Dependence of the Regression of Sarcoma 180 in Vitamin B₆-deficient Mice upon the Immunologic Competence of the Host

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SUMMARY

The incidence of complete regression of Sarcoma 180 (S-180) in vitamin B₆-deficient Swiss mice was significantly reduced in animals thymectomized 1-5 days after birth but not in sham-thymectomized mice, neonatally thymectomized mice implanted s.c. with thymus autografts, mice thymectomized 9 or 30 days after birth, or neonatally splenectomized mice. The initial retardation of the growth of S-180 caused by the dietary depletion was not different in neonatally thymectomized and sham-operated mice; the delayed retardation of tumor growth was reduced in mice which had been thymectomized neonatally. Thus in nontumectomized mice the delayed retardation of tumor growth appears to be caused by both the therapeutic treatment and the immunologic response of the host.

Comparison of the regression of S-180 and the rejection of allogenic skin grafts indicated that dietary vitamin B₆ depletion causes only minor impairment of the immunologic responses of the host at levels sufficient to impair the tumor effectively.

INTRODUCTION

In recent years attention has been focused on the potential role of immunologic factors in the therapy of experimental and human tumors (9, 16, 17, 26) and on the possible interference by antitumor agents with specific host defenses directed against the target tumor cells (20). Crocker mouse Sarcoma 180 (S-180) is a transplantable tumor which has been used extensively in chemotherapeutic studies. This tumor is not strictly strain-specific, and it is not completely compatible in Swiss mice since it is rejected in 5–20% of these animals (17). This incidence of rejection is not increased, however, even when the growth of the tumor is greatly impaired by antitumor agents. In fact, regression of S-180 in Swiss mice has been observed only after treatment with 6-mercaptopurine (6-MP) and related purine analogs (5, 6), with thiopemycin and actinogen (4), and with bifluorocarbazones of α-ketoaldehydes (22, 23) or in animals fed vitamin B₆-deficient diets (4, 19). Therefore, therapeutically induced regressions of S-180 acquire particular significance.

This investigation was concerned primarily with the clarification of the relationships between the inhibitory effects of dietary vitamin B₆ deficiency on Sarcoma 180 and the effects of the host immunologic response elicited by this tumor. The demonstration that S-180 does not regress in vitamin B₆-deficient mice thymectomized shortly after birth indicates that immunologic mechanisms are responsible for the regression of the therapeutically impaired tumor observed in the intact and sham-operated animals fed the deficient diet. Some of these results were presented in a preliminary report (8).

MATERIALS AND METHODS

The solid form of S-180 was used in this study. The standard procedures followed for the implantation of the tumor and the evaluation of its growth have been reported previously (19). The composition of purified diets used was described previously (23). Total body irradiation was given as previously reported (17). Pregnant H/JCR Swiss mice or newborn mice with their mothers were obtained from the Roswell Park Memorial Institute mouse breeding colony. Surgery of newborn mice was performed under light anesthesia achieved by injecting i.p. 20–40 μg of Nembutal per animal. A dissecting microscope was used. The thymus was removed by aspiration following exposure of the organ by a longitudinal section of the proximal part of the sternum. Thymus autografts were placed s.c. in the axillary area through a skin incision. The spleen was excised by a standard procedure through a dorsolateral incision. Skin was grafted according to the Hauschka technic (11) or Billingham's free graft technic (3). In each experiment littermates were used. They were separated from the mother 3–4 weeks after birth and were divided according to sex and to surgical treatment and then distributed into groups fed the 2 purified diets. The diets were fed starting 2 weeks before the tumor was implanted. At the end of the experiments all the thymectomized mice were autopsied. The thymus area was inspected visually with the aid of a dissecting microscope; in doubtful cases, histologic study of the thymus area was performed. Animals with thymus fragments were eliminated from the study.

