Multiple Cases of Leukemia in a Sibship

By F. W. Gunz, P. H. Fitzgerald, P. E. Crossen, I. S. Mackenzie, C. P. Powles and G. R. Jensen

In the past 20 years views on the importance of genetic factors in the etiology of leukemia have undergone repeated changes. In 1947 Videbaek produced evidence to show that both leukemia and cancer were commoner in relatives of leukemic patients than those of controls; he suggested that this was due to a dominant gene of low penetrance which conveyed a predisposition to leukemia. These findings were not confirmed in subsequent publications and were attacked for statistical and methodological reasons in others. More recently there have been reports of an association between mongolism and leukemia, of a 25 per cent concordance rate for leukemia in uniovular twins, and of a probably greater than expected incidence of multiple cases of leukemia in families as well as of personal cancer in chronic lymphocytic leukemia—all of which have tended to suggest that genetic factors may after all be of significance in the causation of certain types of leukemia.

Whether or not statistical information will eventually disclose the presence of a general genetic component in leukemogenesis, evidence has accumulated over the years which shows that at least in some families heredity is likely to be a potent factor. Instances in which 3, 4 or 5 cases of leukemia occurred in the same or successive generations of a single family have been reported, among others, by Anderson, Boggian, Campbell et al., Decastello, Gunz and Dameshek, Hornbaker, Johnson and Peters, Reilly et al., and Steinberg. To these we now add a further family in which 4 siblings died from acute leukemia and a fifth, though living, probably has the same or a related disease.

The T. Family

This is a family of New Zealand Maoris living in an isolated settlement ("Pa") of approximately a dozen houses some 6 miles from a country town with a population of 2000. The pedigree is shown in Figure 1. Of the 9 children born so far, the eldest (Go. T.) is a half-sib whose father is not known. The other 8 are the offspring of Mr. R. T. and Mrs. D. T. R. T. and D. T. have no known recent common ancestor. They come from Maori tribes in widely separated parts of the country. D. T. is said to be a full-blooded Maori. R. T. is half-European.


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Fig. 1.—Pedigree of the T. Family.

In October 1962 Ge. T., one of male twins aged 10 months, was suddenly taken ill and died within a few days from what was clearly acute leukemia. The other twin, J. T., was investigated at the time of his brother’s illness, and though his marrow was abnormal, he survived for nearly 2 more years. He then developed symptoms of acute leukemia and died within 3 weeks, in August 1964, when at the age of 6 he was diagnosed as having acute leukemia from which he died 4 months later. M. T., aged 11 months, developed in November 1963 recurrent chest infections, an abnormal blood and marrow picture suggestive of leukemia, hepatosplenomegaly, and mediastinal enlargement possibly due to a thymic tumor. The signs and symptoms gradually subsided after prednisone therapy, and she is at present well. Go. T. and the 3 other siblings have so far remained well.

CASE REPORTS

Because of the difficulties in reaching the family, and also by reason of racial customs, a complete investigation of these patients has not been possible. In particular, we have little information about family members other than the parents and children. The parents stated, however, that as far as they knew there were no other cases of blood diseases among their relatives. A similar assertion was made by Mrs. T.’s mother.

The father, R. T., is a half-European Maori born in 1931, by occupation a freezing worker (slaughterman). At the age of 17 he sustained a football injury to his right leg which was subsequently amputated. He has had no other illnesses.

The mother, D. T., is a full-blooded Maori born in 1935. At the age of 9 she was in hospital with an illness reputed to be pulmonary tuberculosis. Since then she has remained well. She was 21 when her first affected child, R. I. T., was born.

R. I. T.: This 3-year-old girl was admitted to hospital on 12/22/59 because of general malaise of 1-week duration. She had lost her appetite 3 weeks before admission. On examination she was pale. Her upper lip was swollen and she would not permit inspection of her mouth. There was bruising of the left upper eyelid, enlargement of the submandibular, maxillary and other cervical lymph nodes, splenomegaly and extreme swelling of the abdomen. The next day many ecchymoses were seen and hepatosplenomegaly and generalized lymphadenopathy were confirmed. No history of past illnesses was obtained. The Hb was 8.4 Gm. per cent; WBC was 66,750/cu. mm., with a large proportion of lymphocytes, many of them immature including blasts. Platelets were almost completely absent. The appearances were consistent with a diagnosis of acute lymphocytic leukemia.

She was given prednisone 20 mg. daily for 4 days, after which the dose was reduced progressively. On 12/29/59 Hb was 6.1 Gm. per cent, WBC was 2000/cu. mm., and platelets too few to count. At the parents’ request she was discharged home where she died on 1/10/60. Autopsy was not performed.

