Suppression of the Immune Response to Antigenic Tumors in Isogenic Mice by Whole-Body Irradiation

WERNER ROSENAU AND HENRY D. MOON

Department of Pathology and Cancer Research Institute, School of Medicine, University of California San Francisco Medical Center, San Francisco, California 94122

SUMMARY

It is known that sarcomas induced in mice with 3-methylcholanthrene (MCA) bear tumor-specific antigens which evoke specific immune responses when transplanted to isogenic animals. In this study, MCA-induced sarcomas were transplanted to isogenic C3H mice and the effect of immune suppression by whole-body X-irradiation on tumor growth was examined. The role of radiation dose, interval between irradiation and transplantation, and age was evaluated in animals irradiated before transplantation. The results obtained in animals irradiated before transplantation were compared with those in animals irradiated after transplantation.

Whole-body irradiation prior to transplantation resulted in marked acceleration of tumor growth. The degree of acceleration varied with the size of the dose—within certain limits; 200 rads given 24 hours before transplantation resulted in significant acceleration of growth compared to tumor growth in nonirradiated controls. The rate of growth further increased with a dose of 300 rads; additional increases in dose did not result in further acceleration of tumor growth. However, above 400 rads, a predictable increase in radiation mortality was encountered. The effect of irradiation with 400 rads on tumor growth varied inversely with the time between irradiation and tumor transplantation. The maximum effect was observed with a 24-hour interval; the degree of acceleration of tumor growth decreased as the interval was lengthened—some acceleration was still noted at a 4-month interval. No age related differences in effect were evident in the range 2-15 months of age; however, only a few animals older than 12 months were included in the study. In contrast to these findings, tumor growth was not accelerated when irradiation followed transplantation.

INTRODUCTION

It has been well established that tumors arising in experimental animals have tumor-specific antigens which may evoke immune responses in the primary host as well as in isogenic animals upon transplantation (6, 9). Immune responses may affect neoplasms in a number of ways. Tumor growth may be retarded by the host reaction. Or, the period of tumor induction may be altered: tumors induced in neonatally thymectomized animals may appear under some experimental conditions earlier, on the average, than tumors induced in intact animals, as shown by Miller et al. (8) and by Rosenau and Moon.2 The degree of antigenicity and the rate of tumor growth may be influenced by a selective action of the immune response of the host. By extension, then, it is conceivable that neoplastic change is a relatively common event at the cellular level, but that immune responses often destroy evolving neoplastic cells before tumors have grown sufficiently large for detection.

The most frequently used approaches to the study of tumor-specific antigens have been immunization of intact animals, with subsequent challenge by viable tumor cells, and in vitro tests for humoral and cell-related antibodies. Recently, immune reactions to tumor-specific antigens have also been investigated by comparing the growth of antigenic tumors transplanted to intact animals and to animals made immunologically deficient by whole-body exposure to X-rays. However, the radiobiologic factors involved have not been examined in detail. It was our purpose in the experiments reported here to investigate a number of these factors which affect the growth of antigenic tumors transplanted to isogenic mice. The studies with irradiation preceding transplantation of tumors included varying such factors as the radiation dose, the length of the interval between irradiation and tumor transplantation, and the age of the animals at the time of irradiation. Studies were also carried out with irradiation following transplantation, and the findings were compared with those when irradiation preceded transplantation.

MATERIALS AND METHODS

Animals. All animals used in the experiments were male C3H/Crgl mice. Their isogenicity was tested by the exchange of skin grafts among animals chosen at random from the stock. The grafts were observed for periods ranging from 7 to 12 months; no rejections were seen.

Tumors. The three tumors used in this study were induced by intramuscular injection of 0.1 mg of 3-methylcholanthrene

1 Neonatal C3H/Crgl mice were divided into two groups; the first group comprised intact control animals; the animals of the other group were totally thymectomized within 24 hours after birth. The animals of both groups were injected intramuscularly with 0.1 mg of MCA at 21 days of age. The average induction period for sarcomas at the site of injection was 122 days for the control animals and 75 days for the thymectomized animals. The difference was significant by t-test, P < 0.01 (unpublished data).

