

The application of implants of antagonists in the prophylaxis of opiate dependence in high-risk populations, particularly juveniles, the development of an "immunization" procedure, and the need for more extensive laboratory studies were discussed by Martin (Lexington), Fink, and Cochin (Boston University).

In the present chaos of treatment and prophylaxis of heroin addiction, therapeutic trials with narcotic antagonists represent a unique opportunity to test a rational theory of relapse in opiate dependence, a means for prophylaxis, and a way to reduce the incidence of juvenile dependence on opiates, and of opiate-related deaths.

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10. This meeting was conducted in the course of development of a long-acting narcotic antagonist—part of the addiction research program which is supported by contract with the New York State Narcotic Addiction Control Commission.

Immunological Surveillance

The intriguing suggestion that adaptive immune responsiveness evolved as a general vertebrate protective surveillance mechanism to eliminate spontaneously arising neoplasms was made by Thomas more than 10 years ago. Burnet has since championed and extended this concept, proposing that primordial lymphocytes developed the capacity to recognize and to react destructively against anomalous "not-self" surface characteristics on altered somatic cells. The operation of such a "policing" system would require the prior phylogenetic development of both an extensive genetic polymorphism of detailed topography, including histocompatibility (H) antigens on cell surfaces, and a diversity of immunoglobulin cell recep-

tors which would make possible a continuing subtle distinction between "self" and "not-self," between normal and abnormal, and between what is permissible and what is to be eliminated.

The central position of this concept in immunologic thinking led to the organization by the National Institute of Allergy and Infectious Diseases of an international conference on Immunological Surveillance, held at Brook Lodge, Augusta, Michigan, on 11 to 13 May 1970. As in the two preceding conferences in this series there were no formal presentations, but rather a continuous discussion was developed among the 30 invited participants, who represented a broad spectrum of experience in carcinogenesis, in developmental biology, and in cellular and tumor immunology.

At issue were general questions such as whether vertebrates are indeed equipped with surveillance mechanisms to detect and destroy spontaneously arising neoplastic cells; whether surveillance is mediated principally by cellular immune mechanisms; whether the immune machinery is amenable to augmentation of or interference with its tumor surveillance efficacy; and whether there is a relationship between strong and weak H antigens and tumor antigens.

It was conceded that surveillance mechanisms probably do exist in higher organisms, but there was no firm consensus that they necessarily operate solely by processes involving adaptive immunity. Among the evidence in favor of an immunologic basis for the surveillance mechanism, Good cited the "experiments of nature" involving immune deficiency diseases, noting that patients with thymic deficiencies, such as ataxia telangiectasia and the DiGeorge syndrome, have far higher incidences of solid epithelial and gastric tumors than would be expected from purely statistical considerations. Patients with agammaglobulinemias also display a higher than normal incidence of leukemias. Furthermore, individuals who have been subjected to sustained therapeutic or prophylactic immunosuppression, such as recipients of renal homografts and even those undergoing milder treatment with 6-mercaptopurine (for psoriasis), constitute a high-risk group in terms of the increased incidence of neoplasia. Allison reviewed the evidence for inhibition of tumor growth in mice inoculated with polyoma virus being mediated by cellular immunity and for heritable resistance in some mouse strains against leukemogenic viruses being abolished by

immunosuppression and then restored by adoptive transfer of lymphoid cells. He took the view that immunological surveillance delays oncogenesis, and that inherited resistance of some strains of mice to leukemogenic viruses is due to the immune response of the host rather than to a limitation of the capacity of the virus to transform host cells.

The case against immunological mechanisms playing a significant role in surveillance was marshaled by Prehn. Attention was focused on the following points. (i) Tumors that escape the surveillance mechanism would be expected to be those least antigenic to the host, nevertheless most neoplasms do bear tumor specific antigens. (ii) Tumor induction in an "unpatrolled" environment should be accompanied by the appearance of stronger antigens; yet tumorigenesis in tissue culture and in diffusion chambers rarely involves the expression of new antigens. (iii) Papillomas raised in the skin of BALB/c mice grafted to C3H mice that had been thymectomized, irradiated, and treated with antilymphocyte serum regressed while the skin was accepted—in this instance surveillance did not appear to involve an immunologic mechanism. These situations are the opposite of what would be expected of a surveillance mechanism involving immunity against new surface antigens.

