Further Observations Concerning Effects of Antilymphocyte Serum on Tumor Growth: With Special Reference to Allogeneic Inhibition

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SUMMARY

Antilymphocyte serum (ALS) administration was observed to abrogate preexisting immunity to C3H tumors, permitting them to grow equally as well as, or slightly better than, in nonimmunized animals. Metastases from spontaneous C3H tumors were observed in ALS-treated mice but not in controls, indicating the possible importance of concomitant immunity in the phenomenon of metastases. This was not related to effects of ALS on the tumor cells per se as revealed by the behavior of transplants from treated animals in syngeneic hosts as well as their unaltered subcellular appearance. ALS failed to influence the latent period of 3-methylcholanthrene-induced tumors. These findings are considered in relation to the observations of others on the mechanism of 3-methylcholanthrene tumor induction. Incubation in vitro of tumor cells in ALS was without effect on their subsequent growth in syngeneic hosts. However, such incubation resulted in complete abrogation of the tumor growth-inhibitory effect observed in F1 hybrids (C3H × DBA). The amount of ALS used in the incubation was insufficient to influence tumor growth when administered at a site remote from that utilized for tumor incubation. Prior incubation in ALS allowed C3H tumor cells to grow in allogeneic DBA mice. When F1 hybrid spleen cells or sensitized lymphocytes were incubated with tumor cells before their inoculation into syngeneic hosts, a retardation of tumor growth occurred. Addition of ALS to the incubate eliminated this inhibitory effect. Inoculation of tumor cells alone resulted in a depression of circulating lymphocytes. When cells were injected in ALS or the latter was inoculated at a separate site, depression of lymphocytes was greater and more sustained than after the administration of either alone. Such findings minimize the importance of lymphopenia in accounting for these results, particularly in the F1 hybrid. Considerations pertinent to these observations strongly indicate the nonimmunological nature of allogeneic inhibition, but, also as discussed, tend to minimize the role of the latter as a surveillance mechanism for autochthonous tumors.

INTRODUCTION

The demonstration that antilymphocyte serum could suppress cellular immunity (40), delayed hypersensitivity (38, 39), and humoral antibody responses (21, 28) as well as prolong the survival of organ transplants (27, 41) led to its use for the elucidation of certain facets of tumor biology. Its effect on viral oncogenesis (1, 2, 5, 36, 37), allogeneic (4, 9, 17) and xenogeneic (3, 7, 22, 30, 33) tumor transplants, tumor production in humans after kidney transplantation (10, 29), and tumor cell kinetics (8) have all received attention. Recently, we reported that the administration of ALS resulted in augmentation of “takes,” growth and metastases of mouse mammary tumors (11), and of MCA-induced tumors (14) in their syngeneic hosts (C3H mice in the former and Lewis rats in the latter). Also, ALS was found by us (12) to abrogate completely the phenomenon of allogeneic inhibition, allowing tumors to grow as well in F1 hybrid mice receiving ALS as in the parental strain. The present investigations have been performed in an attempt to clarify mechanisms responsible for these findings, as well as to ascertain the effects of ALS on other parameters of tumor growth.

MATERIALS AND METHODS

ALS and NRS. ALS was prepared in New Zealand female rabbits with the use of lymphocytes from lymph nodes and thymus of either C3HeB mice or Lewis rats according to previously described methods (15). All serum was heated to inactivate complement, was sterilized by filtration, and was stored at —20° until used. Leukoagglutination titers of all batches of ALS utilized were greater than 1:64. NRS and Sprague-Dawley rat serum similarly prepared had a titer of zero. ALS and NRS were administered i.p. 0.25 ml/day to mice and 2.0 ml/day to rats. All ALS preparations were found to reduce effectively the total leukocyte and lymphocyte counts.

Animals and Tumors. Spontaneous mammary tumors occurring in C3H/He mice and MCA-induced tumors in Lewis rats were used in these studies. The latter tumors were produced by the s.c. injection with 10 mg of MCA in 0.5 ml of sesame oil. Eight-week-old C3H mice and Lewis female rats, 150 to 200 g (isogenic strain), were used for tumor transfer. In the studies relative to allogeneic inhibition, C3D2F1/J and DBA/2J female mice were used. Methods of preparation of tumor cell suspensions and technique of inoculation have previously been described in detail by us (13).