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(MCA). Tumor 1 was induced in a neonatally thymectomized mouse and Tumors 2 and 3, in intact adult mice. Tumor 1 was a poorly differentiated rhabdomyosarcoma; Tumors 2 and 3 were poorly differentiated spindle-cell sarcomas.

Antigenicity of Tumors. The antigenicity of the tumors was established by two methods, namely, immunization and subsequent challenge with viable tumor cells (14) and comparison of tumor growth in normal and immune suppressed animals (12). These methods, described in detail previously, are also outlined briefly below.

1. Immunization and challenge: The minimum number of tumor cells that consistently resulted in the growth of tumors in intact animals upon transplantation was determined by injecting graded concentrations of enzymatically dissociated, viable tumor cells into groups of 4 mice each; these mice were observed for the appearance of tumors for 2 months. Several tumors were resected when they had grown to a size ranging from 1.0 to 1.5 cm. One week after resection, the animals were challenged with cells derived from the same tumor. Twice the number of tumor cells that consistently resulted in tumor growth in untreated, intact animals were used for challenge. The failure of tumors to appear upon challenge in animals with previously resected tumors was regarded as evidence of an immune response. The immune reaction was highly specific; immunization with any one tumor was regarded as evidence of an immune response. The immune reaction was highly specific; immunization with any one tumor protected only against challenge with cells derived from the same tumor.

2. Comparison of tumor growth in intact and immune suppressed animals: Tumor cells were injected in graded doses into groups of intact mice to determine the minimum number of cells that consistently resulted in the appearance of a tumor upon transplantation. Each dose group had 4 animals; the time of observation was 2 months. Graded numbers of cells were also injected into mice irradiated with 400 rads 24 hours prior to transplantation to suppress their immune responses. The difference in the number of cells required for growth in intact and in irradiated animals was used as a measure of the antigenicity of the tumor cells.

The antigenicity of all 3 tumors was demonstrated by both methods.

Transplantation of Tumors. A suspension of single tumor cells was prepared by enzymatic dissociation, and their viability was determined by the trypan blue-eosin dye exclusion test, as described previously (14). For transplantation, twice the minimum number of viable tumor cells that consistently resulted in tumor growth upon transplantation to intact animals (as described above) was injected intramuscularly into the left leg. In the case of Tumor 1, this number was 1.5 x 10^6 cells; in the case of Tumors 2 and 3, the number was 5 x 10^5 cells.

X-ray Exposure and Shielding. Both the whole-body-irradiated and the leg-shielded mice received a single exposure. For irradiation, the animals were placed in a wooden box which was divided by Plexiglas partitions into 24 sections. Each section was just large enough to immobilize one animal. The radiation factors were: 250 kv; 30 ma; Thoraeus filter No. 2; HVL 2.1 mm Cu; target distance 80 cm; dose rate 34 rads/min. The difference in dose delivered to the center and to the periphery of the exposure box was <5%.

In the first experiment, the dose delivered to the animals was varied from 200 to 600 rads by varying the exposure time; in all other experiments in which irradiation preceded transplantation, the dose was kept constant (400 rads). In the experiments with irradiation following transplantation, 350 rads and 400 rads were employed. In the latter experiments, the hind leg of some animals was shielded from the X-ray beam with tubular lead shielding 4 mm thick.

Examination of Tumors and Other Tissues. The animals were sacrificed and the leg which had received the transplant was dissected. The tumor was removed, freed of adherent tissue, and weighed on an analytic balance. The significance of differences in tumor weights was evaluated statistically by t-test. The tumors, regional lymph nodes, spleens, and—in two experiments—also the femurs were studied histologically. The tissues were fixed in Zenker's solution, embedded in paraffin, cut at 5 μ, and stained with hematoxylin and eosin.

