Immunosuppression and Malignant Lymphomas in Graft-versus-Host Reactions

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SUMMARY

The immune responses of mice undergoing the graft-versus-host reaction were tested with a battery of four antigens. Three donor-host combinations were selected on the basis of their susceptibility to the development of malignant lymphomas. The results were highly variable. In general, antigens eliciting responses independent of thymus-derived (T) cells (lipopolysaccharide) or bone marrow-derived cells (skin allograft rejection) were normal, whereas antigens eliciting cooperative responses between T- and bone marrow-derived cells (sheep red blood cells and dinitrophenyl-keyhole limpet hemocyanin) were depressed. Augmentation of primary immune responses by the graft-versus-host reaction was found in four different experiments. Evidence for an environmental immunosuppressant could not be found. Deliberate immunosuppression of otherwise normal mice with anti-mouse thymocyte serum failed to cause the appearance of tumors. Those mice with the lowest incidence of lymphomas developed severe depression of certain of their immune responses.

Under the experimental conditions that we studied, it appears that the graft-versus-host reaction can: (a) block cooperation between T- and bone marrow-derived cells; (b) augment certain immune responses, perhaps by means of stimulants released from T-cells; and (c) provoke the development of lymphomas in a setting devoid of significant immunosuppression.

INTRODUCTION

Neoplasms of lymphoid tissue can be initiated in mice by an immunological mechanism, the GVHR (4, 11). Thus far, we have identified 2 important factors in the development of these lymphomas, the vigor of the immune response engendered in the grafted lymphoid cells by histocompatibility antigens of the recipient (15) and activation of leukemia viruses during the early phases of the GVHR (17). One interpretation of these findings is that virogenes (2) are derepressed when lymphocytes respond to histocompatibility antigens (34). The presence of C-type viruses budding from transformed lymphocytes in the spleens of mice undergoing the GVHR (3) supports this concept. Similar particles also bud from transformed lymphocytes in the mixed lymphocyte culture reaction (3), which is the in vitro analog of the GVHR. Cells infected by such viruses presumably undergo malignant transformation, with the resultant development of lymphomas.

This interpretation of how lymphomas develop in mice undergoing the GVHR does not take into account the possible effects of immunosuppression. Immunosuppression, which is well known to occur during the GVHR, has been attributed to damage of the lymphoid tissue of the host by the graft (13). Therefore, it is conceivable that cancers occur in the GVHR because the immunological surveillance mechanism of the host is impaired. In the present work immunocompetence during the GVHR was tested in donor-host combinations with a low, moderate, or high incidence of lymphomas. Particular attention was paid to the early phases of the GVHR, a time when activation of leukemia viruses occurs (18).

MATERIALS AND METHODS

Animals. All mice came from The Jackson Laboratories, Bar Harbor, Maine, or our laboratory bred them from the Jackson stocks. Donor animals were 6 to 8 weeks old and the F1 hybrid recipients were 6 to 7 weeks old when they received the 1st injection of parental spleen cells. The 3 donor-host combinations selected for analysis, together with the incidence of malignant lymphomas 6 months after induction of the GVHR, are shown in Table 1.

Induction of the GVHR. Spleens were minced in Ringer's solution and gently pressed through tantalum gauze with a small test tube. Sterile technique was used and the spleen fragments and cells were chilled during preparation. Cell viability was determined with trypan blue. F1 hybrids received 5 x 107 viable spleen cells i.p. at weekly intervals for a total of 4 doses, except in those experiments where the immune response was tested after the 1st, 2nd, or 3rd injection of donor cells. As a rule, groups of 40 F1 recipients received parental spleen cells from the same pool of donors; every week 10 of the recipients were sacrificed for analysis of immunocompetence. Experiments involving long-term observations were set up in a similar manner. All
The 3 donor-recipient combinations studied in these experiments

<table>
<thead>
<tr>
<th>F₁ hybrid</th>
<th>Symbol</th>
<th>Donor cell</th>
<th>Lymphoma incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6 × DBA/2</td>
<td>B6D2</td>
<td>DBA/2</td>
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</tr>
<tr>
<td>BALB/c × A/J</td>
<td>CA</td>
<td>BALB/c</td>
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</tr>
<tr>
<td>AKR × DBA/2</td>
<td>AKD2</td>
<td>DBA/2</td>
<td>70</td>
</tr>
</tbody>
</table>

* Six months after initiating the GVHR. No 6-month-old control mouse had a lymphoma. Data obtained from Refs. 4 and 15.

control mice were age matched with the experimental animals.