The surface topography of somatic cells which might serve as targets for surveillance and which might be important for cell interactions in differentiation was charted by Boyse. He constructed a new model in order to explain the origin and possible modulation of structural membrane moieties which might be antigenic to the host lymphoreticular system—a synthesis based primarily on his own studies. Normal cell populations exhibit extensive phenotypic diversity of cell surface structure, including specified sets of species, strain or individual specific antigens. Examples of this include the thymocyte-lymphocyte specific, Ly-A, Ly-B, and mouse specific lymphocyte (MSLA) antigens, the plasma cell specific (Pca) antigen, and skin specific (Sk) antigens. Such a phenotypic diversity of cell surface structure could be due to the selective activation of "private" sets of genes different for each tissue. Another order of diversity might be due to unique arrangements of relatively few gene products in the assembly of the surface topography so that the cell need draw on only a small number of genes to achieve an extensive diversity of surface dis-

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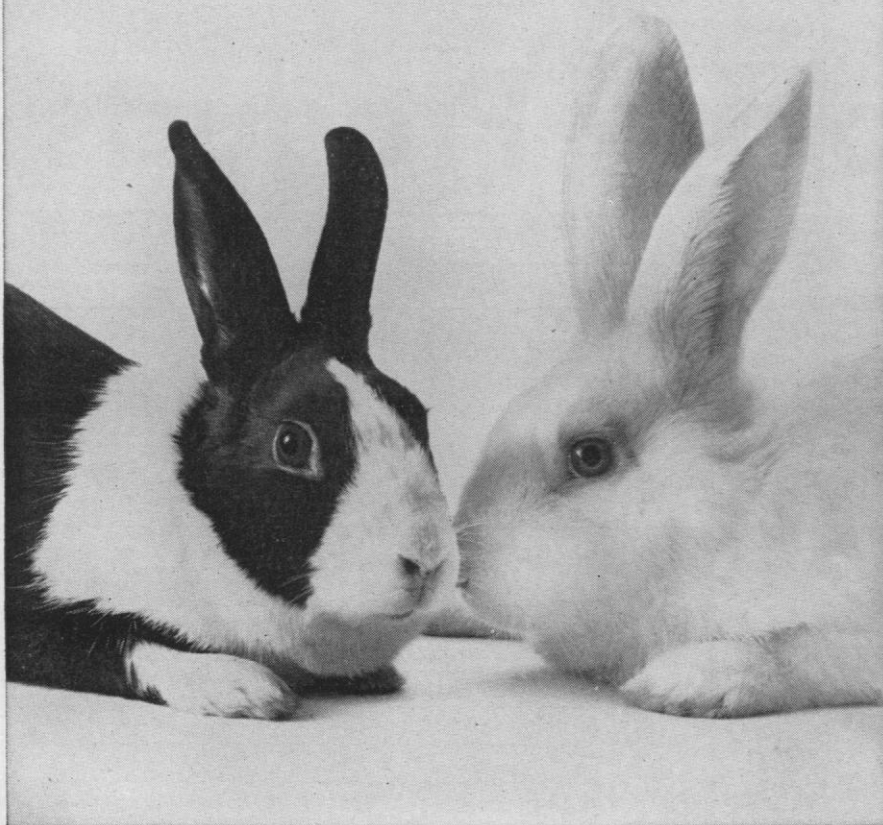
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play. According to this ingenious scheme, specific antigens of a tumor cell, for example the T1 antigen, can be regarded either (i) as a genotypic error, whereby a deviant product is inserted into a grid representing a repeating feature of cell surface topography or (ii) as a phenotypic defect due to the erroneous assembly of normal gene products resulting in aberrant juxtaposition of units comprising the normal grid pattern of the somatic cell's surface. Such structural anomalies were postulated to account for defective recognition in various developmental steps in ontogeny as well as in a surveillance mechanism of a nonimmunologic character.

Triggering events which might lead to the operation of an immunologically mediated surveillance mechanism were identified by Möller, and the various means by which the triggering threshold might be lowered so as to increase the efficiency of the response were considered. Evidence was presented that both "thymus-derived" (T) and "bone-marrow-derived" (B) lymphocytes, which participate in a cooperative immune response, have specific receptors for antigenic determinants. The T lymphocyte function, including memory, could be inhibited by treatment with antiserum directed against theta (θ), for example, a surface determinant specific for T lymphocytes. The interaction of T and B lymphocytes was considered a helper mechanism rather than a mandatory one which makes for increased efficiency of immune reactions by lowering the triggering threshold through multivalent binding. In these cell-cell interactions, the T cell might be replaced by another B cell, a macrophage, or an immunoglobulin-antigen complex, particularly if the antibody were the pentameric, decavalent immunoglobulin M (IgM).