EXPERIMENTAL DESIGN AND RESULTS

The investigation comprised 5 groups of experiments. In the first 4 groups, X-irradiation preceded transplantation; in the

<table>
<thead>
<tr>
<th>X-ray dose (rads)</th>
<th>Tumor weight (mg)</th>
<th>Significance of difference by t-test (P)</th>
<th>Mice used</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (control)</td>
<td>89 ± 37</td>
<td></td>
<td>8/8</td>
</tr>
<tr>
<td>200</td>
<td>344 ± 90</td>
<td>&gt;0.05</td>
<td>8/8</td>
</tr>
<tr>
<td>300</td>
<td>560 ± 65</td>
<td>&lt;0.025</td>
<td>8/8</td>
</tr>
<tr>
<td>400</td>
<td>600 ± 66</td>
<td>&lt;0.001</td>
<td>10/9</td>
</tr>
<tr>
<td>500</td>
<td>487 ± 83</td>
<td>&lt;0.001</td>
<td>12/8</td>
</tr>
<tr>
<td>600</td>
<td>588 ± 62</td>
<td>&lt;0.001</td>
<td>12/2</td>
</tr>
</tbody>
</table>

TABLE 1

X-ray Dose and Tumor Growth: Irradiation 24 Hours before Transplantation

CHART 1. Effect of radiation dose. The average weight of the transplanted antigenic tumors increased with X-ray dose up to 300 rads; higher doses did not result in further increase in tumor weight. Up to 300 rads, there were no deaths due to the irradiation; above this, radiation mortality of the host increased with dose. The interval between irradiation and subsequent transplantation was 24 hours. The period of tumor growth after transplantation was 21 days. Tumor 1.
fifth, transplantation preceded irradiation. The tumors were of the 2nd or 3rd transplant generations; later transplant generations were not used, to avoid the frequently observed loss of antigenicity of MCA-induced sarcomas with successive transplant generations.

**IRRADIATION BEFORE TRANSPLANTATION**

**Effect of Radiation Dose. Procedure.** Five groups of 8 to 12 mice, 8 weeks of age, received 200, 300, 400, 500, and 600 rads, respectively. A group of 8 nonirradiated animals served as controls. Twenty-four hours after the time of irradiation, all animals, both irradiated and control, received an injection of cells from Tumor 1 (see Materials and Methods). Twenty-one days after transplantation the experiment was terminated.

**Results.** All animals of the control group and of the groups receiving 200 and 300 rads survived. At higher doses, mortality increased with dose. The mean weights of tumors were significantly greater in all irradiated groups than in the control group (Table 1, Chart 1). Mean tumor weight increased in the 200-rad and 300-rad groups; the statistical significance of the difference between these two groups was borderline ($P > 0.05$). No further significant increase in tumor weight was found in groups receiving more than 300 rads.

The tumor cells did not differ cytologically in the various radiation dose groups. In the nonirradiated control animals, a moderate, inflammatory infiltrate was observed around the tumors and, to a lesser extend, within the tumors (Fig. 1). This infiltrate varied in intensity in different areas. It consisted mainly of small lymphocytes; however, a number of macrophages and some plasma cells were also present. In animals receiving 200 rads, fewer lymphocytes were present (Fig. 2), and in animals receiving 300 rads or more, there were almost no lymphocytes in or around the tumors (Figs. 3, 4). Nevertheless, in the latter, some macrophages and plasma cells as well as fibroblasts were seen around the tumors.

The lymph nodes in control animals had a distinct cortex with germinal centers (Fig. 5). There was some lymphoid proliferation in the subcortical area. In animals receiving 200 rads (Fig. 6), the nodes often had a slightly thinner cortex, rare germinal centers, and rare cortical foci of lymphocytic depletion with scars. Otherwise the nodes were similar in appearance to those in control animals. In animals receiving 300 rads or more, lymphocytes in the cortex were depleted (Figs. 7, 8).

The spleens of the heavily irradiated animals had marked lymphoblastic proliferation involving the white pulp. The bone marrow showed diminution of red cell elements; nevertheless, the marrow was intensely cellular and was composed of myeloid elements in various stages of differentiation.