Antigens. SRBC (Colorado Serum Co., Denver, Colo.) were washed 3 times in 0.15 M NaCl solution. Each animal received 5 × 10⁶ SRBC i.p. DNP-KLH was prepared according to the method of Campbell et al. (9) in a molar ratio of 189 moles of DNP per mole of KLH, assuming 8 × 10⁴ as the molecular weight of KLH. Each mouse received 0.2 mg/20 mg body weight in complete Freund’s adjuvant i.p. Endotoxin LPS (Difco Laboratories, Inc., Detroit, Mich.; extracted from Escherichia coli 055:B5) was incubated with isologous erythrocytes (27) and 0.1 ml of the LPS-coated cells was administered i.p. Skin allografts were applied according to the method of Billingham and Medawar (6). SRBC, DNP-KLH, or LPS was administered 1 day after the stated number of injections of parental spleen cells, and plaque assays were performed 5 days later. Skin grafts were applied 1 day after the 2nd injection of parental spleen cells.

Immunosuppression. Thymectomy was done by the method of Monaco et al. (28). Rabbit ALS (microbiological Associates, Inc., Bethesda, Md.) was given in a dose of 0.25 ml i.p. every other day for 4 doses. The skin grafts studied in these experiments were applied the day after the lst dose of ALS.

Reconstitution Experiments. Recipients received 850 R at a rate of 46 R/min using a Westinghouse deep therapy unit. The mice were placed in individual Lucite units and rotated on a turntable to ensure uniform delivery of the irradiation. Cell suspensions were prepared as described above. T-cells were obtained from thymuses from which all fascial tags and adjacent lymph nodes were dissected. B-cells were obtained from the bone marrow, which was expressed from femora with the aid of a syringe. As a rule, 10⁷ B-cells and 4 × 10⁷ T-cells were used.

Estimation of Immune Responses. Direct splenic PFC making antibody against SRBC (21), DNP (33), and LPS (2) were enumerated using the methods cited. Hemaggulitin titrations were carried out in microtiter plates, the initial dilution being 1:20. The titer was expressed as the number of the last well in the plate showing an agglutination pattern. Plaster casts were removed 6 days after application of skin grafts. The grafts were inspected and palpated daily and any graft having less than 10% epithelium was scored as rejected.

Enumeration of T-Cells and B-Cells. These tests were kindly performed by Dr. Emil Unanue, Department of Pathology, Harvard Medical School. B-cells were identified by the capacity of their membranes to stain with fluorescein-conjugated rabbit anti-mouse IgG serum (36). T-cells were identified by counting the number of cells killed by a cytotoxic anti-α serum prepared by immunizing AKR mice with CBA thymocytes (32).

RESULTS

SRBC, DNP-KLH, and LPS were chosen for study because the 1st 2 antigens elicit a cooperative interaction between T-cells and B-cells (Y. Borel, U. Jehn, L. Kilham, and D. Golan, manuscript in preparation), whereas LPS provokes an immune response that is independent of T-
cells (2). We presume that the rejection of skin allografts is mediated primarily by T-cells, although this has not been established unequivocally.

**Antibody Responses**

**C57BL/6 × DBA/2 F₁ (B6D2F₁) Mice (Chart 1; Table 2).** Impaired responses to SRBC developed after the 2nd injection of DBA/2 spleen cells and thereafter immunity to this antigen was severely depressed. The number of PFC/10⁶ spleen cells formed after immunization with DNP-KLH was only transiently depressed during the early phases of the GVHR, but by 6 months the experimental mice were barely responsive to DNP. A fluctuating impairment of the responses to LPS was also found.

