

# The Effect of an Allergic Inflammatory Response in the Tumor Bed on the Fate of Transplanted Tumors in Mice\*

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Since tumor transplantation became one of the basic technics in experimental cancer research, a huge number of publications have appeared reporting attempts to identify the mechanisms responsible for the success or failure of tumor grafts. An extraordinary number and variety of factors have been observed to influence the extent and rate of growth of tumor transplants.

The possibility that an inflammatory response in the tissues of the host into which the tumor is transplanted might affect its development is almost universally accepted. Unfortunately, investigations of this problem have yielded seemingly conflicting results. For example, Zahl and Nowak (3) observed that an inflammatory response in the subcutaneous tissues at the site of implantation, produced by excessive trauma at the time of implantation, caused acceleration of the growth of Sarcoma 180 in mice. On the other hand, when Chambers and Scott (1), also using Sarcoma 180, produced the inflammatory response by injecting the tumor graft with starch grains, they observed an inhibition of its growth. Similarly, contradictory results were obtained when the inflammatory response was produced by infecting the tumor graft before implantation or by introducing infectious organisms into the graft site at the time of implantation. These are discussed in the recent review by Snell (2).

In all the experiments cited above, the inflammatory response at the site of implantation was produced by using a tumor graft which had been altered in some way or by introducing an additional exogenous factor at the time of implantation. This report concerns the effects on tumor grafts of an inflammatory response which may be considered entirely endogenous (i.e., one which

arises entirely within the tissues of the host at the implantation site and is independent of the nature of the graft and of the act of implantation). This was accomplished by using mice which had been sensitized by repeated injections of a crystalline antigen so that either a local or a systemic injection of that antigen produced an inflammatory response localized to the tumor graft site.

## MATERIALS AND METHODS

Since neither the direction nor the magnitude of the effect of such an inflammatory action upon the development of the tumor graft was known, two parallel experiments were performed. In one, a well established tumor was grafted into an inbred mouse strain in which it grew well (Fibrosarcoma S621<sup>1</sup> in C Scott mice). In the other, a nonindigenous tumor was used in another inbred mouse strain (Sarcoma I<sup>2</sup> in DBA1/Jax mice), in which it regressed. In all instances, the customary trocar method for transplanting fragments of freshly cut tumor was employed.

### EXPERIMENT 1: FIBROSARCOMA S621 IN C SCOTT MICE

A group of 300 C Scott mice from the R. B. Jackson Memorial Laboratory, 8-10 weeks old, was controlled for freedom from enteric, respiratory, and Bartonella infections. To make certain of the absence of infection, each mouse was given a single intraperitoneal injection of a mixture of an-

<sup>1</sup>S-621 is a fibrosarcoma originally developed in BALB/C mice in 1948 at the R. B. Jackson Memorial Laboratory of Bar Harbor, Maine. Three or 4 days following the implantation of the usual, tiny tumor graft, a nodule can be palpated, and the animals rarely survive more than 3 or 4 weeks. This tumor was made available to us by Dr. G. D. Snell of the R. B. Jackson Memorial Laboratory of Bar Harbor, Maine.

<sup>2</sup>Sarcoma I is a polyhedral cell, a sarcoma originally developed in A strain mice in 1947 at the University of California. Two or 3 days following implantation of the usual tumor graft, a nodule is easily palpated. The average survival time of the tumor animal is 3 weeks. This tumor was made available to us through the courtesy of Dr. G. D. Snell of the R. B. Jackson Memorial Laboratory of Bar Harbor, Maine.

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tibiotics 4 days prior to the inception of the experimental procedure. No reactions to these injections were observed. The mice were divided into seven groups and treated as follows:

*Group A (60 animals).*—Each mouse was immunized by an intravenous injection of crystalline ovalbumin followed by five intraperitoneal injections of the same material at 4-day intervals. Ten days following the last injection, intradermal injection of a skin-test dose of the crystalline ovalbumin was given. Four to 6 hours later, when the characteristic localized inflammatory reaction had appeared, a live tumor graft of Fibrosarcoma S621 was implanted by trocar at that site.

*Group B (60 animals).*—The mice were treated exactly as in Group A. When the grafted tumor had grown to a size of 0.5–0.7 cm. in diameter, a second inflammatory response at the implantation site was produced by an intravenous injection of crystalline ovalbumin.

*Group C (30 animals).*—The mice were treated exactly as in Group A. When the grafted tumor had grown to a size of 0.5–0.7 cm., the second inflammatory response was produced by an intradermal injection of the crystalline ovalbumin at the implantation site.

*Group D (40 animals).*—The mice were immunized in the same manner employed for Group A. Without any other injections, the tumor grafts were implanted. When these had grown to a size of 0.5–0.7 cm. in diameter, an intravenous injection of crystalline ovalbumin was given as in Group B. However, since the site of implantation had not been sensitized by a previous intradermal injection, no localized inflammatory response was observed.

*Group E (40 animals).*—The mice were immunized and the tumors implanted as in Group D. When the tumor graft had grown to a size of 0.5–0.7 cm. in diameter, a skin-test dose of the crystalline ovalbumin was injected at the site of the tumor transplant, resulting in the characteristic localized inflammatory reaction.