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The abbreviations used are: ALS, antilymphocyte serum; MCA, 3-methylcholanthrene; C3H, C3HeB/FeJ mice; NRS, normal rabbit serum; PHA, phytohemagglutinin.
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**Tumor Immunization.** Uniform plugs obtained from C3H tumors from mice by means of a 16-gauge needle were inserted s.c. into the left hind leg at the ankle. When tumors reached 0.5 cm (average 23 days) tumor-bearing limbs were amputated. Subsequent exposure of such animals to a tumor cell challenge was utilized to demonstrate immunity.

MCA tumor plugs from rats were implanted s.c. in the abdomen, and the entire tumor was removed when it reached 2 to 3 cm in diameter (average 2 wk).

**RESULTS**

**Effect of ALS on Tumor Incidence in Immunized Mice.** C3H mice previously immunized to C3H tumor were inoculated with $5 \times 10^5$ C3H tumor cells. One-half of the immunized animals received ALS daily until sacrifice 30 days later. The other half were recipients of similarly administered NRS. A nonimmunized group of C3H mice, inoculated with a similar challenge dose of tumor cells and treated with NRS served as controls. It was observed (Chart 1) that ALS administration abrogated immunity, permitting tumors to grow as well, or even slightly better, than was observed in animals which had not been previously immunized.

**Effect of ALS on Metastases of Autochthonous C3H Tumors.** Twelve C3H mice bearing spontaneous mammary carcinomas were randomly divided into 2 equal groups having tumors of comparable size (3 to 5 mm). Animals in Group I received ALS daily, whereas those in Group II served as controls and received NRS. After 4 weeks of such treatment, all animals were sacrificed, and it was observed that, while none of the control animals demonstrated tumor metastases, 3 of the ALS-treated animals had secondary tumors. In one there was a single lung metastasis; in another there was a liver and lung metastasis; and the third demonstrated axillary node involvement.

**Effect of ALS on Time of Appearance of MCA-induced Tumors.** The daily administration of ALS beginning 100 days after injection of MCA and continuing until tumors occurred failed to enhance the appearance of such tumors in Lewis rats. The cumulative percentage of tumors appearing subsequent to ALS administration was similar to control groups receiving 0.9% NaCl solution. Untreated controls (12) demonstrated some delay in tumor appearance when compared with animals receiving either ALS or 0.9% NaCl solution. The average time of tumor appearance in the ALS-treated animals (12) was 149 ± 22 days; for those receiving 0.9% NaCl solution (12) 146 ± 20 days; and 162 ± 29 days for the controls.

**Growth in Syngeneic Animals of Cells Obtained from Tumors in ALS-treated Hosts.** Cell suspensions were prepared from C3H tumors grown in C3H mice which were daily recipients of ALS or NRS. Normal C3H mice were inoculated s.c. with $5 \times 10^5$ of these cells. The cumulative percentage of animals growing tumors (Chart 2), as well as subsequent growth rates, were not significantly different for tumors obtained from ALS- or NRS-treated animals.

A similar experiment was performed with the use of MCA-induced tumors from ALS- and NRS-treated Lewis rats. Transfer of tumors from such animals to normal hosts demonstrated no better growth when tumors had previously been exposed to ALS. The average time of tumor appearance in normal animals inoculated with tumor cells from ALS-treated animals was 18.3 days (10 to 32 days) and 15.6 days (13 to 24 days) with tumor cells prepared from animals receiving NRS. At 30 days after tumor cell inoculation, tumors averaged 1.3 cm in the former group and 1.4 cm in the latter.

**Effect of In Vitro Incubation of C3H or MCA Tumor Cells in ALS on Subsequent Growth in Syngeneic Animals.** Neither tumor appearance nor subsequent growth in normal C3H mice was specifically influenced by prior incubation of C3H tumor cells in ALS at $37^\circ$ for 2 hr. This was noted when either $5 \times 10^3$, $5 \times 10^4$, or $25 \times 10^3$ cells were used (Table 1, Experiments A, B, and C). In Group IV of Experiment A and Group III of Experiment C, control animals were given injections of nonincubated tumor cells in 0.9% NaCl solution and received

![Chart 2. Growth of cells obtained from tumors in ALS- and NRS-treated hosts.](chart.png)
at a separate site a volume of ALS equal to the volume containing the incubated tumor cells. In none of these experiments was there evidence to indicate that the growth of ALS-treated tumor cells was enhanced.