**BALB/c × A/J F₁ (CAF₁) Mice (Chart 2; Table 2).** Responses to SRBC were promptly, severely, and permanently depressed following injection of BALB/c spleen cells. This system was analyzed in more detail by serial measurement of hemagglutinin titers over a period of 24 weeks. When 10⁶ SRBC were injected 1 week after the 4th inoculation of BALB/c spleen cells, no primary immune response was detected (Chart 3). However, a 2nd injection of 10⁶ SRBC, given 12 weeks after the 1st, elicited a typical anamnestic response in the experimental mice (Chart 3). When 10⁶ SRBC were injected 1 week before the 1st dose of BALB/c spleen cells, the hemagglutinin response was initially normal; within 1 month, however, it began to decline and by the 13th week of the experiment virtually no antibody was detectable in the serum of the experimental mice (Chart 4).

Responses to DNP-KLH were also suppressed in experimental CAF₁ mice, although there was some tendency toward recovery 1 week after the last dose of parental spleen cells. Nevertheless, by 6 months the response to this antigen was only about one-tenth of normal. During the early phases of the GVHR the number of PFC per 10⁶ spleen cells formed after injection of LPS was impaired; however, by 1 week after the 3rd dose of parental spleen cells, responsiveness to this antigen had recovered. The relatively large standard error in this latter group is worth noting; this is due to 2 mice that produced a high number of PFC (116.8 and 202.2/10⁶ spleen cells, respectively, and to 2 mice yielding low numbers of PFC (2.6 and 2.4/10⁶ spleen cells, respectively). Mice tested 6 months after induction of the GVHR had a normal response to LPS.

**AKR × DBA/2 F₁ (AKD2F₁) Mice (Chart 5; Table 2).** This hybrid-parent combination was chosen because of its remarkably high incidence of lymphomas. Notwithstanding
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transiently suppressed responses to DNP-KLH after the 3rd and 4th injections of DBA/2 spleen cells, but at no time were depressed responses to LPS found. At 6 months, moderately impaired responses to SRBC and DNP were found, but in many of these animals the spleen was partially or completely replaced by reticulum cell sarcoma.

Localization of the Cellular Defect in Antibody Production

The function of T-cells and B-cells of mice undergoing the GVHR was tested by challenging with SRBC lethally irradiated, syngeneic recipients that were restored with defined populations of cells from control or experimental mice. The irradiated recipients provided an in vivo "culture" in which the immunocompetence of either T-cells or B-cells, or both, could be tested. Four groups of X-rayed recipients were analyzed for each line of mice: the first, controls, was given a mixture of T-cells and B-cells from normal mice; the second received a mixture

this characteristic, the degree of immunosuppression detected during the early phases of the GVHR was minimal in these animals. Indeed, actual increases in the immune responses to SRBC and LPS were found. There were

Chart 3. Primary and secondary responses to SRBC in CAF₁ mice. Antigen was injected twice, 1 week after the 4th dose of parental cells and 12 weeks later (arrow). Note the absent primary response and the normal secondary response in the experimental mice.

Chart 4. Primary responses to SRBC in CAF₁ mice. Antigen was injected 1 week before 1st dose of BALB/c spleen cells. Hatched bar, time of administration of BALB/c spleen cells.

Chart 5. Antibody responses in AKD2F₁ mice. Note augmented responses to SRBC and LPS.
To test the hypothesis that an environmental immunosuppressant is produced during the GVHR, spleen cells from experimental mice were challenged with antigen in an in vivo "culture" system. CAF₁, B6D2F₁, and AKD2F₁ mice received 4 injections of parental spleen cells and 1 week later $5 \times 10^7$ of their spleen cells were transferred to lethally irradiated, syngeneic hosts. Within 1 hr, recipients of experimental and control spleen cells were challenged with $5 \times 10^8$ SRBC. Eight days later the number of PFC in their spleens was estimated. The results are shown in Chart 9. Spleen cells of the experimental CAF₁ and B6D2F₁ mice produced relatively few PFC in the irradiated recipients, indicating an absolute inability of their immunocompetent cells to respond to SRBC. Spleen cells of experimental CAF₁ mice responded normally. This was anticipated because the responses of the donors are normal (Chart 5).

