Host Defense Mechanisms in the Regression of Sarcoma 180 in Pyridoxine-deficient Mice*

ENRICO MIHICH

(Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York)

SUMMARY

The complete regression of Sarcoma 180 (S-180) in pyridoxine-deficient mice appears to depend upon host defense mechanisms. Whole-body x-radiation of the pyridoxine-deficient mice reduced the incidence of regression of S-180 if administered prior to or up to 3 days after implantation. The incidence of regression was not altered when the depleted mice were irradiated 5 or 7 days after implantation. Displacement of vitamin B6 from x-ray-damaged tissues did not seem to explain the effects observed, since the content of the vitamin in the tumor was not altered by the irradiation.

Feeding pyridoxine to the depleted animals did not alter the incidence of tumor regression if it was begun 11 days after implantation or thereafter. A subline of S-180 capable of growing in pyridoxine-deficient mice (S-180/B6) regresses in mice in which the parent S-180 had previously regressed. The subline was implanted contralaterally to S-180 in pyridoxine-deficient mice at various times after the implantation of the parent tumor. S-180/B6 regressed completely only when it had been implanted 8–14 days after the implantation of S-180.

It is concluded that host defense mechanisms are instrumental in the regression of S-180 in pyridoxine-deficient mice. The host response occurs shortly after tumor implantation but is adequate to bring about the regression of the tumor only 8–11 days after implantation. The nature of the host defense factors involved is discussed in relation to the effects of treatment with 6-mercaptopurine or folic acid antimetabolites.

The progressive growth of experimental neoplasms may be considered to be dependent upon a balance between proliferative and invasive capabilities of tumor cells and the efficiency of host defense mechanisms directed against these cells. Recent observations that host defenses can be elicited in the case of methylcholanthrene-induced tumors, transplanted in compatible inbred mice (17, 48, 49) or similarly induced tumors in the autochthonous host (35), suggest that weak antigenic differences may exist in the case of induced tumors. It is not yet clear whether host factors similar to those involved in allogenic rejection (22) are operating against these experimental neoplasms. The possibility should be considered, however, that similar defense factors may be active in the case of long established transplantable tumors and that, under certain circumstances, they may play a relatively important role against tumors having weak isoantigenic properties.

Although the effects of therapeutic treatments are always accompanied by an alteration of the balance between tumor and host, in most cases the extent to which specific host factors are either activated or depressed during treatment is unknown. Evidence suggesting that host defenses may contribute to the effectiveness of tumor chemotherapy has been obtained only in the case of 6-mercaptopurine (92) and folic acid antimetabolites (21).

Sarcoma 180 (S-180) regresses completely after initial growth in a large percentage of Swiss mice fed a pyridoxine-deficient diet for prolonged periods (38). This tumor is not truly compatible in the Swiss mouse and is rejected in about 5 per cent of the animals. This incidence of rejection does not increase, however, even after treatment with most of those compounds which markedly inhibit its
growth. For this reason the regression of S-180 in pyridoxine-deficient mice, or following therapy with 6-mercaptopurine (11), acquires particular significance and poses questions concerning possible interrelations between these treatments and host defense mechanisms directed against the tumor.

The participation of host defenses in the induction of the regression of S-180 in pyridoxine-deficient mice was suggested by the fact that treatment with cortisone reduced the incidence of regression in the deficient animals. Also, S-180 could not grow progressively in mice fed a complete diet in which a previous implant had regressed completely during a period of depletion of pyridoxine (39). The observation that other tumors, even though significantly inhibited in pyridoxine-deficient hosts, did not regress in other strains of mice (41) suggested that pyridoxine deficiency induces tumor regression only in particular tumor-host relationships.

Further evidence has now been obtained indicating that host defense factors play an essential role in the regression of S-180 in pyridoxine-deficient mice. Total-body irradiation of the host prevented the regression of S-180 when administered before or shortly after tumor implantation. Data obtained also indicate that the defenses of the host, although already activated and radio-resistant by the 5th day after implantation, are able to bring about the regression of S-180 only after 8–11 days of tumor growth.