The current status of specificity as opposed to nonspecificity of action of the cytoactive effector agents of cellular immunity was considered by Bloom in terms of the relevance of these agents to effector mechanisms of surveillance. Lymphocytes from immune donors cultured in the presence of specific antigens elaborate factors such as migration inhibitory factor (MIF), lymphotoxin, (LT), and skin reactive factor, as well as others that are mitogenic or that inhibit DNA synthesis or cloning of cultured fibroblasts; these factors have a variety of effects on different cells. The destruction of innocent-bystander fibroblasts exposed to lymphoid cells from tuberculin-immunized isologous donors that

are triggered by purified protein derivative (PPD) was cited as an example of the nonspecific action of cytoactive substances. What is not clear, however, is how a cellular immunity mediated by nonspecific substances could evoke destructive effects that are seemingly highly specific for "target" neoplastic or normal tissue cells both in vitro and in vivo—for example, the survival of a small minority of histocompatible tumor cells in the midst of a much larger number of histoincompatible tumor cells undergoing violent rejection.

Various options that might be involved in mechanisms of surveillance were discussed by Mitchison, including (i) killing by a nonspecific mediator released by a specific reaction between immune lymphocyte and haptenic determinant; (ii) killing by a specific mechanism at the target cell surface permitting entry of nonspecific mediators; (iii) killing due to direct entry of specific mediators; (iv) adding on to a tumor target cell a "prosthetic" grouping to which an immunity already exists and thereby assisting in the induction of immunity to a specific tumor antigen by an adjuvant effect or some other mechanism that promotes antigen handling.

Examples of situations where tumors apparently escape the consequences of a surveillance mechanism, despite an immune response directed against them, were considered by Hellström. Human tumor cells grown in culture can be destroyed by lymphocytes obtained from the tumor host but not in the presence of the patients' own serum, an indication that cell-mediated immunity had been elicited against the tumor but is inoperative because of serum factors. In addition to cell-mediated immunity, tumors can also elicit the production of antibodies that block the destructive effects of activated lymphocytes. Other situations where tumor cells seem to escape the destructive activities of killer lymphocytes include (i) too few tumor cells to evoke immunity, (ii) masking of tumor cells by mucopeptide surface components making them inaccessible to immune recognition or attack, (iii) various serum factors which cause a depression of cell mediated immunity, and (iv) a state of tolerance to tumor-specific antigens.

A unifying hypothesis accounting for the generation of immunologic diversity, nonreactivity to self antigens, and the functional importance of histocompatibility antigens was developed for the first time by Jerne. It relies on the premise that the germ line contains struc-



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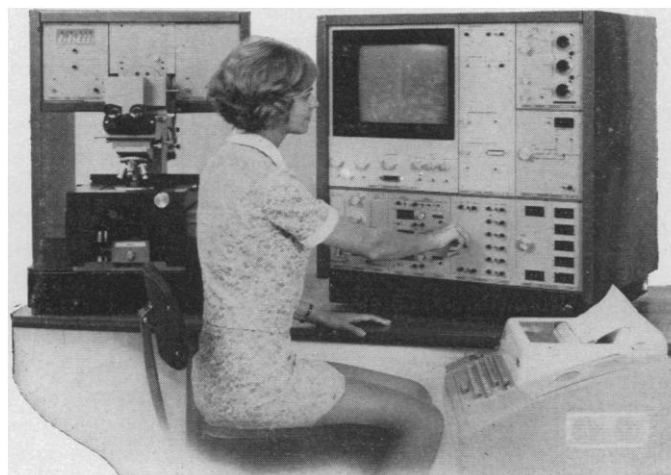
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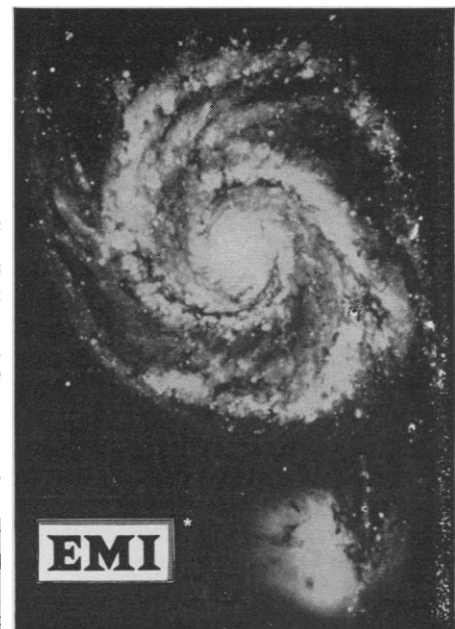
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tural genes which code for antibody molecules specifically directed against the histocompatibility (H) antigens of the species; that mutations occur involving the variable portion cistrons (v), resulting in antibody molecules which code for specificities other than toward H antigens; and that the selective survival of mutant cells is favored by the suppression of non-mutant self-recognizing clones. Jerne postulated that suppression of stem line lymphocytes containing nonmutant gene products takes the form of tolerance to self antigens induced in ontogeny. Since no one individual possesses all the H antigens of his species, the v genes of his germ line must code for antibodies to all of the host's species antigens to insure reactivity against those he does possess. Jerne's model therefore proposes that the portion of germ line cells with v genes determining antibodies against self H antigens are suppressed, and thereby favoring the survival of mutants of this germ line. On the other hand, cells expressing the other set of v genes, coding for H antigens of the species that the individual lacks, are not suppressed and are therefore available in large numbers for reactivity against H antigens of other members of the species. These could be considered as the cellular basis of a surveillance mechanism against neoplasia.