Ge. T.: This male twin aged 10 months was admitted to hospital on 10/21/62 because of pallor, malaise and a general hemorrhagic state; he died on 10/25/62. He and his twin brother had been regarded as identical because of their similar appearance and development, but an examination of their blood groups (see below) showed clearly that the boys were in fact fraternal twins. Ge. T. had on the whole developed a little faster than J. T.
and had put on more weight (birth weight 5 lb., 8 oz.; weight at autopsy 22 lb.). He had always had sores of the scalp and had been admitted to hospital for their treatment when aged 3 months. He had been given 2 doses of Sabin vaccine but had had no inoculations. His mother had not been x-rayed during pregnancy. Ge. T. had had one chest x-ray when aged 5 months because his chest was "rattly." His terminal illness came without warning.

The Hb was 5.2 Gm. per cent, hematocrit 17 per cent, and MCHC 30 per cent. Platelets were markedly reduced. There were 34,000 WBC per cu. mm., with 1 per cent neutrophils, 57 per cent lymphocytes and 40 per cent blasts. A sample of marrow obtained postmortem showed a very high cellularity. Nearly 100 per cent of all cells belonged to the lymphoid series, from mature lymphocytes to blasts. A few erythroblasts and myeloid cells were also present, as well as one or two megakaryocytes.

Autopsy. performed 24 hours after death. showed the body of a well-nourished male infant. There were many petechiae and a subconjunctival hemorrhage of the left eye. The skin and all organs were extremely pale. There were small hemorrhages throughout the serous surfaces in the chest and abdomen, the epicardium and many other organs. The thymus was enlarged (22 Cm.), as were the liver and spleen. No lymph nodes were enlarged. The bone marrow appeared normal macroscopically. Microscopically, there was moderate leukemic infiltration of the hepatic portal tracts and of the splenic pulp. The bone marrow was replaced by masses of leukemic cells.

J. T.: This male twin had a birth weight of 6 lb. At the age of 11 months he was stated to have been always pale. One week after his brother's death (11/2/62) he was examined and found to be anemic. Hb was 4.8 Gm. per cent and the red cells were markedly hypochromic. The platelets were normal. There were 16,800 WBC/cu. mm., with 33 per cent neutrophils. 63 per cent lymphocytes and 4 per cent monocytes. A tibial marrow sample was cellular, with some erythroid hyperplasia and normal myeloid cells and megakaryocytes. In addition there were unusually large numbers of cells belonging to the lymphatic series, patchily distributed and forming 80–90 per cent of all cells in some high-power fields. Most of these appeared mature, but there were also large numbers of immature lymphoid cells, including blasts. The findings were thought sufficiently suggestive of leukemia to enjoin a careful watch for signs of overt disease. The anemia was regarded as the result of iron deficiency, a very common condition in Maori children.

The infant was treated with oral iron, followed by 10 intramuscular injections of 10 mg. iron sorbitol. His condition improved, and on 4/24/63 the Hb was 11.5 Gm. per cent, with slight hypochromia and a WBC of 14,200/cu. mm. and a normal differential count. He remained well until July 1964 when he was readmitted suffering from a septic skin rash and anemia. Multiple petechial hemorrhages were noted in the skin and mucous membranes. The liver and spleen were enlarged, and there was enlargement of the cervical and inguinal nodes. The Hb was now 6.7 Gm. per cent. WBC 113,000/cu. mm., with 2 per cent neutrophils, 96 per cent lymphocytes and blasts. Platelets were 25,000/cu. mm. The findings were characteristic of acute lymphocytic leukemia. Treatment was started with prednisone 40 mg. daily, but there was no response and he died at home 3 weeks after the initial diagnosis. No autopsy was carried out.

H. T.: This boy aged 6 was admitted to hospital on 10/27/64 because his mother had noticed multiple painless bruises on his limbs for the past 6 weeks. Previously he had been well. He was found to have petechial hemorrhages and ecchymoses on all limbs. There was splenomegaly and some lymphadenopathy.

His Hb was 9.5 Gm. per cent and WBC 132,800/cu. mm., with 3 per cent neutrophils. 11 per cent lymphocytes, 86 per cent immature cells and blasts, a typical picture of acute lymphocytic leukemia. He was given a transfusion of 2 units of blood and prednisone 40 mg. daily. On 11/6/64 Hb was 13.5 Gm. per cent, WBC 13,000/cu. mm., and the differential count was normal. Platelets were 100,000/cu. mm. Relapse occurred in February 1965 and he died in a hemorrhagic state on 2/19/65. No autopsy was carried out.