**Effect of Time between Irradiation and Transplantation. Procedure.** Two experiments were carried out; in both, groups of 8-week-old mice were irradiated with 400 rads prior to receiving a tumor transplant. In the first of these experiments, with Tumor 1, the intervals between irradiation and transplantation were 24 hours, 1 month, and 4 months; in the second experiment, with Tumor 2, the intervals were 24 hours and 1 month. A group of nonirradiated animals served as controls in each experiment. The experiments were terminated 21 and 24 days after tumor transplantation, respectively.

**TABLE 2**

<table>
<thead>
<tr>
<th>Interval between Irradiation and Transplantation: Irradiation*</th>
<th>Tumor weight (mg)</th>
<th>Significance of difference by t-test ($P$)</th>
<th>Mice used</th>
<th>Mice surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.E.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonirradiated (control)</td>
<td>62 ± 24</td>
<td></td>
<td>11/11</td>
<td></td>
</tr>
<tr>
<td>24 hr</td>
<td>648 ± 89</td>
<td>&lt;0.001</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>544 ± 87</td>
<td>&lt;0.001</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>198 ± 49</td>
<td>&lt;0.025</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>Tumor 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonirradiated (control)</td>
<td>81 ± 26</td>
<td></td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>24 hr</td>
<td>271 ± 72</td>
<td>&lt;0.05</td>
<td>8/8</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>182 ± 73</td>
<td>&lt;0.05</td>
<td>8/8</td>
<td></td>
</tr>
</tbody>
</table>

* 400 rads.

**Chart 2.** Effect of time between irradiation and subsequent tumor transplantation. The growth of the transplanted antigenic tumors was most striking when the interval was 24 hours. Longer intervals, 1 month and 4 months, were associated with partial repair of lymph node structure and partial restoration of the immune response, as shown by the smaller increases in average tumor weight. The X-ray dose was 400 rads. The period of tumor growth after transplantation was 21 days. Tumor 1.

**Results.** In both experiments, the mean weights of tumors were significantly greater in the irradiated than in the nonirradiated control animals (Table 2). With longer intervals between irradiation and tumor transplantation, the difference between the experimental and control groups was not as great as with the short interval of 24 hours; however, some difference was still detectable after the 4-month interval (Table 2, Chart 2).

When the interval was short, i.e., 24 hours, the tumors were essentially free of lymphocytes; some macrophages and plasma cells were noted at the periphery of the tumors. The lymph node cortex was also depleted. The spleen showed lymphoblastic proliferation involving the white pulp.

When the interval was as long as 1 month, a few lymphocytes could be seen again in and about the tumor. The structure of the
TABLE 3

Age at Irradiation and Tumor Growth: Irradiation* 24 Hours before Transplantation

<table>
<thead>
<tr>
<th>Age (mo.)</th>
<th>Nonirradiated animals</th>
<th>Irradiated animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor weight (mg)</td>
<td>Tumor weight (mg)</td>
</tr>
<tr>
<td></td>
<td>Mean ± S.E.</td>
<td>Mean ± S.E.</td>
</tr>
<tr>
<td>2</td>
<td>110 ± 41</td>
<td>8/7</td>
</tr>
<tr>
<td>6</td>
<td>54 ± 12</td>
<td>17/17</td>
</tr>
<tr>
<td>12</td>
<td>93 ± 61</td>
<td>6/6</td>
</tr>
<tr>
<td>15</td>
<td>139 ± 28</td>
<td>2/2</td>
</tr>
</tbody>
</table>

* 400 rads.

Results. At each age tested, the mean weights of tumors in the irradiated animals were greater than in the nonirradiated control animals (Table 3). The mean tumor weights in irradiated animals of any one of the age groups was not significantly different from that of any of the other age groups; however, the number of animals older than 12 months was small.