Similar series of experiments were performed (Table 2) with the use of MCA tumor cells incubated in NRS, ALS, or 0.9% NaCl solution. The appearance and subsequent growth in Lewis rats of an inoculum of either 1 x 10^6 or 2 x 10^6 cells were unaffected by incubation with ALS.

**Effect of In Vitro Incubation of C3H Tumor Cells in ALS on Subsequent Growth in F1 Hybrid and Allogeneic Hosts.** C3H tumor cells (2.5 x 10^4) incubated in 0.1 ml of ALS for 2 hr at 37° were inoculated s.c. into C3D2F1 mice. Similar numbers of cells incubated in NRS were inoculated into groups of C3H and C3D2F1 mice. Animals were observed for 60 days. A markedly greater incidence of tumors appeared in the parental (C3H) strain than in the F1 hybrid when cells incubated in NRS were utilized. On the other hand, F1 hybrids inoculated with tumor cells incubated in ALS grew tumors better than did the parental (C3H) strain (Chart 3). A single s.c. injection of 0.1 ml (that amount used for incubation) of either ALS or NRS at a site separate from that of tumor cell inoculation failed to affect the growth of nonincubated cells in C3D2F1 mice (Chart 4).

A similar number of tumor cells in 0.9% NaCl solution were inoculated s.c. into DBA mice (Chart 5). No tumor growth occurred in any animal observed for as long as 100 days. When cells were incubated in NRS and injected into DBA mice, tumors appeared in 2 of 7 (29%) at 25 and 31 days after injection. They grew to 2 and 4 mm in diameter and then completed regression so that by 40 days they had disappeared. Inoculated cells similarly incubated in ALS resulted in tumor growth in 2 animals. One which appeared 31 days after injection continued to grow progressively until sacrifice, at

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**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of tumor cells injected</th>
<th>No. of mice</th>
<th>Days to appearance (average)</th>
<th>Days to 0.5 cm (average)</th>
<th>Days to 1.0 cm (average)</th>
<th>% growing by 30 days</th>
<th>% reaching 0.5 cm by 30 days</th>
<th>% reaching 1.0 cm by 30 days</th>
<th>% reaching 2.0 cm by 30 days</th>
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<tr>
<td>Experiment A</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I. NRS</td>
<td>5 x 10^6</td>
<td>6</td>
<td>6.3(5-8)</td>
<td>15.0(13-19)</td>
<td>25.0(21-32)</td>
<td>100</td>
<td>100</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>II. ALS</td>
<td>5 x 10^6</td>
<td>6</td>
<td>13.3(7-15)</td>
<td>19.2(16-25)</td>
<td>27.0(22-35)</td>
<td>100</td>
<td>100</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>III. NaCl solution (0.9%) (no incubation)</td>
<td>5 x 10^6</td>
<td>6</td>
<td>10.0(7-14)</td>
<td>21.0(18-29)</td>
<td>29.3(24-41)</td>
<td>100</td>
<td>100</td>
<td>83</td>
<td></td>
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<tr>
<td>IV. NaCl solution (0.9%) (no incubation) and ALS s.c.</td>
<td>5 x 10^6</td>
<td>6</td>
<td>15.3(7-24)</td>
<td>24.7(16-32)</td>
<td>31.0(24-40)</td>
<td>100</td>
<td>83</td>
<td>50</td>
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**Table 2**