MATERIALS AND METHODS

The solid form of S-180 was used in these studies (39). A subline (S-180/B6) which is capable of progressive growth in pyridoxine-deficient mice has been described previously (40). The standard procedures followed for the implantation of the tumors, the evaluation of tumor growth, and the preparation of the purified diets have been reported in detail (39). The purified diets were fed beginning on the 15th day prior to tumor implantation, unless otherwise specified. The female HaICR Swiss mice which were used weighed between 17 and 91 gm.

Total-body x-radiation of the animals was administered by a General Electric Maxitron machine, Model 250. The dose was calculated in roentgens (r) per mouse, in air, and was given at 250 kvP and 30 ma. with an HVL of 1.5 mm. Cu. A filter of 0.5 mm. Cu, 1.0 mm. Al was used. Five to ten mice were confined in a polyethylene plastic cylinder (18 cm. diameter, 2.5 cm. height) having uniformly distributed holes in the top to insure adequate air supply. The animals were placed at a skin target distance of 30 cm.

RESULTS

In two preliminary experiments, animals fed the complete or the deficient diet were irradiated either with a single dose of 150 or 350 r given 1 day prior to tumor implantation, or with four doses of 150 r given 13, 9, 5, and 1 days before implantation. In these experiments, all the mice fed the complete diet died with large tumors. Among the groups fed the pyridoxine-deficient diet, the tumor regressed completely in 60 per cent of the nonirradiated mice, and in 40 and 30 per cent of those irradiated with a single dose of 150 and 350 r, respectively. No tumor regressed in the mice irradiated 4 times with 150 r. In view of the reduction of the incidence of tumor regression caused by only a single administration of 350 r, single doses of x-ray were given in all subsequent experiments.

The lethal effects of x-radiation were determined in mice fed the complete or the pyridoxine-deficient diet (Table 1). Tumors were not implanted in these animals. A single administration of 300 or 350 r was not lethal to the deficient animals. Most of the lethally irradiated mice died within 2 weeks, regardless of their nutritional condition.

The irradiation of the host with 850 or 300 r for HaICR mice was suggested by the fact that host defense mechanisms directed against the tumor in pyridoxine-deficient mice, or following therapy with 6-mercaptopurine (11), acquires particular significance and poses questions concerning possible interrelations between these treatments and host defense mechanisms directed against the tumor.

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irradiated. In our experience with S-180, the tumor diameter at the last weekly measurement preceding death has been greater than 11 mm. in more than 90 per cent of the control mice. Very few of these mice died bearing tumors smaller than 8 mm. in diameter. For this reason, in these experiments, mortality was attributed to the growth of S-180 when the tumor was greater than 11 mm. at the time of death. In contrast, mortality was considered due to causes other than tumor growth when the animals died bearing neoplasms smaller than 8 mm. in diameter. Tumor growth and/or other factors were considered responsible for the toxic reversal effects of x-ray than column 6, even though control mice fall into both categories, because x-ray toxicity was mostly evident during the first 2 weeks (see Table 1) and might contribute to the death of mice bearing tumors with diameters from 8 to 11 mm. A ridit analysis of these data was performed using the nonirradiated deficient group as the reference set for the ridit transformation (9, 61). If x-ray had no effect, the average ridit would be about 0.5. If x-ray toxicity was responsible for the death of the animals, the average ridit would be less than 0.5. If x-ray allowed the tumor to kill the host by preventing death of animals bearing neoplasms with average diameter ranging between 8 and 11 mm. The possibility that the reduction of the incidence of regression was due solely to toxicity of the treatments was excluded by the data shown in the table.

A more detailed analysis of all the data obtained when irradiation of the deficient mice was given 1 day prior to tumor implantation was performed. Taking the pyridoxine-deficient nonirradiated group and the control group fed the complete diet as the reference sets (Table 3), response categories were arranged in a ranking order under the heading “Frequency Distribution of Animals.” This order was determined by rational arguments. For example, column 5 is less proof for the non-