Chart 10 shows the results of testing the immunocompetence of spleen cells from CAF₁ mice simultaneously with SRBC and LPS. Pooled spleen cells from control or experimental (1 week after the 4th injection of BALB/c spleen cells) CAF₁ mice were inoculated into groups of X-irradiated, syngeneic animals, which were challenged 1 hr later with either $10^6$ SRBC or 0.1 ml of LPS-coated CAF₁ erythrocytes. Eight days later cells forming plaques against SRBC or LPS were enumerated in the spleens of the irradiated recipients. The results demonstrate that, at the time that the immune response of the transferred cells to SRBC was severely depressed, their response to endotoxin was normal. The presence of a nonspecific immunosuppressant elaborated during the GVHR is not supported by these data.
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Chart 9. Aliquots from the same pool of control (C) or experimental (E) spleen cells were injected into syngeneic, irradiated recipients, which were challenged with either SRBC or LPS. The immune response to SRBC is depressed, whereas to LPS is normal.

Chart 8. PFC produced by mixtures of T- and B-cells in irradiated, syngeneic AKD2F1 hosts. Abbreviations as in Chart 6. A mixture of experimental T-cells and normal B-cells produced an augmented response.

Enumeration of T- and B-cells (Chart 11)

Spleen cells possessing surface immunoglobulins (presumably B-cells) or the antigenic marker $\theta$ (presumably T-cells) were enumerated in experimental and control CAF$_1$ mice 1 week after the last injection of parental spleen cells. There was no diminution in the number of $\theta$-positive cells. However, there was a substantial decrease in the number of cells bearing immunoglobulins on their membranes. This was accompanied by a corresponding increase in cells that were negative for both the $\theta$- and immunoglobulin markers, and which, by phase-contrast microscopy, had the appearance of macrophages.

Responses to Skin Allografts

B6D2F1 Mice (Tables 3 and 4). Both strongly (A/J; $H^2$) and weakly (C57L; $H^2$) incompatible skin grafts survived about 2 to 3 days longer on the experimental mice than on the control animals. Skin grafts survived much longer on ALS-treated or on thymectomized and ALS-treated mice than on either control or experimental mice. Tumors failed to develop in any group of mice.

DISCUSSION

Previous studies have disclosed normal (19) diminished (7, 24), or increased (12) immunological responsiveness of animals undergoing the GVHR (see Ref. 13 for review). We also found these 3 states and conclude that the level of immunocompetence during the GVHR depends upon: (a) the nature of the test antigen; (b) the time of the antigenic challenge relative to the time of administration of the im-
assume that animals with extensive destruction of lymphoid tissue should respond only feebly to antigenic challenge.

The preceding conclusions are based on the data reported in this paper, as well as Elkin's (13) analysis of the literature. Our results show, for example, that at a time when B6D2F1 mice were barely responsive to SRBC their responses to DNP-KLH and to skin allografts were entirely normal. CAF1 mice also developed severe impairment of their responses to SRBC, yet they reacted normally to LPS and skin allografts. Finally, AKD2F1 mice suffered virtually no impairment of immunity to any of the 4 antigens with which they were challenged.

We observed augmented immunity in several experiments. Katz and his colleagues (22, 23, 31) have extensively analyzed this phenomenon (the "allogeneic effect") and showed that the injection of allogeneic lymphoid cells can greatly augment the formation of antibodies in primed animals. Our results demonstrate that under certain conditions [the critical importance of experimental conditions has been emphasized by Osborne and Katz (31)], primary

**Table 3**

<table>
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<th>Strain</th>
<th>Graft donor</th>
<th>Group</th>
<th>Median survival time</th>
</tr>
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<tbody>
<tr>
<td>B6D2F1</td>
<td>C57L</td>
<td>Control</td>
<td>12.5 ± 3.6</td>
</tr>
<tr>
<td>B6D2F1</td>
<td>C57L</td>
<td>GVHR</td>
<td>14.5 ± 2.7</td>
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<tr>
<td>CAF1</td>
<td>DBA/2</td>
<td>Control</td>
<td>14.5 ± 1.5</td>
</tr>
<tr>
<td>CAF1</td>
<td>DBA/2</td>
<td>GVHR</td>
<td>17.0 ± 2.3</td>
</tr>
<tr>
<td>AKD2F1</td>
<td>BALB/c</td>
<td>Control</td>
<td>11.4 ± 1.3</td>
</tr>
<tr>
<td>AKD2F1</td>
<td>BALB/c</td>
<td>GVHR</td>
<td>11.0 ± 0.8</td>
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</table>

*a Significantly (p < 0.05) different from control.