Effect of Irradiation on Rate of Tumor Growth. Procedure. Twenty-four 8-week-old animals were irradiated with 400 rads. A group of 24 nonirradiated animals served as controls. Twenty-four hours after the time of irradiation, all animals from both experimental and control groups received identical doses of a tumor cell suspension (Tumor 2). Eight irradiated and 8 non-irradiated animals were sacrificed at each of the following times: 12, 24, and 36 days after transplantation.

Results. Tumors grew slowly in the nonirradiated animals; they reached a mean weight of 217 mg in 36 days (Table 4, Chart 3). Tumors grew significantly faster in the irradiated animals \( P < 0.05 \) compared with the nonirradiated animals, reaching a mean weight of 775 mg in 36 days. Weight increment is shown graphically in Chart 3.

TABLE 4

Rate of Tumor Growth: Irradiation* 24 Hours before Transplantation

<table>
<thead>
<tr>
<th>Tumor growth (days)</th>
<th>Nonirradiated animals</th>
<th>Irradiated animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor weight (mg)</td>
<td>Tumor weight (mg)</td>
</tr>
<tr>
<td></td>
<td>Mean ± S.E.</td>
<td>Mean ± S.E.</td>
</tr>
<tr>
<td>12</td>
<td>16 ± 02</td>
<td>8/8</td>
</tr>
<tr>
<td>24</td>
<td>81 ± 24</td>
<td>8/8</td>
</tr>
<tr>
<td>36</td>
<td>217 ± 87</td>
<td>8/8</td>
</tr>
</tbody>
</table>

* 400 rads.

In this experiment mortality was unusually high in the 2-month-old animals owing to a respiratory infection in the colony.
the mean tumor weight of the nonirradiated group was 243 mg and that of the animals irradiated without shielding was 287 mg; the difference was not statistically significant \( (P > 0.1) \). The mean weight of tumors from animals with shielding of the tumor-bearing leg (314 mg) and the mean weight of tumors from animals with shielding of the non-tumor-bearing leg (168 mg) did not differ significantly from the mean tumor weight of the control group \( (P > 0.1) \). These mean weights likewise did not differ significantly from each other in the experimental groups \( (P > 0.1) \).

With an interval of 12 days, the mean weight of the tumors of experimental groups was not significantly different from that of the control group \( (P > 0.1 \text{ and } > 0.05) \). Among the experimental groups, the difference between the mean tumor weights of Group 2 and Group 4 was not statistically significant \( (P > 0.1) \), but there was a significant difference between the mean tumor weights of Groups 2 and 3 \( (P < 0.005) \) and Groups 3 and 4 \( (P < 0.001) \).

In the nonirradiated control animals, the histologic observations closely resembled those reported above for the nonirradiated control animals in the experiments in which irradiation preceded transplantation. There was a dense inflammatory infiltrate about the tumor consisting predominantly of lymphocytes; this infiltrate varied considerably in density from one area to another. The lymph node cortex was thick, consisted mostly of lymphocytes, and had well-developed germinal centers.

In the animals receiving whole-body irradiation with no shielding, the infiltrate about the tumor was less dense. Also, the infiltrate was more pleomorphic, consisting of a mixture of polymorphonuclear leukocytes, macrophages, plasma cells, and some lymphocytes. There was no evidence of radiation damage to the tumor. The lymph node cortex was less dense and had a few germinal centers. Polymorphonuclear leukocytes and plasma cells in the nodes were more numerous than in the nodes of the control animals. The animals in both Groups 3 and 4, receiving irradiation with local shielding, showed similar changes. In both instances the tumors were surrounded by an infiltrate that was intermediate in density between that in the nonirradiated control animals and the animals irradiated without shielding. Again, the infiltrate was pleomorphic, comprising polymorphonuclear leukocytes, macrophages, plasma cells, and lymphocytes. However, lymphocytes were more numerous than in the animals whole-body-irradiated without shielding. The lymph nodes showed focal areas of cortical thinning; some germinal centers were present, and plasma cells were quite numerous.

