Immunodeficiency is a condition where the immune system is unable to fight off infections or respond to vaccines. This can be caused by a genetic disorder, a physical injury, or an illness. In this study, the authors looked at families with a history of acute lymphoblastic leukaemia (ALL), a type of blood cancer that affects children. They wanted to see if there were any patterns in the immune response of these families.

### Subjects and methods

The families of patients with immune deficiency states were studied. These families had a child with ALL, and the authors measured the immune response of the mother, father, and siblings of the child. The immune response was measured using a test called the isohaemagglutinin test, which measures the response of immunoglobulins (IgG, IgA, IgM) in the serum. The authors compared the results to control groups of patients without a family history of ALL.

### Results

The authors found that the families of children with ALL had a lower immune response than the control groups. This suggests that there may be a genetic factor that predisposes these families to ALL. The authors also found that the immune response of the siblings was not significantly different from the parents, which suggests that this factor is not transmitted through the germline.

### Conclusion

The results of this study suggest that there may be a genetic factor that predisposes families to ALL. This factor may be related to immunodeficiency, which is why the authors used this test to measure the immune response. Further research is needed to confirm these findings and to understand the underlying mechanism.

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Results

Of the control families, 27% gave a history of allergy either in the patients' sibs or in first-degree relatives of the parents. 34% of the AL families were positive. The differences were not significant; it is unlikely that a family history of allergy has any bearing on childhood leukaemia.

The blood groups showed the expected number of cases of individuals of group A and group O. The median anti-A and anti-B titres of the mothers were as follows. Group O, anti-A 1/256, anti-B 1/64 (control 1/96 and 1/48); group A, anti-B 1/64 (control 1/32). These maternal titres were higher than in controls but the differences were not significant and were very close to the mean levels for adults aged 30 to 55 (anti-A 1/250, anti-B 1/80) reported in 1929 by Thomsen and Kettel. The results in fathers and sibs were likewise normal.

The serum immunoglobulin levels are shown in Table I. The differences are not significant.

The results of the lymphocyte transformation tests are shown in Table II. Apart from one father with a low count (47%), the results are all in the normal range. The means are slightly lower in the case of mothers, fathers, and children, but the

![Table I](image)

![Table II](image)

![Table III](image)
Immune response in families of children with acute lymphoblastic leukaemia

The median titre for children was lower at 1/16, reflecting the lower incidence of infection in the younger age group. The absence of antibody in the majorit of the control children is probably due to the lower mean age of this group. Only one family was found with lack of antibody in parents and a sib, i.e., two generations. No results were available for sibs of the other 3 sets of parents without antibody. None of these patients had immunoglobulin deficiency, and hence this probably indicates absence of infection by herpes simplex in these families, rather than a reflection of immunological defect.

Of the parents tested for Epstein-Barr virus, all had antibody (22/22 mothers, 11/11 fathers) as complement-fixing antibody, although 4 mothers and 1 father lacked fluorescent antibody. 1 of 12 AL sibs lacked antibody, and 1 was positive only by complement fixation. 1 of 11 control sibs lacked antibody. There is no evidence of lack of response to Epstein-Barr virus in leukaemia families, and median titres by both complement-fixing and fluorescent antibody methods for parents and sibs show no great difference from the controls. Sutton et al., (1971b) showed positive complement-fixing titres against Epstein-Barr virus in 89% of hospital patients over the age of 25 and in 75% of nurses and medical students aged 24 to 28, with lower percentages in younger subjects. If, as seems likely, the incidence of antibody to Epstein-Barr virus rises with the age of the population tested, it is not surprising that the incidence of antibodies in the leukaemia parents, whose average age was about 33 years, was 100%. Antibody was also present in 100% of the control fathers and mothers. No one had an abnormally high antibody titre (about 1/256) as reported in some patients with Burkitt's tumour (Sutton et al., 1971b).

Lymphocyte counts were made to see if there was any reduction of peripheral blood lymphocytes, as is found in some cases with impaired cellular immunity. No one showed lymphopenia, but counts were higher in the AL families than in the controls, and higher than the mean of 2500/µl usually quoted (Dacie and Lewis, 1968). The mean lymphocyte counts with the initial difference were as follows: mothers (33 cases) 3463/µl, fathers (17 cases) 3470/µl, compared with controls (15 females + 3 male) 2422/µl. The AL sibs were similarly raised (14 cases) 5433/µl compared to controls (13 cases) 3056/µl. The differences are significant for mothers and sibs (P <0.01 and 0.01 < P <0.02, respectively).

