

This Week's Citation Classic®

Cochran A J, Spitz W G S, Mackie R M & Thomas C E. Postoperative depression of tumour-directed cell-mediated immunity in patients with malignant disease. *Brit. Med. J.* 4:67-70, 1972.

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Cell-mediated immunity to tumor-associated antigens was measured before and after surgery (leukocyte migration inhibition test) in 12 patients with breast carcinoma and 12 with malignant melanoma. Postoperatively leukocyte migration inhibition was reduced in all patients for a period from 6 to 22 days. [The SCJ® indicates that this paper has been cited in over 205 publications.]

The experiments were to demonstrate cellular immunity to tumor-derived materials *in vitro* and to determine whether similar results were obtained in longitudinal studies of individual patients. They were not, and this triggered spirited discussions of experimental technique until it was recognized that the apparent inconsistencies were related in time to the intervening surgical operation. Further experiments confirmed transient immune suppression following surgery, possibly caused by the metabolic consequences of surgery and the effects of anesthetic and other drugs. This raised concerns that this window of immune suppression might facilitate the establishment of tumor cells disseminated during surgical manipulation. Such a possibility is hard to study in humans and, despite its importance, has yet to be conclusively proved or disproved. That this was one of the earliest convincing demonstrations of postoperative immune suppression and continuing concern that this event may facilitate metastases are the most plausible explanations of the article's popularity.

Impressed by the possibility that tumor progression might relate to immune suppression, we went on to examine many facets of the immune response in patients with cancer at various stages of progression. We found that general immune competence was maintained in most patients until their disease advanced and they were subject to multisystem failure.²

The team dissolved amicably in the late 1970s, Mackie becoming professor of dermatology at the University of Glasgow, Spitz becoming consultant pathologist at the Victoria Infirmary in Glasgow, and Thomas, having obtained her PhD, marrying and giving up science, at least for a time. I moved to Los Angeles to join other devotees of melanoma immunology at the University of California, Los Angeles. Mackie, in Glasgow, continues to work on a wide range of aspects of melanoma, contributing to World Health Organization clinical studies of the value of nonspecific therapeutic immune stimulation and EORTC studies of the specificity and sensitivity of a wide range of antimelanoma monoclonal antibodies.

Since coming to Los Angeles I have again become interested in the problems of immune suppression and cancer. In a series of papers,³⁻⁵ we have shown that the lymph nodes nearest to melanoma are immune-suppressed, contain abundant presuppressor cells, and permit the survival of small numbers of tumor cells. We have also shown that melanoma-derived products, such as gangliosides, prostaglandins, and membrane lipoproteins, can down-regulate lymph node cells.⁶ We consider that local immune suppression induced by tumor products facilitates the survival of tumor cells and their expansion into metastases. This occurs in patients who are generally immune-competent.

Surgery-Related Immune Suppression in Cancer Patients

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This study developed from investigations of factors predictive of outcome for melanoma.¹ Prognosis could be estimated with substantial accuracy, using a multifactorial clinicopathological score sheet. However, it was clear that factors other than those detectable by clinical inspection and microscopy were important. One factor that was considered relevant was the role of the immune system in neoplasia. The late 1960s was a period of great activity in tumor immunology and the Karolinska's Department of Tumor Biology, with George Klein and Eva Klein, was a mecca to aspiring tumor immunologists. Two years spent there imprinted a firm conviction that immune factors are important in human cancer and should most properly be studied in man.

Back in Glasgow a decision was made to study cellular immunity in melanoma (because of broad hints from the clinic that this was an immunogenic tumor) and breast cancer (because of its frequency and frequently fatal outcome). A highly enthusiastic team formed: Rona M. Mackie, lecturer in dermatology with an interest in melanocytic tumors; Walter G.S. Spitz, lecturer in pathology, interested in experimental pathology; and Catherine E. Thomas, a biology doctoral student interested in working with human material. This was a democratic group in which all were involved in study design, acquisition of materials, and benchwork (though Katie did most experiments).

1. Cochran A J. Method for assessment of prognosis in malignant melanoma. *Lancet* 2:1062-4, 1968. (Cited 35 times.)
2. Cochran A J, Mackie R M, Grant R M, Ross C E, Connell M D, Sandilands G, Whaley K, Hoyle D E & Jackson A M. Examination of immunology of cancer patients. *Int. J. Cancer* 18:298-309, 1976. (Cited 45 times.)
3. Hoon D S B, Korn E F & Cochran A J. Variations/functional immune competence of human tumor-draining lymph nodes. *Cancer Res.* 47:1740-4, 1987.
4. Hoon D S B, Bowler R & Cochran A J. Suppressor cell activity in melanoma-draining lymph nodes. *Cancer Res.* 47:1529-33, 1987.
5. Cochran A J, Wen D-R & Morton D L. Occult melanoma cells in the lymph nodes of patients with pathological Stage I malignant melanoma. *Amer. J. Surg. Pathol.* 12:612-8, 1988.
6. Hoon D S B, Irie R F & Cochran A J. Gangliosides from human melanomas immunomodulate the response of T cells to interleukin-2. *Cell Immunol.* 8:410-9, 1988.

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