### TABLE 2

**EFFECT OF TOTAL-BODY IRRADIATION OF THE HOST ON THE REGRESSION OF S-180 IN PYRIDOXINE-DEFICIENT MICE**

<table>
<thead>
<tr>
<th>PURIFIED DIET*</th>
<th>IRRADIATION† (c/s/sq.cm)</th>
<th>No. Mice</th>
<th>8TH DAY AFTER TUMOR IMPLANTATION</th>
<th>7TH WEEK AFTER TUMOR IMPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Av. Δ weight (gm.)</td>
<td>Mortality (per cent)</td>
</tr>
<tr>
<td>Complete</td>
<td>None</td>
<td>40</td>
<td>+1.3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>40</td>
<td>+0.3</td>
<td>5</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>None</td>
<td>60</td>
<td>+1.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>60</td>
<td>+1.3</td>
<td>2</td>
</tr>
<tr>
<td>Complete</td>
<td>None</td>
<td>50</td>
<td>+0.5</td>
<td>0</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>None</td>
<td>50</td>
<td>+0.9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>40</td>
<td>+0.6</td>
<td>0</td>
</tr>
</tbody>
</table>

* The purified diets were fed starting 2 weeks prior to implantation.
† Total-body irradiation was given 1 day prior to implantation.
‡ No. mice represent three combined experiments for each of the two irradiation doses.
§ Average change in body weight from that on day of implantation.
# Mortality data obtained within 7 weeks of observation are subdivided according to the tumor size observed at the last weekly measurement preceding death.

In view of the evidence that vitamin B₆ could be transferred from other tissues to regenerating liver in pyridoxine-deficient animals (5), the possibility was considered that this vitamin may be liberated from tissues damaged by the irradiation, thereby becoming available to the tumor. A microbiological determination of the content of the vitamin in tumors and livers was performed using *Saccharomyces carlsbergensis* as the test organism. As shown in Table 4, the amount of vitamin found in S-180 grown in pyridoxine-deficient mice was...
about one-fourth of that found in tumors grown in mice fed the complete diet, thus confirming previous observations (40). Since irradiation did not cause any increase in the amount of vitamin in tumors grown in the deficient mice, the prevention of regression observed cannot be attributed to the transfer of the vitamin from the irradiated host tissues to the tumors.

It was of interest to see whether irradiation of the host prior to tumor implantation could alter the rate of growth of the tumors which did not regress. Results of one experiment are reported in Chart 1. The group of irradiated mice fed the complete diet was omitted from the chart, because it was similar in all respects to the corresponding nonirradiated control group. The prevention of the regression of S-180 in the irradiated pyridoxine-deficient animals is graphically shown in the upper part of the chart. No tumor regressed in the mice fed the complete diet. As expected, S-180 grew rapidly in the animals fed the complete diet, and all the hosts died. The tumor did not regress in seven of the pyridoxine-deficient mice. The growth of these tumors during the first week was only slightly greater than that, not shown, of the tumors which did eventually regress and which had the average size of 5.0 mm. in diameter at the first weekly measurement. Each of the seven tumors partially regressed during the second week.
but resumed its progressive growth thereafter. Sarcoma 180 did not regress in 27 pyridoxine-deficient mice which had been irradiated. In this group the tumor partially regressed during the 2d week in only four out of the seventeen surviving mice, whereas it continued to grow in the other thirteen. During the following weeks the rate of growth of all the tumors was similar regardless of irradiation. The major difference attributable to the irradiation of the host was evident, therefore, during the 2d week of tumor growth.

The influence of the time of irradiation, relative to the day of tumor implantation, on the prevention of the regressions is shown in Table 5. The mortality data are presented in the same way as in Table 2 for the reasons already outlined. The growth of S-180 during the 1st week was not significantly altered by the irradiation given either prior to or after the implantation. The incidence of complete regression of the tumors was decreased only in deficient animals irradiated prior to or within 8 days from the day of implantation. The exposure of the transplanted tumors to the radiation shortly after implantation did not decrease their rate of growth. The greatest reduction of regressions was seen in mice which were irradiated 1 day after implantation. It is interesting to note that regression occurred in 80 per cent of animals fed a complete diet and irradiated with 350 r 7 days after implantation. A direct effect of the radiation on the 7-day-old tumors or a rebound response of host defense factors may have contributed to this effect.

