TUMOR AUTOGRaFT RESPONSES IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

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The role of host factors in malignant disease has long intrigued cancer investigators. More recently, emphasis has again been placed on immunologic factors of the host. Much of the work on this aspect of the disease was carried out in experimental animals using transplantable tumors and a vast amount of literature has been accumulated on the subject. The interested reader is referred to the excellent reviews of Gorer,9 Snell,27 and Hauschka.16 These are quite comprehensive and present three fairly distinctive viewpoints.

From this work on animals, a great deal has been learned about the genetic and immunologic factors involved in rejection of transplants. For example, abrogation of the immune mechanism may accelerate the appearance, growth and metastasis of a malignant tumor. In addition, some degree of resistance against transplantable tumors in animals may be obtained by active and passive immunization procedures.

In the human, there is both direct and indirect evidence that host factors play a role in the progress of a malignant disease. The most dramatic examples are found in those cases of authentic, spontaneous regressions of malignant neoplasms.5,15,22 Other evidence is suggested by the following: (1) Prolonged survival of patients after incomplete removal of their cancer or the sudden appearance of widespread metastases many years following apparently successful treatment of the primary lesion.8 (2) Regression of proven metastatic disease following removal of a primary tumor.5 (3) Histologic evidence of histiocytic and lymphocytic responses in the local area of some tumors and in regional lymph nodes.1-3 (4) Reports on the detection of tumor-specific antibodies in the serum of an occasional cancer patient.10,14 (5) The presence of hypersensitivity in certain patients to some component of their tumors.11,12 (6) Changes in immunologic responsiveness which may parallel exacerbations and remissions of certain malignant diseases.18,23 (7) Suggestive evidence that enhancement of tumor growth occurred following the use of cortisone and certain toxic cancer chemotherapeutic drugs.17,19 (8) Evidence that huge numbers of tumor cells are exfoliated into the blood stream and lymphatics of patients with malignant tumors without the development of a comparable number of metastases.4,22,23

This study was undertaken because it was found that patients with advanced malignant disease originating outside of the central nervous system showed a relatively low incidence of “takes” when grafted subcutaneously with their own tumor.13 Moreover, tumor cells from individual cancer patients were propagated in tissue culture (usually for only one or two tissue-culture passages) and then reimplanted subcutaneously into the original donor patient. Even though these patients all had far-advanced disease, the incidence of successful “takes” was likewise low.21

We were particularly interested in the use of brain tumors (glioblastoma multiforme) for similar autograft studies because of the peculiar cell types involved and the fact that
this tumor very rarely metastasizes.\cite{7}

The failure to metastasize is probably not ascribable wholly to the inability of the tumor cells to reach the systemic circulation since tumor cells have been demonstrated in the dural sinuses of patients with brain tumors.\cite{24} The cells may be simply unable to grow outside of the central nervous system or host factors may prevent their survival and proliferation.

In an attempt to clarify some of these questions, we performed tumor autografts in 6 volunteer patients undergoing surgery for incurable glioblastoma multiforme.

**METHODS**

All of the patients studied had fairly extensive tumors. At the time of operation, a portion of the tumor was removed and immediately minced finely in cold Locke's solution. The resulting mince suspension was appropriately diluted to make a 50 per cent suspension w/v. The mince was then drawn into a syringe with a 16 gauge needle attached; 1.0 ml. of the tumor mince was inoculated into each of three subcutaneous sites on the anterior aspect of one thigh. The sites of inoculation were marked with intradermal India ink. An additional sample of the tumor and an adjacent portion of grossly normal brain were collected and stored at $-70^\circ\text{C}$. for future serological and skin-testing studies. The sites of inoculation were observed closely for evidence of local reaction and the appearance of nodules. The first two sites of inoculation were excised serially at intervals of 1.5 to 2 months apart. The first was excised 6 to 8 weeks following inoculation. Unless a successful "take" had occurred earlier, the final site of inoculation was left for indefinite observation. In patients who died, the final sites were excised at the time of autopsy.

Serum was collected from each patient prior to autografting and at regular intervals thereafter. These samples of serum were checked by complement fixation, tanned-red cell hemagglutination and agar-precipitation techniques for antibodies directed against antigens present in saline extracts of both normal brain and tumor. Similar saline extracts of both normal brain and tumor, as well as the insoluble fractions of each, were used for subsequent skin testing of 4 of these patients.

![Fig. 1. Original tumor removed from brain during craniotomy and transplanted subcutaneously into the thigh. Note proliferation of the wall of the vessel in the center. The glial cells are small but show pleomorphism and some mitotic activity which is not apparent in this photomicrograph. (There was heavy proliferation of the mesenchymal tissue, with marked necrosis and hemorrhage but very few giant cells.) Hematoxylin and eosin stain.](image)