<table>
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<tr>
<th>Group</th>
<th>No. of tumor cells injected</th>
<th>No. of rats</th>
<th>No. of days to appear</th>
<th>% growing by 30 days</th>
<th>No. of days to 0.5 cm</th>
<th>% reaching 0.5 cm by 30 days</th>
<th>No. of days to 1.0 cm</th>
<th>% reaching 1.0 cm by 30 days</th>
<th>No. of days to 2.0 cm</th>
<th>% reaching 2.0 cm by 30 days</th>
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<tbody>
<tr>
<td>I. NRS</td>
<td>1 x 10^6</td>
<td>7</td>
<td>4.1(3-6)</td>
<td>100</td>
<td>8.3(5-12)</td>
<td>100</td>
<td>100</td>
<td>13.3(9-18)</td>
<td>100</td>
<td>19.0(16-25)</td>
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<tr>
<td>II. ALS</td>
<td>1 x 10^6</td>
<td>7</td>
<td>3.7(3-4)</td>
<td>100</td>
<td>8.1(5-13)</td>
<td>100</td>
<td>100</td>
<td>10.0(6-14)</td>
<td>100</td>
<td>17.6(12-25)</td>
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<tr>
<td>III. NaCl solution (0.9%)</td>
<td>1 x 10^6</td>
<td>7</td>
<td>5.4(4-9)</td>
<td>100</td>
<td>8.0(6-11)</td>
<td>100</td>
<td>11.1(10-12)</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. NRS</td>
<td>2 x 10^6</td>
<td>6</td>
<td>5.0(4-7)</td>
<td>100</td>
<td>9.0(8-11)</td>
<td>100</td>
<td>100</td>
<td>14.7(14-17)</td>
<td>100</td>
<td>25.1(23-30)</td>
</tr>
<tr>
<td>II. ALS</td>
<td>2 x 10^6</td>
<td>6</td>
<td>10.5(7-14)</td>
<td>100</td>
<td>16.3(12-21)</td>
<td>100</td>
<td>100</td>
<td>21.0(15-25)</td>
<td>100</td>
<td>29.8(23-36)</td>
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</table>
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Chart 5. Effect of ALS on growth of C3H tumor cells in DBA mice.

Chart 4. Effect of ALS or NRS on growth of nonincubated C3H tumor cells in C3D2F1 mice.

which time it measured 2 cm. The other appeared at 66 days, reached a diameter of 6 mm, and then regressed completely. In another group, tumor cells in 0.9% NaCl solution were inoculated s.c., and an amount of ALS equivalent to that utilized in incubation (0.1 ml) was injected at a separate site. At 45 days, 3 of 7 (43%) grew tumors. One appearing at 24 days grew progressively to 2 cm at sacrifice (45 days). A second appeared at 31 days, reached 1.5 cm at 47 days, and regressed completely. In a third animal, tumor appeared at 26 days, reached 0.5 cm at 31 days, and regressed until 63 days, when it again began to grow. It reached 1 cm at 70 days and remained at this size until sacrifice at 89 days.

Effect of In Vitro Incubation of C3H Tumor Cells and Normal F1 Hybrid Lymphocytes (Spleen) with and without ALS on Subsequent Tumor Growth. C3H tumor cells were incubated with spleen cells obtained from normal C3D2F1 mice. The ratio of tumor cells to spleen cells was 1:1000. All incubations were for 2 hr at 37°. Animals received a s.c. inoculation of 5 x 10⁴ of these incubated tumor cells. This experiment was carried out twice—once with the addition of sufficient PHA to bring about closer cell contact of lymphocyte and tumor cells during incubation and once without PHA. In both circumstances, when F1 hybrid spleen cells were incubated with tumor cells and then returned to recipient mice, tumors were observed in animals receiving tumor cells alone, tumor cells + ALS, tumor cells incubated in ALS, and tumor cells + PHA. The percentage of tumors developing was lower in the latter two groups. In general, tumors that appeared after incubation were larger than when tumor cells alone were injected. The size and number of tumors appeared to be influenced by the number of F1 spleen cells injected, but this factor was not systematically studied.

Effect of ALS on subsequent tumor growth. When tumor cells were incubated with ALS and then injected s.c. into C3H mice, the growth of tumor cells was significantly reduced compared to mice injected with tumor cells alone. The results are shown in Chart 6.

Chart 7. Effect of incubation of tumor cells and F1 spleen cells in ALS with PHA on subsequent tumor growth.

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cells incubated with sensitized lymphocytes in NRS was inhibited. When, however, such tumor cells were exposed to sensitized lymphocytes in the presence of ALS, the number of animals developing tumor was greater and the time required for tumor appearance was less than that observed in the other groups (Chart 8).