RESULTS

The effects of vitamin B₆ deficiency on S-180 in neonatally thymectomized and sham-operated mice are summarized in Table 1. Results were similar in males and females. At the end of the 1st week after implantation, the growth of S-180 was re-
Regression of Sarcoma 180 in Vitamin B6-deficient Mice

TABLE 1
Effects of Dietary Vitamin B6 Deficiency on Sarcoma 180 in Neonatally Thymectomized HAI CR Swiss Mice

<table>
<thead>
<tr>
<th>Diet</th>
<th>Surgery</th>
<th>Sex</th>
<th>No. of mice</th>
<th>Δ body weight (gm)</th>
<th>Average tumor diameter ± S.D. (mm)</th>
<th>Δ body weight (gm)</th>
<th>Average tumor diameter ± S.D. (mm)</th>
<th>8th day</th>
<th>15th day</th>
<th>10th week</th>
<th>Mortality</th>
<th>Survival of tumor-free mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete diet</td>
<td>Sham</td>
<td>F</td>
<td>22</td>
<td>+1.2</td>
<td>11.3 ± 2.0</td>
<td>−1.8</td>
<td>15.2 ± 3.2</td>
<td>86</td>
<td>86</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>M</td>
<td>25</td>
<td>+1.1</td>
<td>11.9 ± 2.2</td>
<td>−2.2</td>
<td>17.1 ± 3.7</td>
<td>88</td>
<td>84</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>F</td>
<td>39</td>
<td>+1.1</td>
<td>7.2 ± 1.9</td>
<td>−0.2</td>
<td>5.6 ± 3.2</td>
<td>33</td>
<td>33</td>
<td>0</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>F</td>
<td>24</td>
<td>+0.9</td>
<td>7.6 ± 1.8</td>
<td>−1.1</td>
<td>9.1 ± 3.1</td>
<td>75</td>
<td>58</td>
<td>4</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>M</td>
<td>34</td>
<td>+1.5</td>
<td>7.5 ± 1.5</td>
<td>−1.3</td>
<td>5.9 ± 3.4</td>
<td>53</td>
<td>53</td>
<td>0</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>M</td>
<td>25</td>
<td>−1.0</td>
<td>7.8 ± 1.8</td>
<td>−2.6</td>
<td>11.0 ± 3.7</td>
<td>80</td>
<td>72</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

* Surgery was performed within 24 hr from birth.

* Average change of body weight from that on the day of tumor implantation.

* Mortality evaluated according to tumor size at last biweekly measurement before death.

* Purified diets fed starting 15 days prior to tumor implantation.

* Thymectomy.

duced by the dietary treatment to a similar extent regardless of
the surgical treatment, and the degree of inhibition was comparable
to that seen in previous studies (17, 19). During the 2nd
week, the tumor started to regress in many of the sham-operated
animals. By 10 weeks after implantation, the incidence of com-
plete tumor regression was increased in the sham-operated ani-
mals, however, this increase was almost completely pre-
vented. In fact, in these mice, the incidence of regression was
only slightly higher than that seen in mice fed the complete diet.
Most of the animals died bearing tumors larger than 11 mm in
average diameter. On the basis of experience in this laboratory,
mortality was attributed to the growth of S-180 when the
average diameter of the tumor was greater than 11 mm at the
time of death. About 10-35% of the neonatally thymectomized
Swiss mice died due apparently to wasting disease. Most of these
animals died prior to tumor implantation.

The results obtained when thymectomy was performed 2-5
days after birth are summarized in Table 2. In thymectomized
mice fed the complete diet, the growth of the tumor was slightly
faster than that in sham-operated littermates, and no tumor was
rejected. In mice fed the vitamin B6-deficient diet, the effects
attributable to thymectomy were comparable to those seen in
neonatally thymectomized mice in terms of both the rate of
tumor growth and the incidence of complete tumor regression.
A comparison of the data reported in Tables 1 and 2 suggests
that a fairly constant proportion of littermates is capable of
developing immunologic competence in the absence of the
thymus.