**DISCUSSION**

In experiments on immune responses to tumors, whole-body irradiation has recently been employed as a means of suppressing immunity. However, the effect of various irradiation conditions on the growth of transplanted antigenic tumors in isogenic animals has not been examined previously in detail. Our findings in such experiments with antigenic tumors transplanted to isogenic mice are comparable to the effect of whole-body irradiation on immune responses to other antigens, e.g., sheep red blood cells, reported by others (17). However, detailed comparisons with other studies are difficult because they differ in species and strains employed, in the age of animals used, in the timing of irradiation and the physical factors of irradiation, the type of antigen, and in the antigenic dose—conditions all known to influence immune responses. Furthermore, immune responses have been evaluated by different methods. In the present experiments, the responses of experimental animals to standard inocula of tumor cells were measured by weighing the tumors after a given period of growth and by comparing the results in irradiated and nonirradiated animals. The tumors used were sarcomas which had recently been induced with MCA in isogenic male C3H mice and transplanted to mice of the same strain and sex. Each MCA-induced sarcoma has its own individual, tumor-specific antigens \( (10, 11, 14) \); cross-reactions have been reported only rarely. We have observed that such tumors elicit cytologic changes in regional lymph
nodes that are indicative of an immune response and also produce cellular infiltrates in and about the neoplasm (13).

When whole-body irradiation preceded tumor transplantation, tumor growth increased with the amount of radiation up to 300 rads. In this dose range, there was no radiation mortality. Higher doses of radiation did not produce further increases in tumor growth; however, radiation mortality increased with dose. The LD_{50} was not determined in these experiments with any precision, but it was apparently slightly over 500 rads. Radiation mortality may be influenced by a variety of factors, including the age of the animals. Under the conditions employed, the doses of 300-400 rads resulted in marked suppression of tumor immunity without significant mortality, except in one experiment. A dose of 400 rads was subsequently employed in most of the experiments. At higher doses, 400-600 rads, there were marked changes in lymph nodes which were similar to those described by de Bruyn (3) in rabbits and mice.

A relationship between radiation dose and immune suppression has also been described for other antigens by Dixon et al. (4) and by Taliaferro and Taliaferro (16). Stoner and Hale (15) reported almost complete suppression of the primary immune response in mice irradiated with 300 rads and injected with fluid tetanus toxoid antigen a day later. This finding closely parallels ours with antigenic tumors. The subject of immune suppression by irradiation has been thoroughly reviewed by Taliaferro et al. (17).

Tumor growth also depended on the length of the interval between the irradiation and subsequent tumor transplantation. With an interval of 24 hours, the maximal acceleration of tumor growth corresponded to the maximal suppression of response to other antigens reported in the literature (17). When this interval was lengthened, acceleration of tumor growth was less pronounced. However, even after a 4-month interval, some acceleration was noted. Partial recovery of the immunologic response was accompanied by evidence of repair in lymph nodes as the interval increased.

Only a few studies on the long-term effects of irradiation on immune responses have been reported. Gengozian and Makinodan (5), studying mice irradiated with 710 R and injected with sheep red cells after a 45-day interval, still noted some immune suppression. Taliaferro et al. (17) described recovery of the immune responses of rabbits irradiated with 500-700 R and injected with sheep red blood cells 4-8 weeks later. However, the responses varied over a wide range and some responses remained subnormal after this interval between irradiation and antigenic stimulation. Brooke (2) observed some prolongation of the homograft reaction in rabbits when grafting followed as late as 28 days after whole-body irradiation with 400 R but not as late as 96 to 138 days after irradiation. It appears that weak antigens such as tumor-specific antigens as well as small doses of antigen can be used to advantage in demonstrating the lesser degrees of immune suppression after long intervals separating irradiation and antigenic stimulation, whereas the responses to strong antigen may obscure minor degrees of immune suppression. Dixon (F. J. Dixon, personal communication), on the basis of experiments with heavily irradiated rabbits, suggested that recovery of the immune response may never be entirely complete.

No difference in response was noted in animals 2-15 months of age at the time of irradiation. Unfortunately, only small numbers of the older animals were available for study. Detailed studies with larger numbers of older animals may be of considerable interest, particularly in view of the increasing incidence of malignancy with age in man.