The dietary treatment which conditions the regressions of S-180 may be necessary only until a certain time after implantation, after which feeding vitamin B₆ to the depleted mice may no longer prevent the tumor regression due to the host response. Results obtained in three out of five experiments designed to test this possibility are reported in Chart 2. The results of the remaining two experiments are not included, because many of the tumors regressed completely during the 2d week, thus preventing the completion of the experiments. The incidence of regression was markedly reduced in animals fed the complete diet beginning 1, 5, or 8 days after implantation, but it was only slightly altered when pyridoxine was included in the diet at the end of the 92d week of tumor growth. The fate of S-180 did not depend upon its size at the time pyridoxine was fed. Some tumors as small as 3.5 mm. in diameter resumed their growth when the vitamin was given as late as 15 or 18 days after implantation, whereas other tumors of 8.0 mm. in diameter or more continued to regress in spite of the dietary change. In these experiments the maximum size reached by individual tumors which eventually regressed completely in control mice fed the deficient diet for the whole period of observation ranged between 9.92 and 9.9 mm. in diameter (average, 6.0 mm.).

Other experiments were designed to determine the time at which host defense factors become capable of mediating the regression of the tumor. The subline of S-180 capable of growing progressively in pyridoxine-deficient mice (S-180/B₆) regresses completely after initial growth in mice in which S-180 had previously regressed during a period of pyridoxine depletion. The three experiments reported in Table 6 were designed to find out whether S-180/B₆ grows progressively or regresses when implanted in pyridoxine-deficient mice at various times after the contralateral implantation of the parent tumor. The regression of S-180/B₆ occurred in a large percentage of mice only when this tumor had been implanted 8 or 14 days after the implantation of S-180. This is also the time at which feeding pyridoxine to the deficient animals failed to prevent the regression of S-180 (see Chart 2).

1 Unpublished observations.
### TABLE 5

**Effect of the Time of Irradiation of Host on the Regression of S-180 in Pyridoxine-Deficient Mice**

<table>
<thead>
<tr>
<th>Purified diet*</th>
<th>Irradiation (r/mouse)</th>
<th>Day of irradiation†</th>
<th>No. mice</th>
<th>8th day after tumor implantation</th>
<th>7th week after tumor implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>None</td>
<td>30</td>
<td>20</td>
<td>+1.6 +10 11.8±1.3</td>
<td>98 98 0 0 0 7</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>350</td>
<td>7+</td>
<td>20</td>
<td>+2.0 5 12.2±1.8</td>
<td>70 60 0 0 80</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>None</td>
<td>40</td>
<td>40</td>
<td>+2.2 3 6.1±2.3</td>
<td>10 5 0 0 80</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>350</td>
<td>7+</td>
<td>40</td>
<td>+1.9 3 8.0±2.3</td>
<td>75 33 28 28 20</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>None</td>
<td>40</td>
<td>40</td>
<td>+1.0 0 5.7±1.8</td>
<td>35 0 30 5 63</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>350</td>
<td>7+</td>
<td>40</td>
<td>+1.6 0 14.3±3.1</td>
<td>98 98 0 0 1</td>
</tr>
</tbody>
</table>

* The purified diets were fed starting 2 weeks prior to implantation.
† Total-body irradiation was given on the days indicated, counted from that of tumor implantation.
‡ No. mice represent three combined experiments for the 350-r dose, and five combined experiments for the 500-r dose.
§ Average change in body weight from that on day of implantation.
¶ Mortality data, obtained within 7 weeks of observation, are subdivided according to the tumor size observed at the last weekly measurement preceding death.

**DISCUSSION**

The growth of transplantable tumors is thought to be regulated by immunogenetic mechanisms similar to those which control the transplantation of normal tissues (53). The proliferative and toxic features of the neoplastic cell population and its fluctuating cytogenetic character (27) are, however, superimposed on these regulatory mechanisms and can alter the relationship between graft and host. Thus S-180, a nonstrain-specific type of tumor, takes in 100 per cent and grows progressively in 90 to 95 per cent of HaICR Swiss mice, animals which are not inbred and cannot be considered genetically compatible for this tumor. A selective therapeutic pressure might be expected to impair a tumor such as S-180 and to favor the activity of weak immunogenetic host mechanisms directed against it. Available experimental data, however, do not substantiate this expectation.