*Group F (50 animals).*—The mice were given saline injections by the same routes and intervals used for the immunizing injections given to the mice in the previous groups. A skin-test dose of crystalline ovalbumin was injected intradermally. Four hours later, when no signs of a local inflammatory reaction were to be noted, the tumor grafts were implanted at the site of the intradermal injection.

*Group G (20 animals).*—These mice received no injections. Each received a tumor graft identical to those used in the above groups.

#### EXPERIMENT 2: SARCOMA I IN DBA1/JAX MICE

A group of 152 DBA1/Jax mice were controlled for freedom from enteric, respiratory, and *Bartonella* infections. Four days prior to the start of the experiment, each mouse received a single intraperitoneal injection of mixed antibiotics. The mice were divided into five groups and treated as follows:

*Group A (48 animals).*—Each mouse was sensitized against crystalline ovalbumin by being given an intravenous injection followed by four intraperitoneal injections at 4-day intervals. A fragment of Sarcoma I was implanted by trocar. When the tumor graft reached a diameter of 0.5 cm., a dose of crystalline ovalbumin was injected intradermally into the site of implantation. The characteristic localized inflammatory response was observed in each instance.

*Group B (36 animals).*—Each mouse received the series of ovalbumin injections and the tumor transplant as in Group A. No further injections were given.

*Group C (26 animals).*—Each mouse received the series of ovalbumin injections as in Group A. Ten days following the last injection, an intradermal injection of ovalbumin was given, resulting in the characteristic local inflammatory response. Four hours later, when this response was well marked, the Sarcoma I graft was implanted at that site.

*Group D (18 animals).*—Saline injections were given in the same manner and frequency used for the previous groups. Ten days following the last injection, an intradermal injection of crystalline ovalbumin was given. No inflammatory response was noted. Four hours later, a graft of Sarcoma I was implanted at the site of the injection.

*Group E (24 animals).*—No injections were given. Each mouse received the graft of Sarcoma I in the manner employed for the previous groups.

## RESULTS

#### EXPERIMENT 1: FIBROSARCOMA S621 IN C SCOTT MICE

Several animals in which the localized inflammatory response was elicited by the intravenous injection of the ovalbumin and several in which it was elicited by the second intradermal injection were sacrificed at the peak of the reaction for histologic examination of the tissues at that site. No significant qualitative or quantitative differences in the inflammatory response were noted.

The mice in each group were examined daily, and measurements of the tumors were made twice weekly. The frequency of takes, the rate of growth, and the ultimate fate of the graft and the host were

the same for all groups of mice. Histologic examination of the tumor grafts and of the surrounding host tissues failed to demonstrate any differences among the groups. Thus, in each instance, the inflammatory response produced by an allergic reaction at the site of implantation failed to influence the development of the tumor graft as compared with the untreated control groups.

#### EXPERIMENT 2: SARCOMA I IN DBA1/JAX MICE

The localized inflammatory responses produced in these animals were grossly identical with those observed in the previous experiment. Accordingly, histologic examinations of the tissues at the time of the inflammatory response were not performed.

Each mouse was examined daily, and measurements of the tumors were made twice weekly. As in the previous experiment, neither the presence of an inflammatory response at the site of the tumor graft at the time of implantation nor one produced after the graft had established itself had any effect upon the frequency of takes, on the rate of growth, or the ultimate fate of the graft or the host. In each animal, treated as well as control, the tumor graft established itself, continued to grow for a time, and ultimately regressed. Once again, the histologic examination of the tumor tissue and of the tissues of the tumor bed failed to demonstrate any significant differences between those animals in which the local inflammatory response had been produced and those in which it was absent.

#### DISCUSSION

In these experiments, the presence of an allergic inflammatory response at the site of tumor implantation produced by local tissue reaction to a foreign protein failed to influence either the growth and development of the tumor graft or the reactions of the tissues of the host to the tumor. No differences were observed between those instances in which the graft was implanted directly

into tissues demonstrating an acute inflammatory response and those in which the inflammatory response was produced in the tumor bed following the successful implantation of the tumor. It must be concluded, therefore, that the localized allergic inflammatory response at the site of a tumor implantation *per se* has no effect upon the development of the graft. It suggests that, in those instances in which such effects have been reported, the tumor graft and/or the tissues of the tumor bed were directly altered in some way by the mechanism used to induce the localized inflammatory response.

#### SUMMARY

The effect of a local allergic inflammatory response at the site of transplantation upon the fate and development of the tumor graft was studied in two parallel experiments employing Fibrosarcoma S621 in C Scott mice and Sarcoma I in DBA1/Jax mice. The mice were sensitized by a series of injections of crystalline ovalbumin, and the local inflammatory response was produced by intradermal injections of the ovalbumin at the tumor site. In both experiments, no differences were noted between the animals in which inflammatory responses were produced and the controls. It is concluded, therefore, that an allergic inflammatory reaction at the site of implantation has no effect upon the development of the tumor graft.

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