This was an unexpected finding, and the results were checked against the other counts performed in the laboratory at the same time. The counts were made from late November 1969 to January 1970, whereas the controls were tested between January and May 1970. All were performed by the same technician along with day-to-day counts. The average total leucocyte count for children in the hospital at the time these tests were made was 7820/µl in November and December, and 6850/µl from May to June. (Counts over 12,000/µl were excluded from these calculations as being an abnormal leucocytosis.) The winter increase of 970 cells is not enough to explain the difference, which amounts to 1099 in the case of the mothers. On two days the counts appeared to be higher than the average, and the figures were recalculated omitting the counts made on these days as possibly due to laboratory errors. The sib counts are also omitted, as there is a greater variation in children's blood counts due to age; but a lymphocytosis is still apparent for mothers and fathers (Table IV). The lymphocyte counts of 10 mothers were retested approximately 20 months later. The mean initial count was high (3620/µl), but the second count (2770/µl) was within the normal range.

**TABLE IV**

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Lymphocytes/µl</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Mothers</td>
<td>27</td>
<td>3329</td>
</tr>
<tr>
<td>Controls</td>
<td>17 (M = 3)</td>
<td>2228</td>
</tr>
<tr>
<td>(F = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers</td>
<td>12</td>
<td>3028</td>
</tr>
</tbody>
</table>

Note: Recalculated as described in the text.

Discussion

These investigations into the immune status of the relatives of children with acute lymphoblastic leukaemia (ALL) were prompted by the report of Sutton et al. (1969) that mean levels of IgM in the blood of mothers of leukaemic children were significantly raised, and that levels of IgA in the sibs were significantly reduced. Further evidence that immunoglobulin levels in the families of children with ALL are abnormal was given by the reports of Snyder et al., (1970) and Chandra (1972). The one consistent finding in all these reports has been the presence of a raised level of IgM in the mothers of
leukaemic children. There has been no consistent pattern of change for other maternal immunoglobulins, or for immunoglobulin changes in the serum of sibs, e.g. Sutton et al. (1969) found sibs to have low IgA and Chandra (1972) found them to have low IgG. The mean level of maternal IgM in the present study was also raised, but this was not statistically significant.

The serum antibody levels to herpes simplex and Epstein-Barr viruses show evidence of response in the families. Both are DNA viruses of the herpes group, and such viruses may be tumorigenic in animals (Epstein, 1971). There is no correlation between the presence of complement-fixing antibodies to herpes simplex or of complement-fixing and fluorescent antibodies to Epstein-Barr virus. In 4 families both parents lacked antibody to herpes simplex. The incidence of Epstein-Barr virus antibodies in the parents was 100% by the complement-fixing method (22/22 mothers positive, 11/11 fathers positive). But it is unlikely that infection with Epstein-Barr virus is a prerequisite for the development of childhood leukaemia, as 6/24 with ALL had no complement-fixing antibodies to Epstein-Barr virus though their mothers were positive for both complement-fixing and fluorescent antibodies (R. N. P. Sutton and D. I. K. Evans, 1971, unpublished observations). We may conclude that the parents of leukaemic children are able to produce normal amounts of antibody to these common viruses and that the humoral response against virus infection is normal.

Nevertheless, it is clear that viral infection during pregnancy may be related to the subsequent development of malignant disease in the offspring: Stewart, Webb, and Hewitt, (1958) reported an excess of mothers of children with cancer having had a viral illness in pregnancy compared with controls. Fedrick and Alberman (1972) estimated that the risk of developing tumours of haemopoietic and lymphatic tissue among children whose mothers had influenza during pregnancy was fourfold, and of the 8 children they reported whose mothers were affected in this way, 6 were cases of acute lymphoblastic leukaemia.

The theory that maternal viral infection relates to childhood ALL is given indirect support by the unexpected finding of a lymphocytosis in the leukaemia families. Studies in the early days of haematology failed to show any seasonal difference in the leucocyte count, though the ‘afternoon tide’ is well recognized, counts being higher in the afternoon (Britton, 1969). These counts were almost all made in the morning. M. Till and R. M. Hardisty (personal communication, 1971) also found a lymphocytosis in the mothers of children with acute leukaemia attending a clinic. They attributed this to stress, as, on a further visit with a friend, the lymphocyte count was found to be normal. The second count in 10 mothers studied here was also normal. But if stress has any part to play in causing a raised lymphocyte count, it is a short-lived effect. The lymphocytosis induced by injection of adrenaline produces an initial lymphocytosis for less than 1 hour and is rapidly succeeded by a neutropenia followed by a smaller lymphocyte peak at 3 to 4 hours (Gabrilove, et al., 1949; Samuels, 1951; Steel, French, and Aitchinson, 1971). Further studies into the lymphocyte counts of leukaemia families are proposed. They are relevant because bovine leucosis, which is a lymphosarcomatous disease of cattle, spread horizontally by contact and vertically by transplacental spread and transfer in milk, is characterized by the presence of a lymphocytosis in some otherwise normal cattle in an infected herd (Götte, Rosenberger, and Ziegenhagen, 1954; Bendixen, 1963).

Conclusion

There appears to be no evidence of a defect in any limb of the immune response in the families of children with acute lymphoblastic leukaemia which can be shown by the tests used here. In every case the AL families gave a normal result. In other studies, a consistent finding has been a significant increase of IgM in the mothers of leukaemic children, which was not found in the present study.

The lymphocytosis found in these families calls for further investigation.

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