I. Introduction

Burnet's [25] immunosurveillance theory provides a simple explanation for the high frequency of cancer in conditions of impaired immunologic responsiveness. According to this theory, somatic mutations continuously give rise to neoplastic cells. The TSTA [67, 81, 92] of most of these cells would be sufficiently immunogenic to elicit destruction by thymus dependent lymphocytes; only cells with weak TSTA could escape decision of tumor incidence. 4. The rate of spontaneous malignancies in animals with suppressed cellular immunity does not differ significantly from that of non-immunosuppressed animals. 5. Immunosuppressive treatment may be co-carcinogenic by mechanisms other than weakening immunosurveillance.

Key words: Immunosuppressive agents, neoplasms, immunity, lymphoma, transplantation immunology.

Immunosuppression and Neoplasia.

I. Critical Review of Experimental Carcinogenesis and the Immunesurveillance Theory*

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Summary. The immunesurveillance theory assumes that correlations between immunosuppression1 and augmented tumor rates are due to a lack of cellular immune response against the TSTA2 of neoplastic cells, and that a depression of cellular immunity causes an increased formation of spontaneous neoplasms. However, the following objections are raised: 1. The promoting effect of immunosuppressive treatment on lymphomagenesis is greatly facilitated by lymphatic hyperproliferation. Immunosuppression alone is probably insufficient for inducing malignant lymphomas9. 2. With viral carcinogenesis, the increase in tumor incidence observed under immunosuppression cannot clearly be attributed to a deficient immunologic response against the virus-induced TSTA. 3. Suppression of the cellular immune response during the latent period of chemical carcinogenesis causes at best a moderate increase in tumor incidence. 4. The rate of spontaneous malignancies in animals with suppressed cellular immunity does not differ significantly from that of non-immunosuppressed animals. 5. Immunosuppressive treatment may be co-carcinogenic by mechanisms other than weakening immunosurveillance.

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Immunosuppression and Neoplasia.

* All references are listed in the second paper to appear in this issue of this journal.
1 The term immunosuppression here connotes a complete or partial depression of cellular and/or humoral immune response.
2 Abbreviations:
ALS antilymphocyte serum, or antilymphocytic globulin, or antilymphoet serum, respectively
DMBA 7,12-dimethyl-benz(a)-anthracene
GVHR graft versus host reaction
MCA 3-methylcholanthrene
SRBC sheep red blood cells
TSTA tumor specific transplantation antigens.
3 These terms malignant lymphomas, lymphoreticular neoplasms, and lymphoproliferative disorders [32] are used synonymously for malignant tumors of the lymphoreticular tissue.

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the immune surveillance theory, it must be emphasized that diminished immune responsiveness is not the only feature by which mice undergoing a chronic GVHR differ from normal mice. In normal mice, the immune response to a given antigen is brief and effective. Within a limited period of cell proliferation during the primary response, a small number of specific memory cells is formed which can eliminate the antigen even more effectively in a secondary response. During the chronic GVHR, however, hyperproliferation of the lymphoreticular tissue accompanied by poor immunologic response to a given antigen is brief and effective. With feature by which mice undergoing a chronic GVHR in many strain combinations. In the combination the immunesurveillance theory, it must be emphasized proliferation and the genetically determined susceptibility to leukemia exists. Although lymphomas rarely develop even though a considerable alleled by the activation of leukemogenic viruses [5, 69] and can result in unrestricted malignant growth in many strain combinations. In the combination DBA/2→(C57BL/6×DBA/2) F₁, however, the extent of lymphoreticular hyperproliferation is small, and lymphomas rarely develop even though a considerable depression of humoral immunity exists. Although cellular immunity in these mice has not been studied, this finding suggests that the development of a lymphoproliferative disorder results from factors in addition to immunosuppression, e.g. a state of persistent hyperproliferation and the genetically determined susceptibility to leukemogenic viruses [56].