On the one hand, severe growth inhibition of S-180 by such potent carcinostatic agents as N-methyl-formamide (10), or 6-diazo-5-oxo-L-norleucine (DON) (12), is followed by progressive growth of the inhibited tumor upon cessation of treatment. A simultaneous specific inhibition of
host defense mechanisms by these drugs may explain why the impaired tumor is not rejected. On the other hand, the regressions of S-180 following treatment with 6-mercaptopurine (11) may be carried out by host defense mechanisms (62). Recent observations have indicated, however, that 6-mercaptopurine inhibits the inductive (7, 52, 55) and perhaps the productive (13, 52) phases of antibody formation, and prolongs survival of skin homografts (58, 64). Also, the participation of host defense mechanisms in some of the chemotherapeutic effects of folic acid antimetabolites is suggested by the observation that a subline of leukemia L1210 resistant to antifolics (L1210—M46R) regress in (DBA/2J X BALB/cAn)F1 mice treated with 3',5'-dichloroamethopterin, in which the sensitive parent L1210 is regressing (91). In addition, mice in which L1210 regressed following antifolic therapy are resistant to reinoculation with the same tumor (90). According to the "laws of transplantation" (53), L1210, a DBA/2 specific tumor, would not be expected to elicit a typical homograft reaction in the host used. Indeed, evidence indicating that F1 hybrids are not immunologically neutral toward grafts from either of the parental stock (14, 26, 28) may be pertinent to the findings with L1210. Also, the regression of choriocarcinoma, a tumor of fetal origin, in patients treated with amethopterin (29, 31, 36) may be related to host mechanisms similar to those active in F1 hybrids (19). Nevertheless, the regression induced by the antifolics must be reconciled with the observations that amethopterin itself inhibits antibody formation (18) and prolongs homograft survival (21, 47, 63).

The observation that the regression of S-180 in pyridoxine-deficient mice can be prevented by treatment with cortisone suggested that host factors may be involved in the effects of the specific dietary treatment. This possibility was further supported by the fact that mice, in which the tumor had regressed during a period of deficiency, were resistant to reimplantation of S-180 (39). This resistance may be analogous to that observed in other circumstances (1, 8, 15). Results of the present investigation provide additional evidence that host defense mechanisms are indeed essential for these regressions.

Single total-body x-radiation of pyridoxine-deficient mice reduced the incidence of complete regression of S-180 only when administered prior to or up to 3 days after implantation. Irradiation

### TABLE 6
GROWTH AND REGRESSION OF S-180/B6 IN PYRIDOXINE-DEFICIENT MICE PREVIOUSLY GIVEN IMPLANTS OF S-180

<table>
<thead>
<tr>
<th>Purified diets*</th>
<th>Tumor</th>
<th>Day of implantation of S-180/B6†</th>
<th>No. mice</th>
<th>Week preceding death av. tumor diam. (MM.)</th>
<th>8th week after implantation of S-180</th>
<th>Complete regression (per cent)</th>
<th>Survival mice without tumors (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>S-180</td>
<td>29</td>
<td>30</td>
<td>19.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyridoxine-deficient</td>
<td>S-180</td>
<td>0</td>
<td>30</td>
<td>8.3</td>
<td>58</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>S-180/B6</td>
<td>0</td>
<td>30</td>
<td>16.0</td>
<td>13</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>S-180/B6</td>
<td>5</td>
<td>20</td>
<td>14.0</td>
<td>50</td>
<td>80</td>
<td>5</td>
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<td></td>
<td>S-180/B6</td>
<td>8</td>
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<td></td>
<td>S-180/B6</td>
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<td>30</td>
<td>16.4</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>S-180/B6</td>
<td>8</td>
<td>30</td>
<td>16.4</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
</tbody>
</table>

* The purified diets were fed starting 2 weeks prior to implantation of S-180.
† Day of implantation of S-180/B6 counted from the day of implantation of S-180.
‡ Tumor diameters observed at the last measurement taken prior to the death of the animals within the 8 weeks of observation.
§ Tumors implanted bilaterally in the same mice.
of the depleted animals 5 or 7 days after implantation did not alter the incidence of regressions. Yet, host factors seem particularly effective during the second week of implantation (see Chart 1). It is possible that, 7 days after implantation, the host defenses are at a radioresistant phase. The data also suggest that the growth inhibition of S-180 caused by the nutritional deficiency is distinguishable from the subsequent tumor regression which seems dependent upon radiosensitive host defense factors.