The growth of the tumors which did not regress in mice
operated within 4 days after birth is shown in Chart 1. It is ap-
parent that, under each dietary condition, the size of S-180 was
comparable regardless of surgery when it was evaluated at the
end of the 1st week after implantation. Also, a comparison of
these data with those reported in Tables 1 and 2 indicates that
at this time the average size of the tumors which did not ulti-
mately regress was similar to that of tumors which regressed.
Thus, in these experiments, as well as in those reported previ-
ously (17), no correlation was seen between initial tumor growth
retardation and ultimate tumor regression. At the end of the
2nd and 3rd week after implantation, the tumor was larger in
the thymectomized mice than in the sham-operated animals. For
each dietary condition, these differences were statistically signifi-
cant at the 5% level. In contrast, the differences noted between
the 2 groups of B6-deficient animals at the end of the 4th week
and later were not statistically significant. At each week, the
difference between the average diameter of the tumor in sham-
operated mice fed the complete diet and that in thymectomized
B6-deficient animals was statistically significant at the 5% level.

The relationship between time of thymectomy and incidence of
tumor regression is shown in Chart 2. The few mice in which
the tumor was smaller than 11 mm and was not growing pro-
gressively at the time of death were excluded from this evalua-
tion. The incidence of regression in the vitamin B6-deficient mice
was reduced in animals which had been thymectomized within
5 days after birth but was not significantly altered in animals
thymectomized 9 or 30 days after birth.

The data summarized in Table 3 demonstrate the causal rela-
tionships between neonatal thymectomy and reduction of the
incidence of S-180 regression. The differences in tumor growth
and regression seen between sham-operated and thymectomized
B6-deficient mice were comparable to those reported in Tables 1
and 2. In neonatally thymectomized mice which had received a
s.c. thymus autograft, the effects of the dietary treatment were
indistinguishable from those in sham-thymectomized animals.
Thus, replacement of the ablated organ restored the thymic
function responsible for the development of the capacity of the
host to bring about the regression of the tumor. The patterns of
tumor growth and regression in splenectomized vitamin B6-
deficient mice were not significantly different from those seen in
the corresponding sham-operated littermates (Table 3).

The experiments summarized in Table 4 were carried out in

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**TABLE 2**
Effects of Dietary Vitamin B<sub>6</sub> Deficiency on Sarcoma 180 in HaICR Swiss Mice Thymectomized a Few Days after Birth

<table>
<thead>
<tr>
<th>Diet</th>
<th>Surgery</th>
<th>Day of surgery</th>
<th>No. of mice</th>
<th>8th day</th>
<th>15th day</th>
<th>10th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality (%)</td>
<td>Survival of tumor-free mice (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All mice (%)</td>
</tr>
<tr>
<td>Complete diet&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All mice (%)</td>
</tr>
<tr>
<td>Sham</td>
<td>2–4</td>
<td>42</td>
<td>+3.0</td>
<td>11.2 ± 2.6</td>
<td>+0.2</td>
<td>7</td>
</tr>
<tr>
<td>Thy X</td>
<td>2–4</td>
<td>22</td>
<td>+3.3</td>
<td>13.4 ± 3.7</td>
<td>−1.9</td>
<td>12</td>
</tr>
<tr>
<td>Sham</td>
<td>5</td>
<td>6</td>
<td>+2.6</td>
<td>14.5 ± 4.1</td>
<td>+1.9</td>
<td>8</td>
</tr>
<tr>
<td>Thy X</td>
<td>5</td>
<td>22</td>
<td>+2.5</td>
<td>15.5 ± 3.4</td>
<td>−1.3</td>
<td>18</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt;-deficient diet&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All mice (%)</td>
</tr>
<tr>
<td>Sham</td>
<td>2–4</td>
<td>44</td>
<td>+1.5</td>
<td>5.7 ± 0.6</td>
<td>+1.3</td>
<td>3</td>
</tr>
<tr>
<td>Thy X</td>
<td>2–4</td>
<td>43</td>
<td>+0.3</td>
<td>5.6 ± 2.6</td>
<td>−0.2</td>
<td>9</td>
</tr>
<tr>
<td>Sham</td>
<td>5</td>
<td>46</td>
<td>+0.1</td>
<td>9.6 ± 3.2</td>
<td>−0.2</td>
<td>0</td>
</tr>
<tr>
<td>Thy X</td>
<td>5</td>
<td>36</td>
<td>+1.4</td>
<td>9.7 ± 3.4</td>
<td>+1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Counted from the time of birth.
* Average change of body weight from that on the day of tumor implantation.
* Mortality evaluated according to tumor size at last biweekly measurement before death.
* Purified diets fed starting 15 days prior to tumor implantation.
* Thymectomy.

