The Effect of Antilymphocyte Serum on the Recognition of Tumor-Specific Transplantation Antigens[1] (34865)

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It has been shown by Fisher *et al.* (1) that the administration of antilymphocyte serum (ALS) will accelerate the appearance, growth, and metastasis of transplantable murine tumors. However, their studies were terminated following death of the tumor recipients and therefore, it was not determined whether or not immunosuppression prevented host recognition of tumor-specific transplantation antigens (TSTA). This report provides evidence that ALS not only augments the growth of a transplantable tumor but also interrupts the normal development of induced tumor resistance following excision and rechallenge.

Materials and Methods. All experiments were performed using a syngeneic tumor–host system, *i.e.*, a 20-methylcholanthrene-induced fibrosarcoma of recent origin maintained by serial transplantation in C57BL/6J mice. ALS was harvested from New Zealand rabbits after immunization with Freund's adjuvant and thymocytes from ICR Swiss mice (2). Normal mice were given five injections of 0.1 ml of ALS subcutaneously on days —2, 0, 2, 4, and 6, a course which significantly prolongs the survival of skin allografts. On day 0, mice were challenged in the hind leg with quantitative doses (ranging from 10^2–10^7 cells) of an enzyme-prepared tumor suspension. Control groups received only normal rabbit serum (NRS) and tumor. Mice were observed for the appearance of tumors, two-dimensional measurements were made, and volumes were calculated according to the method of Attia and Weiss (3). The significance of observed differences was tested using the Wilcoxan-Mann-Whitney Rank Order Test.

Immune resistance was assayed by amputating a growing tumor and rechallenging the host with tumor cells 1 week later. However, ALS was never given at the time of rechallenge. Final tumor incidence was compared using fourfold table analysis (chi-square).

Results. In an initial experiment, mice receiving ALS exhibited a significantly increased tumor growth rate, an effect which was clearly related to the challenge dose (Table I). Those receiving an overwhelming challenge (10^6 cells) soon developed tumors concurrent with and at the same growth rate as controls. Since tumor incidence following 10^2 cells was quite low, this was considered

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TABLE I. Effect of Antilymphocyte Serum on Tumor Appearance and Growth Rates.

Initial tumor challenge (no. of cells)	Treatment (0.1 ml × 5 sc)	Tumor incidence		Mean tumor vol (mm^3) at 30 days	Significance (Wilcoxan test)
		At 15 days	At 30 days		
10^6	ALS	10/10	10/10	253	—
	NRS	10/10	10/10	266	
10^4	ALS	8/10	10/10	276	$p < .05$
	NRS	2/10	10/10	169	
10^2	ALS	0/10	1/10		—
	NRS	0/10	1/10		

TABLE II. Effect of Antilymphocyte Serum on the Induction of Tumor-Specific Immunity.

Initial tumor challenge (no. of cells)	Postamputation challenge (no. of cells)	Tumor incidence		Significance (chi-square)
		ALS treated	NRS treated	
10^4	10^4	10/10	4/10	$p < .05$
10^2	10^3	4/7	3/5	—
10^3	10^3	7/9	2/8	$p < .10$
10^4	10^3	6/7	0/7	$p < .01$
Cumulative incidence:		27/33	9/30	$p < .02$

to be a subthreshold dose. However, at the midpoint of the dose range (10^4 cells) a distinct difference in both rate of appearance and rate of tumor growth was observed.

The second experiment was designed to examine the immunity of immunosuppressed mice after tumor exposure. Normally, mice are resistant to subsequent challenge following tumor amputation. After their tumors were surgically removed, mice were rechallenged with 10^4 cells 1 week later. ALS-treated mice soon developed tumors whereas controls receiving NRS were resistant. This experiment was repeated three times and the results are summarized in Table II.

Discussion. These studies confirm the findings of Fisher *et al.* (1) that ALS can speed the appearance and growth of transplantable tumors, an observation which is in agreement with reported clinical experience; namely, that metastatic tumor, when inadvertently transferred with a renal allograft, grows well in the new allogeneic host as long as the recipient was receiving immunosuppressive drugs (4).

In addition, these studies provide evidence that ALS can block the recognition of tumor-specific antigens. This is in accordance with the findings of Levey and Medawar (5) showing that ALS prevents both sensitization and the development of immunologic memory following skin allograft rejection. This similarity is not unexpected since it has been shown that tumor immunity, like allograft rejection, is a cell-mediated immune function (6, 7).

Schwartz (8) has recently reviewed a considerable body of evidence which suggests that immunosuppressive chemotherapy of advanced cancer may be self-defeating. Similarly, these data cast doubt on the propriety of administering adjunctive immunosuppressive chemotherapeutic drugs to patients at the time of excisional surgery, a time when patients may still be able to recognize and respond to tumor antigen(s).

Summary. Antilymphocyte serum, when administered to mice together with transplanted tumor, not only induces augmented neoplastic growth but also blocks host recognition of tumor-specific antigens.

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