The experiments in which pyridoxine was fed in the depleted mice beginning at various times indicate that, about 10 days from the implantation of S-180 and thereafter, the host is capable of bringing about the complete regression of the neoplastic graft despite the dietary change. The intrinsic growth capacity of S-180 does not seem to be the critical factor in the ultimate regression if evaluated on the basis of the size of the tumor. Alternatively, the regression of the tumor may be dependent upon the establishment of irreversible damage to the neoplastic cells, not correlated with the size of the tumor. Although irreversible cellular damage induced by specific antibodies has been observed (28, 43), such injury may also be the result of a metabolic alteration caused by the vitamin depletion. It appears to be most likely that host defense factors are effective only at a certain time after tumor implantation and are the determining mechanism for the ultimate regression of S-180. This possibility is also consistent with the results of the experiments in which S-180/B₆ implanted contralaterally in deficient mice already bearing S-180, regressed completely only when it had been implanted about 10 days after the implantation of S-180 (see Table 6).

The over-all evidence reported seems to indicate that, in pyridoxine-deficient mice, host defense mechanisms are activated shortly after the implantation of the tumor and that this activation can be inhibited by whole-body x-radiation. The host response, however, does not become able to bring about the regression of the tumors until approximately 10 days after implantation. At this time both the parent S-180 and the resistant subline S-180/B₆ are subject to the defenses of the host.

The nature of the defense mechanisms operating against S-180 and S-180/B₆ in pyridoxine-deficient mice is unknown at present. The possibility that antibodies are formed against these tumors must be considered. The effects of x-ray, and the time element apparent from all the experiments described, suggest a parallel with analogous observations made in relation to antibody responses (37, 59). This possibility is further supported by the fact that in two experiments the resistance to re-implantation of S-180 could not be altered by x-radiation of mice in which the tumor had previously regressed. The lack of effects of x-ray in this case is reminiscent of the analogous inability of irradiation to alter a secondary immune response (51, 58–60).

The hypothesis that antibodies are instrumental in the regression of S-180 in pyridoxine-deficient mice is, however, not consistent with the observations that antibody formation is markedly depressed in animals depleted in vitamin B₆ (8, 4, 25, 57) or treated in addition with 4-deoxypyridoxine (2, 3, 56). Although the depression of antibodies was apparent in various species including Swiss mice (25), the possibility of strain-specific differences in such response cannot be excluded. A selective inhibition of the tumor may also be the basis for the apparent paradoxical picture considered.

Complete regressions of S-180 have been observed in mice infected with Bacillus Calmette-Guérin (BCG) (44). In addition, the phagocytic activity of the reticuloendothelial system (RES) has been correlated with the growth of S-180 (45). If an RES stimulation occurs in the pyridoxine-deficient mice and plays a role in the host reaction leading to the regression of S-180, this stimulation should be of the proliferative, estradiol-induced (34) rather than of the endotoxin-induced type (30), since only the former is inhibited by ionizing radiations (33). Interestingly, endotoxin treatment, although it causes hemorrhagic necrosis of S-180 (42) is by far less effective than BCG infection in inducing tumor regression (45). Furthermore, administration of Zymosan, a yeast polysaccharide causing rejection of S-180 (8), induces RES stimulation (6, 50) of the proliferative type (50). The possibility that stimulation of the RES is related to the regression of S-180 in pyridoxine-deficient mice deserves investigation.

An enhancement of tumor growth by specific antibodies has been clearly demonstrated in certain cases (23, 54), even though the mechanism by which it occurs is not yet completely understood (32). It is possible that HaICR Swiss mice form specific antibodies which enhance the growth of S-180. Pyridoxine deficiency might limit the production of antibodies; thus, the formation of enhancing antibodies may be reduced and the tumor cells in the treated animals be exposed to the effects of host cellular defenses. These cellular defenses are, in turn, likely to be inhibited in the x-radiated deficient mice. This hypothesis, which

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1 Unpublished observations.
admittedly lacks direct experimental evidence, would reconcile the paradox discussed previously.

A question of paramount importance is whether the host defense mechanisms which are instrumental in the regression of S-180 in pyridoxine-deficient mice can be expected to operate also against autochthonous neoplasms. The same question is directed against autochthonous tumors in animals treated with 6-mercaptopurine (38, 64) or antifolics (63). Further work is required to clarify whether some of these defense mechanisms are in any way related to the host defenses which are directed against autochthonous tumors in animals (35, 48) or, possibly, in humans (24).

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Host Defense Mechanisms in the Regression of Sarcoma 180 in Pyridoxine-deficient Mice

Enrico Mihich