Immune Surveillance Revisited

THE THEORY OF IMMUNE SURVEILLANCE proposed by Burnet (7) and extended by Thomas (2) and by Burnet (3, 4) postulates that one function of the immune system is to eliminate or prevent the multiplication of nascent malignant cells. This theory has generated much experimental work on a possible relationship between oncogenesis and the immunologic status of the host. Often, results have been contradictory. Studies demonstrating tumor-specific antigens on human and animal tumors, reports of facilitated carcinogenesis by immunosuppression, and clinical observations of the increased incidence of malignancy in immunosuppressed or immune-deficient patients are all cited as evidence in support of immune surveillance (5-8). On the other hand, the finding that some tumors do not seem to be antigenic and the failure to demonstrate enhanced carcinogenesis with immunosuppressive treatment in some studies are cited as evidence against the immune surveillance theory (9-11). We do not present a case for or against immune surveillance, as this has been done many times in recent years (9, 12-16). Instead, we ask whether it is possible to settle this issue at all by either clinical observations or experimental evidence.

Evidence from clinical studies that favors immune surveillance is twofold: A high frequency of malignancy is observed in patients with various immune deficiency diseases (17), and an increased frequency of autochthonous malignancies occurs in immunosuppressed patients with kidney transplants (18). However, there are several reasons why immunosuppression (or immunodeficiency) is not the sole explanation for the increased risk of cancer in these patients. For example, whatever caused the immune deficiency disease may be responsible also for the increased susceptibility to cancer. Furthermore, immunodeficient and immunosuppressed patients with transplants are exposed to persistent antigenic stimulation; there is ample evidence from animal models that persistent antigenic stimulation under various conditions can lead to excessive lymphoproliferation and ultimately to lymphomas and reticular cell sarcomas (19). An examination of the type of tumors in these patients showed that the excess risk of cancer was largely due to lymphoreticular neoplasms, particularly reticulum-cell sarcomas (17, 20).

The basic premise underlying the experimental studies is that, if immune surveillance exists, its abrogation should result in the development of malignancies in addition to those tumors which would occur in the presence of an intact surveillance system. Attempts to test this hypothesis have been made by determining the effects of immunosuppressive treatment on the development of transplanted syngeneic tumors and autochthonous tumors. Experiments with transplanted tumors have little bearing on the issue of immune surveillance. Once a tumor has arisen in an immunologically intact host, it has already circumvented the immune surveillance system. The mechanical insertion of a relatively large number of preselected tumor cells into a secondary host is in no way analogous to the appearance and growth of a primary autochthonous tumor cell within its unique microenvironment.

In studying the effect of immunosuppressive agents on chemical carcinogenesis, most investigators have looked for increased tumor incidence and growth rate and a decreased latent period. Where such alterations could not be detected, the authors have concluded that immune surveillance was inoperative (10, 21, 22). However, such negative results do not necessarily contradict the immune surveillance theory. An immune surveillance mechanism would eliminate only tumor clones possessing sufficient antigenicity to be recognized as foreign. If several clones arise at the same time, all must be eliminated to prevent tumor formation. In chemical
carcinogenesis, it is not possible to determine whether a tumor arises from the most successful of several competing clones or from a single unopposed clone. However, if many clones originate at the same time, it is likely that at least one will be weakly antigenic and will escape immune surveillance. Under these conditions, the abrogation of immune surveillance might only result in an increased proportion of highly antigenic tumors among those which arise.

Many studies have demonstrated that immunosuppressive treatment can potentiate oncogenesis by certain viruses (15, 23, 24). Although these findings could be interpreted to support the concept of immune surveillance, this is not necessarily true. More likely, these results reflect the abrogation of an immune response against the infecting virus, and they may be unrelated to immune surveillance against autochthonous neoplastic cells [cf. (14)].

In addition to obstacles unique to certain experimental systems, 2 general limitations apply to all studies of this type. The first is the inability to detect and measure immune surveillance directly. Instead, one actually measures an immune response. Such a detectable immune response is the net result of an extensive amplification process. Immune surveillance, on the other hand, might function at a cellular level and interferes with cellular proliferation or differentiation. Agents that interfere with cellular proliferation or differentiation may have a dramatic effect on a detectable immune response but no influence on immune surveillance. For this reason, one can never claim with certainty that the effect of an immunosuppressive agent or procedure on carcinogenesis results from the alteration of an immune surveillance system against autochthonous cancer cells. Conversely, certain agents might abrogate immune surveillance without apparent depression of immunologic responses. For example, appropriate doses of certain carcinogens can depress immune responses (25). Even when carcinogen administration does not lead to systemic immunosuppression, a local effect on immune surveillance may prevent the destruction of nascent tumor cells in the area of carcinogen application. If such a phenomenon actually occurs, then the addition of an immunosuppressive agent during chemical carcinogenesis could not be expected to contribute dramatically to tumor induction.

The second limitation in studies of immune surveillance is the inability to abrogate even the measurable immune responses without alteration of other physiologic or homeostatic mechanisms. This is obvious with cytostatic drugs and antimetabolites whose activity is clearly not restricted to lymphoid cells. Even with antilymphocytic serum (ALS), the most selective immunosuppressive agent employed in this context, there may be considerable side effects affecting nonimmunologic processes (26). In several studies in which ALS treatment potentiated chemical carcinogenesis, there was evidence that this effect was not directly related to the immunosuppressive properties of the ALS (27, 28). These problems of immunosuppressive treatment have been circumvented by the induction of tumors in vivo in cells confined in a Millipore chamber (29, 30). In this instance, carcinogenesis occurs in the absence of cell-mediated immunologic influences. However, the objection remains that these tumors arise in an environment also devoid of other nonimmunologic regulatory mechanisms. Thus in all experimental systems, it is difficult to attribute the effects of an agent or procedure on oncogenesis solely to its alteration of immunologic function.

What, then, is to be gained from studying the effects of immunosuppressive agents on carcinogenesis? It seems impossible, at present, to design an experiment that will prove or disprove the existence of an immune surveillance mechanism. What we can do is ask a much simpler question. Which agents or procedures are likely to increase the probability of neoplastic disease? We might predict at the outset that, under certain conditions, many "immunosuppressants" will markedly influence neoplastic processes; under other conditions, these agents would be irrelevant to the course of malignancy. A practical benefit from such studies would be to identify the agents capable of augmenting neoplasia and to define the conditions where this is apt to occur. This is especially important because more and more patients will receive long-term immunosuppressive therapy. Current experimental efforts could be directed toward these practical considerations, though they may have no direct bearing on the question of immune surveillance.

REFERENCES

(4) ---: Immunological Surveillance, Sydney, Pergamon Press, 1970
(5) ---: Immunological surveillance in neoplasia. Transplant Rev 7:3—25, 1971
(9) PRESHIN RT: Immunosurveillance and oncogenesis. Prog Exp Tumor Res 14:1—24, 1971