Inhibition by Testosterone of Radiation-induced Lymphoid Tumor Development in Intact and Castrate Adult Male Mice

HENRY S. KAPLAN AND MARY B. BROWN

(Starcum Institute School of Medicine, San Francisco, Calif.)

Immature C57 black mice of both sexes develop lymphoid tumors with equal frequency after irradiation, and their susceptibility is not modified by gonadectomy (5). Several years ago, however, Murphy (12) noted that exogenous testosterone partially inhibited the development of spontaneous leukemias in Rockefeller Institute female mice, and Gardner (2) recently reported a reduced incidence of lymphoid tumors in irradiated female BC mice after testosterone administration. A pronounced degree of inhibition has been observed in post-pubertal male mice under the conditions of the experiment described herein.

METHODS

Litter-mate male C57 black mice were distributed among four groups at the time of weaning. Groups II and IV were castrated at 2 months of age, by a single-stage lower abdominal operation; the other two groups remained intact. Whole-body irradiation of all groups was started 3—4 days later, and a total dose of 673 r was delivered in four equally fractionated treatments at intervals of 4 days.1

Immediately after each irradiation, and continuing twice weekly for a total of 10 weeks, animals of groups III and IV were injected intramuscularly with 0.02 cc. of an aqueous suspension containing 0.5 mg. testosterone. Groups I and II were similarly injected with an equal volume of the suspension medium alone.

All animals were identically caged and maintained on Purina Laboratory Chow and water ad libitum. Mice that died of any cause before the time of appearance of the first lymphoid tumor were omitted. Obviously moribund animals were killed, and all animals were carefully examined at autopsy; representative tissues were taken for histologic examination in all instances except where the presence of a mediastinal or disseminated lymphoma was obvious on gross inspection.

RESULTS

The data are summarized in Table 1, and cumulative incidence curves are presented in Chart 1. A striking inhibition of lymphoid tumor development resulted from the administration of testosterone to both intact and castrate adult male mice. Many animals of groups III and IV are still alive.

TABLE 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Material injected</th>
<th>Net no. of mice</th>
<th>Mice with lymphomas</th>
<th>Average latent period (days)</th>
<th>No. dead</th>
<th>No. alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intact irradiated</td>
<td>52</td>
<td>39 75</td>
<td>106 2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Castrate irradiated</td>
<td>52</td>
<td>45 87</td>
<td>102 3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Intact irradiated</td>
<td>49</td>
<td>4 8</td>
<td>203 5</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Castrate irradiated</td>
<td>50</td>
<td>5 10</td>
<td>204 2</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

1 Aqueous suspensions of testosterone, 25 mg/cc, stabilized with 9.5 per cent aluminum phosphate, and placebo vials of 0.55 per cent aluminum phosphate suspension were generously supplied by Dr. Edward Henderson of the Schering Corp., Bloomfield, N.J., with the information that such suspensions are somewhat more potent, in experiments of short duration, than testosterone propionate in oil. No studies relative to optimal dosage levels have as yet been made in our laboratory.
alive, but virtually no additional lymphoid tumors have appeared recently after an observation period of about 1 year, indicating that actual suppression or prevention, rather than mere delay in onset, has been effected. The slightly higher incidence among the castrate groups did not differ significantly from that of their respective intact controls. All the tumors were lymphocytic or lymphoblastic lymphomas, identical in histologic appearance and invasive behavior with those described previously (6).

An incidental observation during the period of injection was a considerable loss of hair, particularly over the ventral surface of the body, in the testosterone-treated animals. No similar alopecia was noted in the placebo-injected controls. There was a gradual return of hair after the series of testosterone injections was completed.

**DISCUSSION**

In experiments of short duration both testosterone and irradiation cause involution of lymphoid tissues (1, 13, 14). Information is sorely needed on the possible synergistic effect of the simultaneous administration of both agents on lymphoid tissues, and on the effect of testosterone on recovery of lymphoid tissues from radiation injury. Lacking such data, it seems premature to speculate at length upon the possible mechanism by which testosterone exerts such a striking inhibitory influence on the induction of lymphoid tumors.

The various steroid hormones that have been thus far studied do not exert a generically similar influence upon lymphoid tumor development. For example, estrogens induce lymphoid tumors in susceptible strains of mice (4, 9) and may synergize with x-radiation in their induction, whereas testosterone has not been independently leukemogenic (9) and tends to suppress leukemogenesis following irradiation. More recently, it was found that cortisone inhibits the development of lymphomas in irradiated mice, while desoxycorticosterone has no effect (7). The nature of the interaction between these hormones and lymphoid tissue is not sufficiently well understood at this time to permit an explanation of these diverse results.

Orchidectomy has been followed by an increase in spontaneous lymphoma incidence under certain experimental conditions (10–12). A similar result was not observed in the present investigation, possibly because the interval between castration and the first x-ray exposure was too short. Detailed studies of the optimal time intervals for castration and irradiation, and for irradiation and testosterone administration, are clearly indicated. It is of interest that the inhibitory effect of cortisone was still manifest when its administration was deferred until 6 weeks after irradiation (7). Parallel studies with testosterone are in progress.

**SUMMARY**

Intact and castrate male C57 black mice were irradiated and injected twice weekly for 10 weeks with an aqueous testosterone suspension; the corresponding litter-mate control groups were also irradiated and injected with a placebo of the suspension medium alone. Net lymphoid tumor incidence by groups was: (a) intact + x-ray + placebo, 39 of 52 mice (75 per cent); (b) castrate + x-ray + placebo, 45 of 52 mice (87 per cent); (c) intact + x-ray + testosterone, 4 of 49 mice (8 per cent); and (d) castrate + x-ray + testosterone, 5 of 50 mice (10 per cent). Some possible mechanisms for this pronounced inhibition are briefly discussed.

**REFERENCES**

6. KAPLAN, H. S.; BROWN, M. B.; and MARDER, S. N. Adrenal Cortical Function and Lymphoid Tumor Inci-
Inhibition by Testosterone of Radiation-induced Lymphoid Tumor Development in Intact and Castrate Adult Male Mice

Henry S. Kaplan and Mary B. Brown


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/11/9/706

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.