Effect of a Single Injection of ALS, Tumor Cells, Tumor Cells Incubated in ALS, or Tumor Cells and ALS at Separate Sites on Circulating Lymphocytes of the Mouse. The inoculation of 0.1 ml of ALS s.c. (Chart 9) resulted in the production of a significant decrease in circulating lymphocytes in C3HeB, C3D2F1, and DBA mice 24 hr after injection. Counts remained depressed for variable times in the 3 strains; the most prolonged effect was observed in the DBA animals. Seven days after inoculation counts had not yet returned to the preinjection level. When tumor cells in 0.9% NaCl solution were inoculated into such animals, all demonstrated a similar pattern of lymphocyte depression. In C3H mice, a marked decrease in lymphocytes was found 48 and 72 hr after injection; in the C3D2F1 and DBA animals, this was evident only 48 hr after injection. When ALS and tumor cell suspensions were injected at separate sites or tumor cells incubated in ALS were inoculated, the reduction in circulating lymphocytes was greater and more sustained than that observed after inoculation of each alone. The procedure of repeated blood counts in normal animals of any strain failed to influence the lymphocyte count.

Attempt to Localize ALS by fluorescent Antibody Technique and Effect of ALS on Tumor Cell Ultrastructure. Transplanted C3H and MCA-induced tumors growing in their syngeneic hosts which were treated with ALS or NRS daily for 2 weeks were removed after the conclusion of treatment. Portions were immediately frozen on Dry Ice and fixed in either Zenker acetic fluid or 1% osmium tetroxide buffered to pH 7.4 with Veronal. Sections prepared from paraffin blocks of Zenker’s fixed tissue were stained with hematoxylin and eosin. Ultrathin sections of material imbedded in Maraglas after osmium fixation were stained with lead citrate and examined with a Philips EM 300 electron microscope.

Frozen tissue was sectioned in a cryostat, stained with anti-rabbit γ-globulin conjugated with fluorescein isothiocyanate, and examined by ultraviolet fluorescence microscopy. Smears of suspensions of tumor cells incubated in ALS and NRS were also examined by this fluorescent antibody technique.

Inconsistent and inconclusive fluorescence was detected in cell cytoplasm and plasma membranes of cells from tumors of both ALS- and NRS-treated animals, as well as in those incubated in ALS or NRS. No differences in tumor cells were appreciated by light or electron microscopy.

DISCUSSION

We have demonstrated the ability of ALS to suppress the primary immune response to tumors, resulting in enhancement of various parameters of their growth, including metastases, in syngeneic hosts with the use of both first and later generations of transplanted tumors (11, 13). The present studies revealed...
that, when animals bearing autochthonous tumors were treated with ALS, metastases resulted. This did not occur in untreated controls. Findings thus suggest that ALS suppressed immunity to tumor rather than histocompatibility antigen(s) which might have occurred with grafted tumors. The abrogation of established tumor immunity by ALS is analogous to its effect in inhibiting second-set allograft reactions (23, 28). Moreover, such findings indicate the importance of concomitant immunity in the metastatic process.

It has been suggested (31) that the carcinogenic activity of MCA is related to inhibition of immunological responsiveness. MCA has been noted to depress humoral antibody response (6, 24). Recently, a depression of immune response which extended over a period of time corresponding to the latent period of primary sarcomas induced by a single exposure to the carcinogen has been demonstrated (34, 35). Our failure to observe acceleration of MCA-induced tumors after prolonged ALS administration is not necessarily contradictory. If immunity was depressed by MCA, then the comparable activity of ALS might have been masked and its effect on tumor growth would not be evident. It would seem that, at least in the terminal portion of the tumor latent period, immunological manipulation is without consequence in this system. These findings are in keeping with those of Haughton et al. (16) who noted that the prolonged administration of ALS neither increased the incidence nor decreased the latency of primary tumors induced by MCA.

The observation by Snell (32) that a transplanted lymphoma grew better in syngeneic mice than in F1 hybrids and the demonstration of this phenomenon in other tumor lines has led to speculation concerning its mechanism(s). This deficient tumor growth in hybrids has been designated "allo-
genic inhibition" (18–20). Recently, we observed (12) that ALS abolished allogeneic inhibition. Tumors grew as well in F1 hybrid mice receiving ALS as in syngeneic hosts. Such findings suggest that allogeneic inhibition is the result of immunological mechanisms rather than the nonimmunological factors postulated by the Hellströms (18–20) and the Möllers (25, 26). The possibility was considered, however, that ALS could have exerted its effect by locally interfering with the interaction of tumor cells and host cells containing foreign histocompatibility antigens. That the incubation in vitro of tumor cells with ALS before their inoculation into a F1 hybrid resisted allogeneic inhibition seems to support the non-

immunological nature of the phenomenon.

