Letter to the Editor

Correspondence re: O. C. A. Scott, Tumor Transplantation and Tumor Immunity: A Personal View. Cancer Res., *51:* 757–763, 1991.

Oliver Scott's recent "Perspectives in Cancer Research" article on tumor transplantation and tumor immunity (1) raises an old issue but one which remains highly relevant. He makes a number of important points, one of which is the questionable genetic homogeneity of inbred animal strains used in early studies of tumor immunology. He suggests that some instances of apparent weak immunogenicity might have arisen as a result of residual heterozygosity. One example he cites (2) forms part of a series of studies carried out over a period of 25 years at the Cancer Research Campaign (CRC) Laboratories (University of Nottingham, U.K.). The main purpose of this letter is to clarify and amplify this particular point.

The animal strain in this example was an inbred rat colony, originally referred to as Wistar and later designated WAB/Not. This strain had a low incidence of spontaneously arising tumors in the breeding stock, and these tumors, at different times, were tested for immunogenicity by immunization and cell challenge experiments, in comparison with carcinogen-induced tumors. Tumors arising during the first 25 or so generations of inbreeding within the CRC Laboratories (following a previous undetermined period of inbreeding by the original suppliers) were predominantly nonimmunogenic by the most sensitive criteria we could devise, but 44% of them elicited a low level of resistance to challenge (3–5). A subsequent series of spontaneous tumors was then obtained, after an intervening period of extensive inbreeding during which newly arising tumors were ignored. The later tumors were derived from animals of more than 35 generations of inbreeding, and a total of 28 were tested for immunogenicity, with uniformly negative results (2). We were unable to explain the discrepancy between the two groups of tumors at the time of publication, although we did mention the elapse of 11 generations of separation from common ancestry (2). As pointed out by Oliver Scott, an explanation was subsequently provided by Bailey (6), who showed that heterozygosity could persist in inbred strains for many more generations than had previously been supposed by tumor immunologists. It thus seems likely that our "positive" results with earlier arising tumors may have been due to remaining weak histocompatibility differences of which we were not aware, and that this artifactual situation was removed by 11 or more generations of further inbreeding. It is to be noted that during our earlier studies we had used tumors of recent origin, carefully matched transplant donors and recipients within 3 generations of common ancestry, included normal tissue controls in many of the immunogenicity tests, and tested for compatibility by exchange of skin grafts, without evidence of overt histoincompatibility.

In comparison with the spontaneous tumors, sarcomas induced by 3-methylcholanthrene were usually highly immunogenic, whether induced early or late in the above inbreeding program (7, 8), indicating that their high antigenicity is a reproducibly acquired characteristic which is not dependent on minor histocompatibility differences between the original host and immunized animals. However, it is important to note that tumors induced by the aromatic amine 2-acetylaminofluorene (and others induced by urethan and diethylnitrosamine; summarized in Ref. 9) were either nonimmunogenic or very weakly immunogenic. This weak immunogenicity was demonstrable during relatively early generations of inbreeding, and its significance is therefore open to doubt. The unequivocal possession of tumor rejection antigens is probably characteristic of neoplasms induced by very few carcinogens (notably polycyclic hydrocarbons), so that strictly speaking these are also artefacts, albeit of a different kind.

The continued belief held by many researchers that almost all rodent tumors can elicit rejection responses in the autochthonous or syngeneic host is clearly erroneous, and any speculation about the existence of host immune responses to human cancer based on such beliefs is misleading. The present generation of researchers in biological response modifiers and other experimental therapeutic modalities would do well to heed Oliver Scott's warnings and evaluate their model systems and their thoughts critically.

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References

1. Scott, O. C. A. Tumor transplantation and tumor immunity: a personal view. Cancer Res., *51:* 757–763, 1991.
2. Middle, J. G., and Embleton, M. J. Naturally occurring tumors of the WAB/Not rat strain. II. Immunogenicity of transplanted tumors. J. Natl. Cancer Inst., *67:* 637–643, 1981.
3. Baldwin, R. W. Tumour-specific immunity against spontaneous rat tumours. Int. J. Cancer, *1:* 257–264, 1966.
4. Baldwin, R. W., and Embleton, M. J. Immunology of spontaneously arising rat mammary adenocarcinomas. Int. J. Cancer, *4:* 430–439, 1969.
5. Embleton, M. J., and Middle, J. G. Immune responses to naturally occurring rat sarcomas. Br. J. Cancer, *43:* 44–52, 1981.
6. Bailey, D. W. How pure are inbred strains of mice? Immunol. Today, *3:* 210–214, 1982.
7. Baldwin, R. W. Immunity to methylcholanthrene-induced tumours in inbred rats following atrophy and regression of transplanted tumours. Br. J. Cancer, *9:* 646–651, 1955.
8. Pimm, M. V., Embleton, M. J., and Baldwin, R. W. Multiple antigenic specificities within primary 3-methylcholanthrene-induced rat sarcomas and metastases. Int. J. Cancer, *25:* 621–629, 1980.
9. Embleton, M. J., and Baldwin, R. W. Antigenic changes in chemical carcinogenesis. Br. Med. Bull., *36:* 83–88, 1980.