IMMUNOLOGY OF THE EYE

WORKSHOP I:
IMMUNOGENETICS AND
TRANSPLANTATION IMMUNITY

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(A Special Supplement to Immunology Abstracts)

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Preface

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The concept for the need of a series of immunology workshops as presently planned by the National Eye Institute (NEI) grew out of several program planning reports which were developed by the National Advisory Eye Council (NAEC). In these documents, the need was clearly identified for an expansion in research effort involving immunological aspects of ocular diseases and for the application of newer concepts and methodology in immunology to the study of the visual system. To accomplish these objectives, the NAEC felt it essential that immunologists active in research outside of the vision field be encouraged to direct their efforts towards research on ocular tissues and ocular systems. An initial approach to the stimulation of dialogue and of collaborative research efforts between vision researchers and immunologists took the form of a grant announcement published by the NEI in the NIH Guide for Grants and Contracts on August 4, 1978, titled "Immunological Aspects of Ocular Disease." A second approach included the development of this workshop series as a joint effort between the National Eye Institute and the National Institute for Allergy and Infectious Diseases (NIAID). In planning sessions between the two Institutes, major research areas were defined which were believed would have the greatest impact upon vision research in the future. Expert investigators who represent each of the subsections of these research areas were identified by NIAID staff members, Drs. Sheldon Cohen and Robert Goldstein, and the

NEI would like to express its appreciation to them for carrying out this important role.

This workshop represents the first in a series of three ocular immunology workshops conducted by the NEI. All workshop participants were divided into task groups to develop a list of research recommendations and priorities perceived by each group as providing the most impetus to vision research.

A second immunology meeting dealing with "Autoimmune Phenomena and Ocular Disorders" was held on March 5-7, 1980, and the third workshop, "Infection, Inflammation and Allergy" was held June 25-27, 1980. The proceedings of these workshops will also be published as special supplements to Immunology Abstracts.

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SESSION I

Genetic control of immune response

Summary of Discussion

Included in this section are informal presentations by E. Shevach on the capacity of the immune system to mount a specific immune response* and by H. Cantor on the analysis of lymphocyte types involved in the immune reaction, with emphasis on response to tumors.

Specific Immune Response

Immune response (Ir) genes responsible for control have been shown to be thymus dependent. Characteristics of nonresponder animals include failure to demonstrate antibody production and delayed hypersensitivity *in vivo* and the lack of their cells to proliferate or secrete lymphokine products in *in vitro* procedures. Ir gene control is effected at the level of interaction of antigen specific T lymphocytes with macrophages or other antigen presenting cells. Thus, activation of a T cell proliferative response of primed T lymphocytes from responder X nonresponder F_1 guinea pigs can only be induced by the antigen-pulsed macrophages from the responder parent but not those taken from a nonresponder parent. When F_1 macrophages are utilized as a source of antigen presenting cells, the proliferative response of F_1 T lymphocytes can be inhibited only by anti-Ia antibody specific for responder antigens but not those of the nonresponder parent, suggesting that the Ir gene product is the Ia antigen. Ir gene control may also be exerted during the interaction of carrier primed T helper cells and

* For background literature, see reference 1

hapten primed B lymphocytes in the induction of antibody response. This phenomenon is seen in the primed responder X nonresponder F_1 T helper cells collaborating only with B cells of the responder parent; the defect is identified at the level of the B lymphocyte. While the molecular basis for genetic unresponsiveness in these systems is still unknown, the favored view is that expression of the defect is in both the antigen presenting macrophage and in the B lymphocyte, reflecting a failure of association of the nominal antigen with the Ia antigen gene product. Emphasis was placed upon the role of macrophages in determining the level of immune responsiveness to various antigens. While it is felt that suppressor cells also may be involved in determining levels of immune responsiveness, in most systems studied an exact role has not yet been defined.