M. T.: This girl aged 1 year developed lethargy, fever, vomiting and cyanosis, and when admitted to hospital on 12/21/63 she showed rapid respiration and dullness to percussion of the left pulmonary base. There was slight hepatosplenomegaly, and an x-ray showed a mass of uncertain significance in the right chest. This soft tissue shadow enlarged rapidly until on
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On admission on 12/21/63 the blood count was as follows: Hb 12.9 Gm. per cent, WBC 39,750/cu. mm. with 18 per cent neutrophils, 78 per cent lymphocytes, mostly mature, and 4 per cent monocytes. The marrow showed normal erythroid and myeloid precursors, an occasional megakaryocyte, and many platelets. The picture was dominated by large numbers of lymphocytes, mostly mature, but also with many immature cells, including blasts. A further marrow sample taken in March 1964 showed larger numbers of blasts.

The child was treated with prednisone 20 mg. daily for 4 weeks in December 1963 and January 1964. There was a very gradual improvement in her condition. The hepatosplenomegaly disappeared but some widening of the mediastinal shadow remained. On 9/2/64 the blood count was normal, and a marrow sample taken on 11/4/64 was also normal. This patient has not been seen since early in 1965.

Blood and Serum Groups

The blood group of RIT is not known. The groups of the other members of the family are shown in Table 1. It can be seen that the twins, Ge. T and J. T., had groups differing in the Rh and P systems and could not therefore have been uniovular. All the children's groups are consistent with those of their parents; that of Go. T., who had a different father, could also have resulted from the mating between R. T. and D. T. No distinctive groups were found in the patients who developed leukemia.

Chromosome Studies

These were made on the blood or marrow of both parents, of J. T. before he developed overt leukemia, of M. T. while she had a "leukemoid" blood and marrow picture, and of N. T. during his illness, before treatment. The bloods were cultured by the method of Moorhead et al., and the marrows were examined without culturing as previously described by us. The findings are shown in Table 2. No consistent abnormalities were seen in any blood or marrow. The modal chromosome number was 46 in all cases, and the 18 karyotypes prepared from the patients' specimens were all normal. Only a few cells were aneuploid, most of them having hypodiploid chromosome numbers which were probably caused by accidental chromosome loss during preparation. The presence of acentric chromosome fragments in cells from J. T. and M. T. indicated some degree of chromosome breakage in these possibly leukemic cells. These studies thus showed evidence neither of inherited nor of major acquired chromosome abnormalities.

Living Conditions of the T. Family

The family lives in a very small Maori community. Only 4 or 5 houses of the settlement are now occupied, one of them by the children's maternal grandmother. No blood diseases or other unusual illnesses have occurred in the other families. No known or suspected virus diseases were prevalent before any of the T. children developed leukemia. Only one other case of childhood leukemia occurred in the wider area during the years from 1953 to 1963 inclusive.

The settlement lies on a rise in the middle of rolling green dairying country. The soil is volcanic. Measurements of the background radiation and of the
Table 1.—Blood Groups

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<th>Case</th>
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<th>MsNs</th>
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<th>Le&lt;sup&gt;a&lt;/sup&gt;</th>
<th>K&lt;sup&gt;+&lt;/sup&gt;</th>
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<th>Hp</th>
<th>Tf</th>
<th>CC</th>
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<td>Fy&lt;sup&gt;-&lt;/sup&gt;</td>
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<td>Hp 1/1</td>
<td>Tf CC</td>
<td></td>
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<td>Hp 1/1</td>
<td>Tf CC</td>
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<td>Fy&lt;sup&gt;-&lt;/sup&gt;</td>
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<td>Fy&lt;sup&gt;-&lt;/sup&gt;</td>
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*Patient had leukemia.
†Patient probably has leukemia.

Table 2.—Chromosome Studies

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<td>1 41 26 32</td>
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*Two of these cells had an additional large acentric fragment.
†One of these cells had a large acentric fragment.

radioactivity in milk from the locality have been made by the National Radiation Laboratory and have shown no unusual levels compared with other parts of the country. (The fallout level is low in New Zealand in comparison with that in the Northern hemisphere.) Insecticides or agricultural sprays have not been used in greater than customary amounts. The family has had no access to industrial or other poisons.

**DISCUSSION**

This report concerns a family with 9 children, 4 and possibly 5 of them with acute leukemia. In spite of somewhat incomplete investigations, there can be no doubt of the diagnosis in the first 4 siblings, including both fraternal twins. The fifth child had an illness with highly suggestive clinical and hematologic features, most of which cleared up after treatment with prednisone. It remains to be seen if a relapse will occur.

In this connection it is interesting that J. T., the second twin, had bone marrow changes considered suspicious of leukemia as long as 21 months before the clinical onset of the disease. It could be that this child, predisposed to leukemia, showed an atypical marrow reaction in response to the stress of iron...
deficiency. It could also be that the leukemia was present in a subclinical form long before it led to the onset of symptoms. The clinical course in M. T., who has not yet developed overt symptoms of leukemia, could be similarly explained.