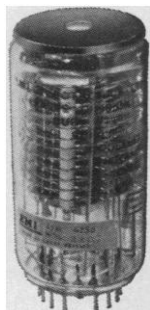
This theory was considered by most of the conferees to be a quantal leap forward in current immunological concepts and to provide a novel and particularly acceptable explanation for two basic immunologic phenomena heretofore inexplicable, namely, the large number of lymphocytes reactive to H antigens in graft-versus-host reactions in vivo and in mixed lymphocyte interactions in vitro, and the special relationship between H antigens and the responder-nonresponder status of animals immunized with antigens having a restricted degree of heterogeneity. In Jerne's model, individuals have different ranges of antibody patterns because they possess different H antigens and because diversity evolves from mutation. Accordingly, each individual (or inbred strain) expresses only a fraction of the antibody diversity range available to the entire species; this could account for the genetic nonresponsiveness of certain inbred strains to certain antigens and for responsiveness, under autosomal dominant genetic control, to others.

A number of basic predictions emerged in the lively discussion of



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Jerne's hypothesis. For example, antibody to H antigen should be monoclonal; the frequency of plasmacytomas producing myeloma proteins with specificity directed against H antigens should be high; and progeny of matings between parental responders and non-responders of different allotype, or allophenic mice derived from these parental strain animals, should be responders and make specific antibody of the nonresponder allotype. Information presented at the conference supports the first two of these predictions. Ramseier and Lindenmann's experiments demonstrated that serum obtained from A/B F₁ animals that had been inoculated with immunologically competent parental strain A lymphocytes contains factors which specifically block stimulation of A strain lymphocytes by B strain antigens. The explanation offered for this intriguing finding was that A/B animals were making antibody against receptors on A strain lymphocytes specific for B strain H antigens; this implies that receptor sites on A lymphocytes for B strain antigens are relatively homogeneous. Walford presented data indicating that of ten human myelomas thus far examined, three were directed against HLA antigens, and two of these three were directed against HLA-5.

The large number of host lymphocytes reactive to H antigens of other members of the same species was discussed extensively. Essentially four different points of view emerged as possible explanations: the Jerne model; the Möller-Mitchison view that the high density of H antigen determinants on lymphocyte membranes activates cells with low affinity binding sites and causes them to undergo blastogenic transformation and to produce mediators of cellular immunity; the Cohn-Good-Lawrence hypothesis that the large number of reactive cells represents prior antigenic experience of the animal with cross-reacting environmental antigens or with tumor specific antigens on neoplasms suppressed successfully; and finally the "antyclonalist" concept of Simonsen that these cells are basically multipotential.

The edited proceedings of this conference will be published by Academic Press as the third volume of the series "Perspectives in Immunology."

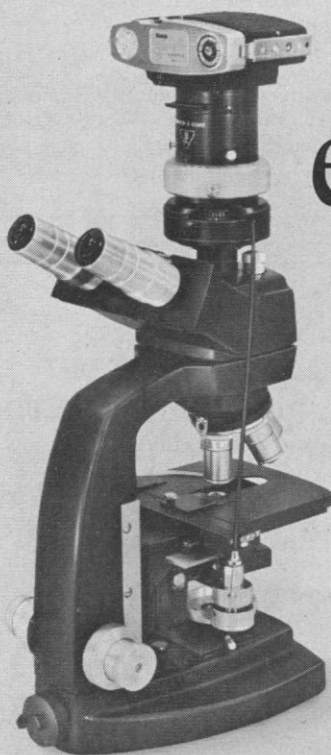
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