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This Week's Citation Classic

Kaliss N. Immunological enhancement of tumor homografts in mice. A review.
Cancer Res. **18**:992-1003, 1958.
[Roscoe B. Jackson Memorial Laboratory, Bar Harbor, ME]

The groundwork is described for the initial experiments establishing an immune basis for the enhancement of cancer allografts in actively or passively immunized mice. Immunological enhancement may be applicable to normal tissue allografts and may represent a broad range of other immunological manifestations. [The *SCI*® indicates that this paper has been cited over 390 times since 1961.]

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"I came to the Jackson Laboratory in July 1947 as a senior fellow of the American Cancer Society. My introduction to 'enhancement' was a seminar that summer by George Sneil describing attempts to preimmunize mice with homologous freeze-dried tumor against subsequent tumor allografts. Paradoxically, some of the grafts, rather than experiencing accelerated rejection, grew progressively. This was intriguing since cancers were involved, and the immediate question was whether a 'cancer stimulating substance' was the effector. I addressed myself to this but my research was interrupted by the Laboratory's destruction in an October 1947 forest fire.

"With work resumed in the rebuilt laboratory, I found that pretreatment with freeze-dried normal tissues, specifically and necessarily from mice of strains indigenous to the test allografts, resulted in progressive graft growth. These results militated against the assumption of an 'enhancing substance.' My subsequent use of antiserum was suggested by literature reports of accelerated wound healing in rabbits receiving anti-rabbit spleen serum.[1] My treatment of prospective hosts with either rabbit anti-mouse or mouse anti-mouse tissue serum did ensure the tumor allografts' survival.

"The experiments which eventually established an immunological basis for enhancement, and related 'active' and 'passive' enhancement, were sparked by a report of intraperitoneal (ip) metastases appearing in mice given freeze-dried tumor and cortisone ip and a subcutaneous inoculum of live tumor.[2] (I could not confirm these results experimentally and concluded that live cells in inadequately freeze-dried tumor were the progenitors of the ip 'metastases.')

"Cortisone treatment involutes lymphoid tissues and inhibits antibody production, and this was the tool I used to demonstrate that antigraft antiserum in the host, actively or passively acquired, was the requisite for tumor allograft survival (hence the term 'immunological enhancement'). Indeed, subcutaneous allografts were rejected by mice pretreated simultaneously with a supernatant of freeze-dried homologous tumor and cortisone. The grafts survived in animals given supernatant alone or (and this was the decisive result) pretreated with supernatant and cortisone and in addition given antigraft alloantiserum at the time of tumor grafting. The grafts also grew progressively in mice given alloantiserum plus cortisone or antiserum alone.

"Immunological enhancement, whose expression involves fundamental immunological interactions still to be elucidated, is a definitive area of concern in immunobiology and tissue transplantation. The broad outlines of its experimental conditions for cancer allografts were detailed in my 1958 review, thus accounting for its frequent citation. Clinically, enhancement should promise the survival of normal grafts, seemingly the case with human kidnev grafts.' but it poses a hazard in cancer immunotherapy. As the complexities of immunology are unraveled, however, the hope is to be able to manipulate reactions so as to avoid cancer enhancement and facilitate normal allograft survival. "

1. **Pomerat C M.** A review of recent developments on reticulo-endothelial immune serum (R.E.I.S.). *Quart. Phi Beta Pi* **42**:203. 1946.
2. **Molomut N, Spain D M, Gauit S D & Kreisier L**. Preliminary report on the experimental induction of metastases from a heterologoui cancer graft in mice. *Proc.Nat. Acad. Sci. US* **38**:991-5. 1952.
3. **Batchelor J R & Weish K I.** Mechanisms of enhancement of kidney allograft survival: a form of operational tolerance. *Brit. Med. Bull.* **32**:113-17. 1976.