In mice, lymphoreticular hyperplasia and subsequent malignancy can also be induced by repeated injections of an antigen [98]. This antigen-induced hyperplasia of the lymphoreticular tissue, comparable to the hormone-induced hyperplasia of hormone-dependent tissues, is a preneoplastic alteration [98].

Mice which are not exposed to antigens remain in a state of lymphatic hypoplasia [42, 58], unless they react against self-antigens. In germ-free NZB mice, malignant lymphomas develop after spontaneous autoimmunization and subsequent lymphatic hyperproliferation [42, 43]. Presumably, the lymphatic hyperproliferation in these mice is favored by stimulation with endogenous antigens. Similarly, the injection of malaria parasites into mice infected with leukemogenic viruses causes considerable lymphatic hyperplasia which significantly increases the development of malignant lymphomas [168]. That foreign histocompatibility antigens can induce malignant lymphomas is demonstrated by the chronic GVHR in mice where malignant lymphomas can develop out of normal parental lymphocytes after persistent exposure to incompatible F₁-hybrid antigens [30, 55].

Because of these animal models, persistent antigenic stimulation is considered a cause for certain lymphoproliferative disorders in man. Many clinicians draw attention to the fact that in patients as well as in NZB mice autoimmunization can precede or occur simultaneously with a malignant lymphoma [4, 32, 45, 76, 100, 131]. The progressive reticulum-cell hyperplasia of the Wiskott-Aldrich syndrome which often terminates as a lymphoreticular neoplasm can be interpreted as an incomplete compensatory hyperplasia due to abnormal stimulation of a genetically defective immune system [145]. A similar pathogenesis is assumed for the organ infiltrations resembling malignant lymphoma in patients with the Chediak-Higashi syndrome [36]. Persistent immunologic stimulation by holoendemic malaria has been suggested to be the first step in the pathogenesis of Burkitt’s lymphomas [107]. Several authors [6, 83, 107] assume that the development of malignant lymphomas in kidney transplant recipients is favored by the persistent immunologic stimulation from histocompatibility antigens of the graft. The incidence of malignancies in these patients is about eighty times greater than the incidence in the general population of a similar age [112]. About 40% of these neoplasms are reticulum cell sarcomas and lymphomas [112, 156]; whereas, in an average population, these tumors contribute less than 3% of all new neoplasms [137].

III. Immunosuppression and the Formation of Malignant Tumors

The hypothesis that the increased tumor formation in kidney transplant recipients is due to a reduced immunologic surveillance of TSTA [12, 25, 57, 78, 112, 119] is based on numerous experimental and clinical situations in which a high incidence of malignancies is linked to impaired immunity (for review see [12, 25, 57, 78, 92, 112, 115, 119, 142]). Even though the statistical correlation between immunosuppression and tumor growth is significant, can this correlation be explained by the single immunologic mechanism claimed by the immune surveillance theory, or do additional pathogenetic factors account for it?

Without specification, many authors [25, 57, 78, 119] use general terms such as “neoplasms” or “malignances” and include an unproportionally high percentage of malignant lymphomas. Because it appears impossible to decide whether an impaired immune response is a cause or a result of tumor growth in malignant lymphomas [92, 115], the induction of malignant lymphomas in immunosuppressed animals is discussed separately from other models of tumor induction during immunosuppression in this review.

Two different observations in humans show an increased incidence of non-lymphoreticular neoplasms in conditions of impaired immunity: first, an unusually high rate of carcinomas, especially of the skin and the uterine cervix, in organ transplant recipients [77, 112, 117, 144, 156], and second, a possibly abnormal frequency of non-lymphoreticular malignancies in patients with spontaneous immunodeficiency syndromes [46, 51]. Even though both observations support the immune surveillance theory, they are not entirely conclusive. In objection to the first observation, the observed tumor incidence in transplant recipients is compared with that of a normal population and not with a control group which would have the same disease and the same treatment except for immunosuppressive therapy. Moreover, all transplant recipients were treat-