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IMMUNOLOGY OF THE EYE

WORKSHOP II:

AUTOIMMUNE PHENOMENA AND OCULAR DISORDERS

(A Special Supplement to Immunology Abstracts)

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Preface

Ralph J. Helmsen

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The concept for the need for this series of immunology workshops sponsored by the National Eye Institute grew out of several program planning reports which were developed by the National Advisory Eye Council . 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 methodologies in immunology to the study of the visual system. To accomplish these objectives, the National Advisory Eye Council 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 in the NIH Guide for Grants and Contracts on August 4, 1978, Vol. 7 no. 10 titled "Immunological Aspects of Ocular Disease." The second approach was the development of this workshop series as a joint effort between the National Eye Institute and the National Institute of Allergy and Infectious Diseases . In planning sessions between the two Institutes, major research areas in immunology were defined which should have the greatest impact upon vision research in the future. Expert investigators who represent these research disciplines were identified by Drs. Sheldon Cohen and Robert Goldstein of the National Institute of Allergy and

Infectious Diseases, and the National Eye Institute would like to express its appreciation to them for carrying out this important role.

This workshop represents the second in a series of three ocular immunology workshops conducted by the National Eye Institute: the topic of the first meeting was "Immunogenetics and Transplantation Immunity" and the third workshop dealt with "Infection, Inflammation and Allergy". Participants in all workshops met in task groups to develop a list of research recommendations and priorities perceived by each group to provide the most impetus to future vision research. Their recommendations summarizing the conclusions of each workshop will be of service to the research planning efforts of the National Eye Institute.

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SESSION I

OCULAR AUTOIMMUNE PHENOMENA

Moderator: Bruce Rabin

Summarizer: Roberta Meyers-Elliott

Overview of ocular autoimmune diseases

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ABSTRACT

The eye appears to be the target of a number of autoimmune processes some of which produce blinding disease. Rigid criteria, established for classical autoimmune diseases in other tissues of the body, have generally not been met in the eye. The eye develops as an embryonic outpocketing of the brain; the blood vessels of the retina and those of the brain have certain striking similarities. Because of this and other tissue similarities, the brain and the eye appear to be the common targets of certain autoimmune processes. This is particularly true of the Vogt-Koyanagi-Harada syndrome, multiple sclerosis, and Behcet's syndrome. Other factors, as yet unidentified, link autoimmune diseases of the joints with those of the eye. In the majority of cases these latter diseases are immunogenetically determined but may have infectious triggers.

INTRODUCTION

Autoimmunity, the seemingly relentless attack of the body's immunologic defense system upon its own tissues, is represented in the eye by a number of well characterized diseases. These diseases affect a wide variety of structures extending from the lids and conjunctivae, anteriorly, to the retina and optic nerve posteriorly. It should be pointed out, however, that many of the conditions that are alleged to be autoimmune in origin do not fulfill the rather strict criteria for autoimmune diseases established by Witebsky[1]; and in this sense, the origin of many of the so-called autoimmune diseases of the eye is not nearly so well documented as it is in the classical examples of autoimmune thyroiditis, aspermatogenesis, or experimental allergic encephalitis.

In the rather limited space allotted to me for this overview, I can do little more than survey the diseases of the eye that are thought to be autoimmune in origin, presenting the preliminary evidence that these maladies represent abnormal autoaggressive behavior on the part of the patient's reticuloendothelial system. I am assured by those in charge of this Workshop that this is a reasonable goal and that such a presentation might be of

particular value to those participants who have relatively little familiarity with the eye and its diseases.

DISEASE ENTITIES

Beginning with the anterior segment of the eye, diseases such as discoid lupus are encountered on the lids. The relationship of this disease to disseminated lupus erythematosus has not been fully determined, but Davis et al.[2] have found antibodies to DNA in discoid lupus; and in certain female patients, identification of a sex-linked autoimmune disease associated with so-called "chronic granulomatous disease" can be made.[3] The latter is essentially an inborn enzyme deficiency in granulocytes that results in the subnormal production of hydrogen peroxide and permits the persistence of various infections that would ordinarily be taken care of by the body's defense system.