**CHART 1.** Growth of Sarcoma 180 in mice subjected to thymectomy or a sham operation within 4 days after birth. The number on top of each point represents the number of mice surviving at the time indicated. X—X, sham-operated, complete diet; X—X, thymectomized, complete diet; •—•, sham-operated, B<sub>6</sub>-deficient diet; •—•, thymectomized, B<sub>6</sub>-deficient diet.

In order to investigate the effects of neonatal thymectomy on the survival of skin grafts in Swiss mice fed the complete or the vitamin B<sub>6</sub>-deficient diet. In neonatally thymectomized mice fed the complete diet, the survival of skin grafts from C57Bl/6/Ja mice was slightly prolonged with respect to that in control animals, and in only 1 case did the graft appear to be viable 30 days after transplantation. In the other experiment performed by Hauschka's technic (Lines 3–5), the survival of the graft was only slightly prolonged in intact mice fed the B<sub>6</sub>-deficient diet. In contrast, in neonatally thymectomized mice fed the vitamin-deficient diet, the survival of the C57Bl/6/Ja skin graft was significantly prolonged, and 30-day "takes" with hair growth were seen in about one-third of the cases. Comparable differences were observed in an experiment performed using Billingham's free graft technique. Also, when DBA/2 mice were used as skin donors the greatest prolongation of graft survival was observed in neonatally thymectomized mice fed the vitamin B<sub>6</sub>-deficient diet. The evaluation of the skin graft survival was terminated at 30 days. All the animals were then fed the complete diet for 2–4 weeks to allow vitamin repletion. At the end of this period the animals were again fed the corresponding diets. They were implanted with S-180 2 weeks later. In each group, tumor growth and regression were comparable to the results shown in Tables 1 and 2.
DISCUSSION

The investigation described herein is concerned essentially with the relationships between the effects of a therapeutic treatment against a tumor and those against the immunologic host response elicited by that tumor. Knowledge gained in the study of such relationships is potentially important in cancer chemotherapy. The data described cannot contribute directly to basic knowledge in the area of tumor-specific immunity since S-180 is a so-called nonspecific tumor growing in noninbred mice. When this transplantable tumor is implanted in Swiss mice, however, the antigenic differences between tumors and hosts are slight enough to permit the progressive growth of the tumor in no less than 80–100% of the cases. As a consequence, this tumor-host system provides a model useful in the study of the balance between the effects of therapy against tumor and against immunity under circumstances in which weak antigenic differences exist between tumor and host. Within this frame of reference the fact is rather immaterial that nonspecific tumor antigens, and not tumor-specific antigens, are probably involved in determining the antigenic differences between tumor and host.

The concept that the growth of tumors is conditioned by a balance between the proliferative capacity of tumor cells and the efficiency of the host defenses directed against these cells requires evaluation of the extent to which this balance can be altered by treatments affecting either or both of these 2 factors. Although favorable alteration of this balance might be achieved by some chemotherapeutic agents, truly curative effects have not been seen in the case of primary tumors in autochthonous mice except when surgical procedures were applied in conjunction with chemotherapy (14). Even among the various transplantable tumors used for chemotherapeutic studies, there are only a few examples of complete cures. In most of these cases it is likely that specific host immunity actually contributed to the therapeutic effects seen. For example, the curative effects of certain therapeutic agents observed in CD8 or BDF1 mice inoculated with leukemia L1210 (L1210) were accompanied by the development of host resistance to reimplantation of the same leukemia (9, 26). Since this effect was not clearly seen in the DBA/2 strain of mice, the question may be asked whether the curative effect was partly due to an immunologic response to L1210 specific antigens or to a phenomenon similar to hybrid immunity.