In further support of a nonimmunological mechanism was the observation that tumor growth in F1 hybrids was not affected by the administration at a separate site of an amount of ALS equal to that injected with tumor cells after their incubation. If results after incubation were related to the immunosuppressive action of ALS, it might be expected that ALS injected at a separate site would be equally effective. The observation that incubation of F1 hybrid spleen cells with C3H tumor cells before injection could partially prevent tumor growth, and that the addition of ALS interfered with this effect, likewise supplies support for a nonimmunological mechanism. The finding that circulating lymphocytes were depressed by ALS injected alone or together with tumor cells, or by tumor cells alone tends to minimize the importance of lymphocyte reduction—and consequently immunity—as the mechanism responsible for allogeneic inhibition.

If the effect of ALS is nonimmunological, other modes of action require consideration. Despite inconclusive evidence obtained with the fluorescent antibody technique, coating of tumor cells with ALS may have been responsible. Such covering of antigen sites might have interfered with the confrontation between cells containing different H-2 isoantigen(s). The possibility also existed that a single injection of a small amount of ALS at a site separate from the tumor cells may have depressed the immune response to a degree not recognizable. Such a slight depression in conjunction with target cells coated with ALS by incubation may have permitted the tumor growth effect in the F1 hybrid. Consideration must also be given to the possibility that coating of tumor cells may have interfered with antigen release.

The effect of ALS on C3H tumor growth in DBA mice also offers evidence in support of the nonimmunological considerations given to the tumor effect observed in F1 hybrids. As a result of strong histocompatibility difference, C3H tumor cells completely failed to grow in untreated DBA hybrids. The observation that some growth did occur when tumor cells were prior incubated in ALS, as well as when tumor cells and ALS were inoculated at separate sites, suggests that the small amount of ALS was able to interfere with the host response to the homograft (tumor cells) sufficiently to permit its "take." That tumors grew slight and then-regressed after incubation of tumor cells in normal serum indicates that this was the consequence of a local effect of NRS on tumor cells. The greater and more progressive growth of tumors when ALS was administered implies that a systemic as well as a local effect could have resulted. Perhaps a state of partial tolerance was induced in allogeneic hosts, permitting subsequent tumor growth. If such be so, it might have been anticipated that such tolerance would have been more readily accomplished in F1 animals. Failure to observe an increase in tumor growth in such animals when ALS was injected separately credits this mechanism as being responsible for overcoming this hybrid effect seen when tumor cells were inoculated in ALS. It also suggests that tumor growth effects observed in F1 hybrids and in the allogeneic animals as a result of ALS were related to different mechanisms.

Failure to alter tumor growth when either C3H or MCA tumor cells were incubated in ALS before their injection into normal syngeneic hosts, or when cells obtained from tumors in ALS-treated hosts were inoculated into untreated suitable hosts, lends further credence to the concept of allogeneic inhibition. Because there was no histocompatibility difference between tumor cells and syngeneic host cells such as existed between F1 hybrid cells and tumor cells, there was no interference with cellular confrontation.

Because the ALS used in these studies was raised against C3H lymphocytes without exposure to tumor antigen, it seems possible that ALS incubation with tumor cells could result in its binding to histocompatibility antigens (C3H) while not affecting tumor antigen(s). The ability of such cells to grow, despite their encounter with cells containing foreign histocompatibility antigens (derived from the DBA parent in the F1 hybrid), suggests that allogeneic inhibition might occur.
only between cells containing dissimilar strong histocompatibility antigens, and that confrontation between tumor antigen and H antigen does not result in tumor growth inhibition. If that be so, then the importance of allogeneic inhibition as a tumor surveillance mechanism may be markedly diminished. For, in autochthonous tumors no such histocompatibility difference between tumor and normal cells should exist.

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REFERENCES


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