In the conjunctiva two highly troublesome disorders of possible autoimmune origin are encountered, one of which produces severe scarring and ultimate blindness. This disease, designated cicatricial pemphigoid, produces sub-epithelial bullae that eventually rupture, allowing fibrotic reaction to occur at the base of the lesion as well as subsequent shrinkage of the affected tissues. Areas bared of their epithelium may adhere to each other, producing symblepharon and ultimate obliteration of the conjunctival fornices. Mucous glands of the conjunctiva are also destroyed by the process with a resultant loss of normal mucus content of the tears. Ultimately, the ductules that conduct tears into the conjunctival sac are also destroyed, leading to a dry, irritated eye. This, combined with the abrasive action of in-turned lashes, leads to the scarring of the cornea and to eventual blindness. The basement membrane of the conjunctival epithelium binds autoantibody and complement, leading to the attraction of inflammatory cells and to the release of serous fluid. The immunopathology observed here is very similar to that observed in bullous pemphigoid of the skin, and indeed, the two diseases may be part of the same spectrum.

Pemphigus vulgaris may also cause bullous lesions of the conjunctiva, but these appear to be totally different in their origin and evolution from the lesions of cicatricial pemphigoid. The lesions consist of intraepithelial bullae resulting from extensive acantholysis in the prickle cell layer. These bullae may also be painful and may rupture, but they do not leave a surface that is bare of epithelium, and for this reason there is little or no tendency to scarring unless secondary infection supervenes. This disease, unlike pemphigoid, is associated with circulating antibodies

to an intracellular substance that is present in the deeper layers of the epithelium. Levels of antibody are increased immediately before the onset of an attack,[4] and these antibodies can be demonstrated by indirect fluorescence when the patient's serum is layered onto frozen sections of normal rat tracheal epithelium. Again, there is good evidence for complement binding at the site of antibody-antigen reaction in the diseased tissue. Although pemphigus vulgaris carries a worse prognosis for life than cicatricial pemphigoid, it produces much less damage to the eye itself.

The cornea is the site of several presumptive autoimmune diseases some of which have disastrous consequences. Mooren's ulcer is most likely an autoimmune disease representing a cytolytic attack on the substance of the corneal stroma. The lesion is characterized by progressive infiltration and thinning of the cornea, producing an undermined edge as the disease marches across the cornea from the periphery to the visual axis. Eosinophils have been found in histologic sections of this undermined edge. It is likely that an antigen which is derived from the epithelium diffuses into the anterior third of the cornea. Here it acts as an autoantigen, providing a target for destructive immunologic reactions. It is of interest that the segmental removal of conjunctival epithelium in an area adjacent to the location of the ulcer provides at least temporary amelioration and sometimes complete cure of the condition.[5] Histologic sections of this excised conjunctiva have revealed large numbers of plasma cells in the tissue.[6]

In the peripheral cornea, cellular infiltration accompanied by a gutter-like thinning of the stroma may be seen in rheumatoid arthritis. It is likely that the terminal loops of the limbal circulation are the sites of antigen-antibody complex deposition in this disease. Such deposits may bind complement and trigger the attraction of inflammatory cells that ultimately result in the destruction of collagen. A similar melting of collagen also occurs in the sclera with or without the presence of frank scleral nodules. In those cases where scleral nodules have been examined histologically, occlusive vasculitis surrounded by fibrinoid necrosis and concentric lamellae of chronic inflammatory cells, has been seen; and this pathology is essentially the same as that seen in the cutaneous nodules of rheumatoid arthritis.

The role played by infection in the initiation of autoimmune diseases of the cornea has not been fully ascertained. Thus, herpetic infection of the cornea may alter the normal antigenic composition of its infrastructure