The development of the syngeneic animal system permitted tumour transplanta-
tion experiments to be conducted without interference from genetically determinaled
antigens, and provided systems in which acquired 'neo-antigens' could be studied. Under carefully manipulated conditions several different immunological ma-
nouevres were shown to be capable of slowing the growth of tumours in experi-
mental animals (see review, Alexander, 1974), and the two most promising methods
that emerged which were applicable to man were non-specific stimulation of the
immune system using agents such as B.C.G. (Halpern, et al 1959) and specific stim-
ulation with tumour cells (Haddow and Alexander, 1964).

In all the animal experiments successful anti-tumour effects were only seen if
the tumour load was very small. Leukaemia in man is therefore a particularly
good model in which to test immunotherapy because patients in remission have
undetectable numbers of cells remaining but if left untreated they inevitabably re-
lapse. A prerequisite for active specific immunotherapy for leukaemia in man was
the demonstration (see Powles review 1974a) using mixed cell cultures of sur-
face components on human leukaemia cells which behaved like tumour specific
transplantation antigens (T.S.T.A.'s). This provided a rationale for using killed
leukemia cells in addition to B.C.G. for immunotherapy in man. Thus, in the
last ten years specific (killed tumour cells) and non-specific (B.C.G.) immuno-
therapy have been used in a number of controlled clinical trials in man.

The first comparative study was initiated by Mathe (Mathe, 1969), who
selected a group of patients with A.L.L. who had been in remission for at least
two years. For some all treatment stopped and the rest were given weekly Pasteur
B.C.G., killed allogeneic A.L.L. cells, or both B.C.G. and cells. All 10 of the un-
treated patients relapsed within 130 days, whereas half of the 20 immunotherapy
patients remained in remission for greater than 295 days, some of them for many
years. The numbers were too small to decide which of the immunological regimes
was best.

Several attempts have been made to confirm the value of B.C.G. alone in A.L.L.
during remission. In Britain, the Medical Research Council arranged a trial
(M.R.C. 1971) which compared the use of twice weekly Methotrexa with B.C.G.
or no treatment. They found no benefit from the use of B.C.G. but it must be
remembered that a different form of B.C.G. (i.e. Glaxo) was used. A similar study
in the U.S.A. by Leukaemia Study Group A, (Heyn et al 1973) also failed to show benefit from B.C.G. More recently the Houston Group (Gutterman et al 1974) have used Pasteur B.C.G. for the maintenance of remission of all forms of adult leukaemia, and although they report benefit in A.M.L. (see below) there was no evidence that Pasteur B.C.G. prolonged remission in A.L.L. In the related disease Burkitt's Lymphoma, Ziegler (Ziegler and Magrath, 1974) used Pasteur B.C.G. given for a limited period by scarification and also found no therapeutic effect in maintaining remission in these children.

Table I: Bart's 2, 3, + 4 trial of maintenance chemotherapy versus maintenance chemotherapy plus immunotherapy.

<table>
<thead>
<tr>
<th>Days</th>
<th>Proportion in remission</th>
<th>Proportion surviving*</th>
<th>Proportion Surviving after relapse</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C**</td>
<td>C+I***</td>
<td>C</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
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<td>82</td>
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<td>200</td>
<td>50</td>
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<td>70</td>
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<td>32</td>
<td>54</td>
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</tr>
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<tr>
<td>800</td>
<td>10</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>1000</td>
<td>10</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>No. pts.</td>
<td>22</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>No. Remaining</td>
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<td>1</td>
<td>2</td>
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</table>

P. value***

<table>
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<th>difference</th>
<th>C to C+I</th>
<th>C to C+I</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. S.</td>
<td>0.03</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

* From onset remission.
** C Chemo maintenance only.
*** C+I chemo plus immunotherapy maintenance.
**** Log rank non-parametric method (Peto and Peto, 1972).

At present, the place of immunotherapy for A.L.L. remains speculative since only Mathé has reported a therapeutic effect and no other study has done exactly as he did in giving Pasteur B.C.G. and cells. Whether it is at present necessary to use immunotherapy as a primary method of treatment for A.L.L. in the face of the outstanding results produced by intensive combination chemotherapy and prophylactic treatment of the central nervous system as developed by Pinkel and his colleagues (Simone, 1974) remains to be tested. Initially A.L.L. was selected as the best disease to test immunotherapy because so few patients with Acute Myelognous Leukaemia A.M.L. obtained remission with chemotherapy and so it was impossible to conduct a trial. This situation, however, has changed.

A joint Barts Hospital/Marsden Hospital study (B. 2, 3, 4.) was started in