**Table 4**

<table>
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<th>Strain</th>
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<tr>
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<td>12.5 ± 3.6</td>
<td>0/11</td>
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<tr>
<td></td>
<td>GVHR</td>
<td>14.5 ± 2.7</td>
<td>0/11</td>
</tr>
<tr>
<td></td>
<td>ALS</td>
<td>18.0 ± 4.5</td>
<td>0/11</td>
</tr>
<tr>
<td></td>
<td>Tx + ALS</td>
<td>39.0 ± 14.7</td>
<td>0/26</td>
</tr>
<tr>
<td>CAF1</td>
<td>Control</td>
<td>13.0 ± 1.0</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>GVHR</td>
<td>12.5 ± 2.0</td>
<td>7/30</td>
</tr>
<tr>
<td></td>
<td>ALS</td>
<td>30.0 ± 3.0</td>
<td>0/21</td>
</tr>
<tr>
<td></td>
<td>Tx + ALS</td>
<td>41.0 ± 6.6</td>
<td>0/30</td>
</tr>
<tr>
<td>AKD2F1</td>
<td>Control</td>
<td>12.0 ± 1.4</td>
<td>1/33</td>
</tr>
<tr>
<td></td>
<td>GVHR</td>
<td>11.8 ± 0.8</td>
<td>14/35</td>
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<tr>
<td></td>
<td>ALS</td>
<td>36.6 ± 3.3</td>
<td>0/22</td>
</tr>
<tr>
<td></td>
<td>Tx + ALS</td>
<td>25.6 ± 3.3</td>
<td>1/25</td>
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</tbody>
</table>

*a Significantly (p < 0.05) different from control.

*b Tx, thymectomy.*

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immune responses are also augmented by the GVHR. This was seen in at least 4 experiments, the immune responses of intact, experimental AKD2F₁, mice to LPS and SRBC and the ability of T-cells from experimental CAF₁, and AKD2F₁, mice to augment the formation of anti-SRBC PFC by normal B-cells.

Currently, the allogeneic effect is thought to circumvent the need for T-cells, which are required for immune responses to several types of antigens. How the GVHR produces this “short circuit” in the immune response is unknown, but a leading possibility is that allogeneic T-cells, when “activated” by recipient antigens, release substances that stimulate the B-cells of the host to engage in antibody synthesis (22). This could explain how the GVHR can cause: (a) accelerated immunological maturation of chick embryos (26); (b) responsiveness to a synthetic polypeptide [(T,G)-A -L] in mice lacking the T-cells required for the production of IgG antibodies to it (30); (c) responsiveness to (DNP-D-GL), a hapten conjugate that is normally nonimmunogenic in mice (31); (d) augmented antihapten secondary responses, which require participation of carrier-primed T-cells (22, 23); (e) accelerated rejection of tumor grafts by guinea pigs (14); (f) augmented primary responses, as we observed; and (g) the “super" T-cell effect noted in Charts 7 and 8.

The mechanism of immunosuppression during the GVHR is less well understood. Destruction of lymphocytes is an obvious possibility, and our data indicate significant losses of B-cells from the spleens of CAF₁ mice undergoing the GVHR. Reduced numbers of B-cells could explain the impaired responses to SRBC and to DNP-KLH, antigens that elicit cooperative interactions between T- and B-cells (Y. Borel, U. Jehn, L. Kilham, and D. Golan, manuscript in preparation). However, evidence against simple depletion as the mechanism is given by the generally normal responses to LPS, an antigen that provokes responses only in B-cells (2). Furthermore, the elicitation of a secondary response to SRBC in animals unable to produce a primary response to that antigen is inconsistent with an absolute deficiency of immunocompetent cells. These findings, coupled with the “curative” effect of normal T- or B-cells on their counterparts from experimental mice, suggest the existence of a block in the ability of T- and B-cells to cooperate during the GVHR. Such a block might consist of the lack of a soluble mediator; the production of a substance that discourages T-B-cell cooperation; or a disorder of macrophages, which are involved in the cooperative interaction between the 2 kinds of cells (35).

