have been carried out on a mongol woman with acute leukemia, her mongol brother, and five phenotypically normal relatives. The results show standard trisomy-21 karyotypes for the two mongols and normal karyotypes for the phenotypically normal members of the family. Although the significance of the association of familial mongolism and leukemia is not clear, it is possible that something more than chance is responsible for the appearance of leukemia in a patient whose mongolism, though of the standard trisomy-21 type, is familial.

REFERENCES

1. STEWART, A. M. AND HEWITT, D.: *Brit. Med. Bull.*, 15: 73, 1959.
2. WALD, N. *et al.*: *Lancet*, 1: 1228, 1961.
3. TOUGH, I. M. *et al.*: *Ibid.*, 1: 411, 1961.
4. JOHNSTON, A. W.: *New Engl. J. Med.*, 264: 591, 1961.
5. GERMAN, J. L., III, DEMAYO, A. P. AND BEARN, A. G.: *Amer. J. Hum. Genet.*, 14: 31, 1962.
6. MOORHEAD, P. S. *et al.*: *Exp. Cell Res.*, 20: 613, 1960.
7. BUCKTON, K. E. *et al.*: *Lancet*, 1: 171, 1961.
8. BAIKIE, A. G. *et al.*: *Ibid.*, 2: 1003, 1961.
9. MAMUNES, P. *et al.*: *Ibid.*, 2: 26, 1961.
10. KEMP, N. H., STAFFORD, J. L. AND TANNER, R. K.: *Ibid.*, 2: 434, 1961.
11. FORD, C. E. *et al.*: *Ibid.*, 1: 709, 1959.
12. UCHIDA, I. A. AND BOWMAN, J. M.: *Ibid.*, 2: 1094, 1961.
13. THERMAN, E. *et al.*: *Amer. J. Hum. Genet.*, 13: 193, 1961.
14. MILLER, O. J. *et al*: *Lancet*, 2: 78, 1961.
15. HAMERTON, J. L. *et al.*: *Ibid.*, 2: 788, 1961.
16. CARTER, C. O. AND EVANS, K. A.: *Ibid.*, 2: 785, 1961.
17. LUBS, H. A., JR.: *Ibid.*, 2: 881, 1961.