TABLE 3
Causal Relationship between Neonatal Thymectomy and the Prevention of Sarcoma 180 Regression

<table>
<thead>
<tr>
<th>Diet</th>
<th>Surgerya</th>
<th>No. of mice</th>
<th>8th day</th>
<th>15th day</th>
<th>10th week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\Delta ) body weight (gm)*</td>
<td>Average tumor diameter ± S.D. (mm)</td>
<td>(\Delta ) body weight (gm)*</td>
</tr>
<tr>
<td>Complete diet</td>
<td>Sham</td>
<td>16</td>
<td>+2.0</td>
<td>10.8 ± 2.0</td>
<td>-2.6</td>
</tr>
<tr>
<td>Vitamin B6-deficient diet</td>
<td>Sham</td>
<td>29</td>
<td>+0.2</td>
<td>7.3 ± 1.3</td>
<td>-1.6</td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>13</td>
<td>-0.6</td>
<td>7.4 ± 1.0</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>Thy X + Thy</td>
<td>31</td>
<td>+0.3</td>
<td>8.0 ± 2.0</td>
<td>-2.4</td>
</tr>
<tr>
<td></td>
<td>Spleen X</td>
<td>38</td>
<td>+1.2</td>
<td>6.5 ± 1.3</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

* Surgery was performed within 24 hr from birth. Thy X = thymectomy; Thy graft = thymus autograft implanted s.c.; Spleen X = splenectomy.

* Average change of body weight from that on the day of tumor implantation.

* Mortality evaluated according to tumor size at last biweekly measurement before death.

* Purified diets fed starting 15 days prior to tumor implantation.

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Thus, the antigenic differences between S-180 and HalCR Swiss mice appear to be sufficiently marked to be still recognized after thymectomy of adult mice, provided that the tumor is implanted within 5 days after birth greatly reduced the incidence of regression of S-180 in the vitamin-depleted animals. It is well known that the development of immunologic competence in mice is dependent upon the presence of the thymus (15, 24). Neonatal ablation of this organ prevents or reduces the capacity of the animals to reject normal and neoplastic tissues differing at a strong H locus, whereas thymectomy of adult mice has no such effect (15). The rejection of tissues differing in weak histocompatibility systems is also impaired when adult mice are thymectomized (15). In view of these findings, the observation that thymectomy of HaICR Swiss mice performed within 5 days from birth markedly impairs the overall effects seen. These are the therapeutic effects. Thymectomy of adult mice did not affect the incidence of regression of S-180 in the vitamin-depleted animals. Thus, the antigenic differences between S-180 and HalCR Swiss mice appear to be sufficiently marked to be still recognized after thymectomy of adult animals, provided that the tumor is impaired by therapeutic treatments.

The immunodepressant action of vitamin B6 deficiency (1, 2, 10) is in contrast to the induction of complete regression of S-180 caused by this dietary treatment in Swiss mice. It is likely that the antitumor effects are dependent upon the degree of selectivity of the treatment, namely, upon the difference between the level of vitamin deficiency required for an effective impairment of the growth of S-180 and that necessary to inhibit the immunologic response of the host. The administration of 4-deoxypyridoxine to vitamin B6-deficient Swiss mice prevented the regression of S-180 otherwise induced by the dietary treatment (21). Other observations also suggested that different functions may be affected to a different extent by the dietary depletion and by the antimetabolite (25). In this study, slight impairment of the rejection of allogenic skin grafts was observed in the vitamin B6-deficient mice. It is noteworthy that survival of the graft was greatly enhanced in neonatally thymectomized mice. On the one hand, the weak effect of the dietary deficiency in prolonging the survival of C57Bl/Ja or DBA/2 skin grafts in Swiss mice suggests that only a minor depression of the immunologic host reaction to the S-180 graft occurs at levels of nutritional depletion sufficient to inhibit the tumor effectively. On the other hand, the decreased rejection of skin grafts in neonatally thymectomized mice depleted of the vitamin is consistent with the prevention of the dietary-induced regression of S-180 seen under similar conditions. Indeed, in this instance thymectomy and dietary deficiency may have synergistic effects.