Lymphocyte Types

Virtually all natural killer (NK) cells have been shown to carry the Ly5 marker, as exemplified in the nude mouse model where all NK activity is alleviated by treatment with anti Ly5 plus complement. It has been possible to characterize other properties of NK cells by the successful development of a cell clone carrying Ly5 as the Qa2 antigens (Cantor). Good killing capacity is exhibited by these cells in the ratio of one NK:10 target cells. When tested against a battery of lymphoma cells, cloned NK cells have been found to be cytotoxic almost exclusively to virus infected cells. The suggestion that the target components for the NK cells are virus associated is further supported by the finding that killing activity can be specifically inhibited by certain viruses. NK cells also have the capacity to lyse activated B lymphocytes (e.g., LP5-stimulated) but do not affect activated T cells; B cell killing may also be inhibited by lymphoma cells. The existence of cross reacting components on tumor cells and normal spleen cell inhibition of killing by NK cells of El-4 cells but not YAC cells.

Other work mentioned was that of another group (Bloom) who originally

had demonstrated that the capacity of such cell lines as HeLa to kill nude mice was reduced when infected with measles or other viruses. Additionally, when HeLa become infected with viruses in vitro susceptibility to killing by NK cells ensues. The role of interferon (IF) promoting NK cell activity has also been demonstrated in the following approaches: (1) antibodies to IF enhance the growth of tumor cells in nude mice, (2) IF increases the activity of NK cells, and (3) IF can convert cells to $Ly5^+$ with full killing capacity. Preliminary data further suggest that $Ly5^+$ cells may release IF which in turn contribute to the recruitment of new NK cells.

A system used to analyze the phenotypes of lymphocytes involved in immunity against cancer was described[2] (Cantor). Derived data indicate that the Ly $1,2,3^+$ population contained precursors for cytolytic T cells which become active following conversion to the Ly $2,3^+$ phenotype. Ly 1^+ also were found to be active against certain tumors, e.g., MSV-induced sarcoma, probably through secretion of specific antivirion substances. However, Ly 1^+ cells were not active against such tumors as the MLV^+ lymphoma which was affected only by cytolytic Ly $2,3^+$ cells.

In consideration of this material it was emphasized that insights concerning the general mechanisms involved in immune responses to antigens such as those relevant to sheep RBC should be applied in studies extended to analyses of immune responses against viruses, bacteria and auto-antigens.

Inquiry was made into whether deficiency in NK activity in humans may be associated with disease and autoimmune phenomena related to increase in NK activity. In this connection it was noted that in the Chediak Higachi syndrome there is a demonstrable lack of NK activity which is also seen in the Beige mouse, an experimental model for this disease. Additionally noted was the increased interferon activity inducing NK activity and the demonstration of increase in interferon levels seen in newborn mice devel-

oping autoimmune diseases. From the clinical standpoint, decreased NK activity has been associated with HLA 7 and 3 and in patients with primary biliary cirrhosis. Regarding the Beige mouse, attention was directed to the report of the high incidence of spontaneous tumors in this model.

Discussion then centered about the relationships between Ly subsets in mice and subset determinants in humans. Two human T cell subsets have been described, $(T3+T4)^+$ and $(T3+T5)^+$. The gene product recognized by the monoclonal antibody T 3 is found on all peripheral cells that are E rosette positive; it is capable of mediating all T cell functions in vitro including mitogen reactions. T 3 antibodies block antigen-induced lymphocyte proliferation. The antigen recognized by T 4 antibodies is found on 30 percent of T cells, specifically those that induce B cells to secrete immunoglobulins and induce cytotoxicity in other T cells. T 5 is found on 20-25 percent of T cells which are cytotoxic effector and suppressor cells and capable of preventing B cells from producing immunoglobulins. Regarding the immunochemistry of the Ly system, the Ly 1 product is a polypeptide with a molecular weight of 60,000 and the Ly 2 product a dimer bridged by disulfide bonds; each chain having a molecular weight of 30,000. By immunoprecipitation methods utilizing monoclonal antibodies to human T 4 and T 5, similarity was demonstrated between these components and Ly 1 and Ly 2,3.

Inquiries were then made into the possible relationships between the human TH 1-TH 2 and the mouse Ly systems. It was suggested that designations of the new monoclonal antibodies have significant advantage in the human system over that noted in the mouse in that they permit the enumeration of lymphocyte subsets in human disease to be correlated with disease activity. This is exemplified by the autoantibody found in juvenile rheumatoid arthritis patients (JRA) where the 30-40 percent of T cells reacting with JRA autoantibody manifest the equivalent of the Ly 1, 2, 3 subset. In