Makinodan and Peterson (7) studied the relative antibody-forming capacity of mouse spleen cells as a function of age by transfer of spleen cells to irradiated recipients that had been injected with sheep red blood cells. They observed a rapid increase in antibody-forming capacity of the spleen cells from donors 1-8 months of age, when the maximum antibody-forming capacity has been achieved. A gradual decrease in this capacity seemed to take place over the subsequent 21 months. The effect of age on the capacity to form isoantibodies to transplanted homologous leukemia cells in mice was also investigated by Aoki and Teller (1), who observed a decreased rate of rejection by mice 18 months of age compared with those 3 months of age.

In striking contrast to the accelerated rate of tumor growth when irradiation preceded transplantation was the finding that significant acceleration of tumor growth did not occur when irradiation followed transplantation. Although tumor growth was not accelerated, the lymphoid infiltrates surrounding the tumors were lighter than in control animals. Thus, when irradiation followed transplantation, an inverse correlation between tumor growth and lymphocytic infiltrate was not observed—the opposite of the case when irradiation preceded transplantation. The failure to suppress tumor immunity by whole-body irradiation when irradiation followed transplantation is in line with observations by some other investigators who failed to suppress immune responses when irradiation followed antigenic stimulation. Dixon et al. (4) as well as Taliaferro and Taliaferro (16) found that, in general, antibody formation in rabbits was not seriously depressed when irradiation followed injection of antigen. Taliaferro and Taliaferro (16) even noted a heightened immunologic response to antigenic stimulation. Thus the early phase of induction of immune responses to tumor antigen as well as other antigens is radiosensitive, in contrast to later phases of the response which are relatively radioresistant.

ACKNOWLEDGMENTS

The capable technical assistance of Mrs. Rosemary Lund is gratefully acknowledged.

REFERENCES


Figs. 1-8. All tumors were from the site of transplantation in the muscular tissue of a leg. In each instance, the period of tumor growth was 21 days after transplantation. The lymph node sections shown were from the regional (inguinal) lymph nodes of the tumor-bearing leg. The sections were stained with hematoxylin and eosin.

Fig. 1. Nonirradiated control: tumor. The sarcomatous neoplasm consists of poorly differentiated, spindle-shaped cells. The dense mononuclear cell infiltrate at the periphery consists predominantly of small lymphocytes with an admixture of macrophages and plasma cells. A lesser degree of infiltration is present within the tumor. × 300.

Fig. 2. Dose: 200 rads 24 hours before tumor transplantation: tumor. Lymphoid cells are present at the periphery and within the tumor in much smaller numbers than in the nonirradiated control animals. × 300.

Fig. 3. Dose: 400 rads 24 hours before tumor transplantation: tumor. Lymphoid cells are present at the periphery and within the tumor. × 300.

Fig. 4. Dose: 200 rads 24 hours before tumor transplantation: tumor. The periphery is devoid of lymphocytes, but a few plasma cells, macrophages, and fibroblasts are present. × 300.

Fig. 5. Nonirradiated control: lymph node. The cortex consists primarily of small lymphocytes with an admixture of diffusely dispersed lymphoblasts and reticulum cells. A few germinal centers are present. The medullary area has diffuse lymphoid proliferation. × 300.

Fig. 6. Dose: 200 rads 24 hours before tumor transplantation: lymph node. The cortex consists predominantly of small lymphocytes; germinal centers are present but are not shown here. In general, the structure of the nodes in this group is similar to that in the nonirradiated control animals. × 300.

Fig. 7. Dose: 400 rads 24 hours before tumor transplantation: lymph node. The cortex is thin and has no germinal centers, or only a few. × 300.

Fig. 8. Dose: 600 rads 24 hours before tumor transplantation: lymph node. The node is markedly decreased in size and lymphocytic elements are almost absent. No cortex or germinal centers are present. Most of the residual node is made up of macrophages, reticuloendothelial cells, and fibroblasts. × 300.
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