The results of this study clearly indicate that 2 types of actions are responsible for the overall effects seen. These are the therapeutically induced inhibition of the growth of the tumor and the immunologically dependent regression of the impaired tumor. In fact, the data shown in Tables 1 and 2 and in Chart 1 indicate that the impairment of the growth of S-180 during the 1st week was quite comparable in the nutritionally depleted mice regardless of the type of neonatal surgery performed and regardless of subsequent regression. During the 2nd and 3rd week, however, the tumor grew faster in the thymectomized mice than in the

### TABLE 4

<table>
<thead>
<tr>
<th>Donors</th>
<th>Surgery†</th>
<th>Purified diets‡</th>
<th>Scar formation av. day ± S.D.¶</th>
<th>Time of scar formation※</th>
<th>30th day†† takes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>7-10 days</td>
<td>11-20 days</td>
<td>21-30 days</td>
</tr>
<tr>
<td>C57Bl/Ja</td>
<td>None</td>
<td>CD</td>
<td>8.7 ± 1.0</td>
<td>31/32</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>CD</td>
<td>9.0 ± 3.7</td>
<td>22/29</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>CD</td>
<td>8.6 ± 1.7</td>
<td>9/10</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>BDD</td>
<td>12.7 ± 5.9</td>
<td>10/19</td>
<td>53</td>
</tr>
<tr>
<td>C57Bl/Ja</td>
<td>None</td>
<td>CD</td>
<td>7.7 ± 2.0</td>
<td>10/11</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>BDD</td>
<td>6.1 ± 1.2</td>
<td>10/10</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>BDD</td>
<td>14.4 ± 2.9</td>
<td>1/12</td>
<td>8</td>
</tr>
<tr>
<td>DBA/2</td>
<td>None</td>
<td>CD</td>
<td>10.5 ± 3.7</td>
<td>5/10</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>BDD</td>
<td>10.8 ± 3.6</td>
<td>8/12</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Thy X</td>
<td>BDD</td>
<td>20.6 ± 7.9</td>
<td>1/6</td>
<td>17</td>
</tr>
</tbody>
</table>

* Thymectomy was performed within 3 days from birth. Thy X = thymectomy.
† The purified diets were fed starting 2 weeks prior to skin grafting. CD = complete diet; BDD = vitamin B6-deficient diet.
‡ Counted from the day of skin grafting.
¶ The skin was grafted according to the Hauschka technic.
※ The skin was grafted according to the Billingham free graft technic.
sham-operated ones. Indeed, at this time statistically significant differences in average tumor diameter were found between S-180 growing in sham-operated and in thymectomized B- deficient mice. The observation that a comparable difference also occurred at the same time in mice fed the complete diet indicates that immunologic reactions to the tumor occurred in the absence of therapy. In this case, however, the proliferative capacity of S-180 could not be overcome by the immunologically competent host. Under both dietary conditions the host response became evident during the 2nd week of tumor growth.

The observations that immunologic mechanisms of defense can operate in conjunction with therapeutic treatments in mice inoculated with an antiflc-resistant subline of L1210 (9) or implanted with S-180 have similar implications. With both tumors, the therapeutic treatments alone or the host immunologic reaction alone was unable to cause complete regression. In contrast, the combination of these 2 factors led to cures in a significant number of animals. Effective therapy, therefore, would seem to depend upon the availability of agents sufficiently selective to inhibit the growth of the tumor without impairing the immunologic response of the host.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Messrs. G. Papp and K. Beresenyi for their proficient technical assistance.

REFERENCES

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