What is the reason for these multiple cases in the same family? We can eliminate the element of chance, for the risk of 4 or 5 leukemias occurring randomly in one sibship of 9 is so vanishingly small as to be negligible. It is possible to speculate that external leukemogens were primarily involved. If so, their nature has not been discovered. It is indeed difficult to conceive of an agent or agents which would by itself cause the disease in members of this family and in no others in the neighborhood. Radiation, the only proved cause of human leukemia, has been excluded, both in the background and in the personal histories of the patients. There was no history of exposure to drugs or industrial poisons. Viruses, though strongly suspected nowadays as human as well as animal leukemogens, have not yet been incriminated in any actual cases in man, and in the T. children there were no reports of any diseases suggestive of virus origin. These negative statements do not, however, exclude any of these agents absolutely; indeed, it is likely that no single case of leukemia is produced by a single “cause,” but that in addition to the primary leukemogen one or more promoting agents are also required before the disease occurs. In the case of the T. family there has been no hint as yet of the nature of any promoting agent which might be involved.

The case for genetic factors as a background to the troubles besetting this family is very strong. Even those authors who most determinedly deny the general importance of genetic factors in leukemogenesis (e.g., Steinberg19) admit their probable existence in families such as ours. It is perhaps significant that in several of these families there was a striking uniformity of the age of onset in the affected siblings. In that of Anderson all cases occurred in children aged 5–8 years; Campbell’s cases were neonates; those in the T. family were aged from 10 months to 6 years.

If heredity is involved in these families, its mode of operation has remained disputed. Videbaek21 proposed a dominant gene with a low penetrance; Steinberg19 thought a recessive gene more likely, because in 2 of the 3 families discussed by him consanguineous marriages were responsible for the production of multiple leukemic children. The parents of the present family are unrelated to each other. The approximately 50 per cent incidence of leukemia in their children might suggest that the disease occurs in those children who have inherited a dominant mutant gene, with full penetrance, which occurred in the germ cells of one of the parents. Because of the early age of onset of the leukemia, such a mutant gene would not be expected to survive the present generation. On the other hand, a recessive inheritance cannot be absolutely ruled out.

No major chromosome abnormalities were found in either parents or leukemic children, and in the only other similar family known to us in which cytogenetic studies were carried out,4 the chromosomes were also normal. This is in contrast to the situation in mongolism in which a constant abnormality of
the chromosomes (21 trisomy or its equivalent) is present and apparently predisposes to a greatly increased leukemia incidence. It would seem likely that any alterations to the genome present in leukemic members of the T. family are of submicroscopic size (point mutations). There was no evidence of linkage between such a gene concerned with leukemia and those determining blood or serum groups.

The future of this family is of much interest. It will be necessary to observe the remaining children closely for symptoms of leukemia, and in this connection Go. T. is of particular importance since his father was not the same as that of the other siblings. Should Go. T. also develop the disease, this would furnish a very strong argument for the view that a dominant mutation is present in the germ cells of the mother and would eliminate the possibility of a recessive inheritance.

Attention must finally be drawn again to the fact that the T. family is one of extremely few in the literature in which leukemia affected multiple close relatives in the same generation. This paucity of reports is unlikely to be due to lack of recognition. It suggests rather that such occurrences are the result of a highly unusual genetic constellation which differs greatly from that in most other individuals with leukemia. Today it seems increasingly probable that genetic factors are involved in the etiology of at least a proportion of leukemia cases at large; if this is so, the mechanism is unlikely to be the same as that which produced such devastating results among the members of the family described in this paper.

**Summary**

In a New Zealand Maori sibship of 9 (one a half-sib), 4 definite cases and 1 possible case of acute leukemia occurred in a space of 5 years. The children, 2 of whom were fraternal twins, developed symptoms at ages between 10 months and 6 years. One child had a marrow picture suspicious of leukemia nearly 2 years before the onset of symptoms.

Cytogenetic studies showed no major chromosome changes in either the parents or the 3 affected siblings examined. No linkage was found between the leukemias and any blood or serum group.

The nature of the factors causing the disease in this family is discussed.

**SUMMARIO IN INTERLINGUA**

In un fratricia Maori de Nove Zelanda de 9 membros (incluse un semifraterno), 4 casos definite e 1 caso possibile de leucemia acute occurreva intra un spatio de 5 annos. Le victimas, 2 del quales esseva geminos mascule, disveloppava symptomatas a etates de inter 11 menses e 6 annos. Un habeva un tableau medullari suspecte de leucemia quasi 2 annos ante le declaration de symptomatas.

Studios cytogenetic monstrava nulle major alterationes chromosomatic in o le parentes o le 3 afficite fraternos examine. Nulle nexo esseva trovate inter le leucemias e un gruppo particular de sanguine o de sero.

Le natura del factores causante le morbo in iste familia es commentate.
ACKNOWLEDGMENTS

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