The data lead us to conclude that the outcome of antigenic stimulation during the GVHR represents the final result brought about by: (a) destruction of immunocompetent cells; (b) nonspecific stimulation of B-cells by the allogeneic effect; and (c) suppression, perhaps by inhibitory substances released from “activated” T-cells (31), of certain functions of immunocompetent cells, such as cell-cell cooperation. Each of these effects, acting singly or in combination, could give rise to the various immunological phenomena observed during the evolution of the GVHR.

As for the pathogenesis of lymphomas induced by the GVHR, we are unable to state that immunosuppression is relevant for the following reasons. (a) The donor-host combination with the highest incidence of lymphomas (DBA/2 — AKD2F₁) had the least degree of immunosuppression. Indeed, as mentioned earlier, this was the only combination in which augmented antibody synthesis was found in the intact animal. (b) Cellular immunity, as represented by the capacity to reject allografts, was intact in most experimental mice. Experimental AKD2F₁, mice were able to reject even H-2-compatible skin grafts normally. The ability to reject such weakly antigenic tissue seems highly relevant in reactions to tumors of the type that we studied. (c) Severe immunosuppression, as seen in either intact or thymectomized mice treated with ALS, was not associated with the development of lymphomas. Indeed, in the highly susceptible combination, DBA/2 — AKD2F₁, the experimental maneuver producing lymphomas was the GVHR and not the induction of immunosuppression by ALS. It might be argued that thymectomy eliminates the target cell involved in the development of certain lymphomas, but this is not so, as we (R. S. Schwartz, unpublished observations) and others (1) have noted in the case of reticulum cell sarcoma.

Immunosuppression may be important in the development of lymphoid neoplasms, especially in humans with certain kinds of immunodeficiency diseases (37). However, review of the literature dealing with the induction of lymphomas in experimental animals reveals that immunosuppression plays a significant role in only 2 circumstances, when the animal is also deliberately infected with an onco- genic virus (16) or when there is a genetic predisposition to the spontaneous development of lymphomas (8). The failure of severe immunosuppression alone to promote the development of lymphomas is illustrated not only by our data but also by those of Nehlsen (29), who treated 250 CBA mice with injections of ALS 4 times weekly for 18 months. The severity of the immunosuppression in these animals was demonstrated by a very prolonged retention of both xenografts and allografts; nevertheless, only 2 lymphoblastic lymphomas were found in this large group of mice.

Since, as stated earlier, leukemia viruses are activated during the GVHR (17), it is conceivable that this, combined with immunosuppression, causes the neoplasms. We cannot exclude this possibility. However, 2 findings argue against it. (a) Activation of leukemia viruses occurs in the combination DBA/2 — B6D2F₁ (M. S. Hirsch and S. M. Phillips, unpublished observations) and, as the present results show, immunosuppression is readily detected in these mice. Yet they do not develop neoplasms. (b) In the high lymphoma combination, DBA/2 — AKD2F₁, leukemia viruses are also present (M. S. Hirsch and S. M. Phillips, unpublished observations), but immunosuppression is minimal. We recognize that this line of reasoning is flawed because specific antitumor immunity was not measured in our experiments; the remote possibility remains that the AKD2F₁ mice that we studied were unable to react to tumor-specific antigens because of a specific form of immunosuppression induced by the GVHR.

We therefore conclude that, although immunosuppres-
vision may occur during the GVHR, it is not an essential element in the pathogenesis of GVHR-induced lymphomas. Indeed, as previously mentioned, the GVHR may, under certain conditions, actually promote the rejection of neoplastic cells (14). Furthermore, since immunological activation of leukemia viruses, as seen in the GVHR, can also be demonstrated in an entirely in vitro system, the mixed lymphocyte culture (18), we cannot attribute this event to immunosuppression. It seems more likely that the lymphomas arise from the action of oncogenic viruses that are activated within immunologically transformed lymphocytes and that the continuous recruitment of such cells, which is a striking feature of the GVHR (5), supplies the expanding mass of neoplastic tissue.

ACKNOWLEDGMENTS

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