The immune system has evolved to protect the body against infectious microbes and toxic insults. To achieve this mission, the immune system contains a plethora of well-choreographed defense mechanisms. Cells of the immune system, such as specific killer T cells, natural killer cells, polymorphonuclear leukocytes, and macrophages, directly attack pathogens. Cells involved in humoral and cellular immunity produce additional mediators of immune protection, including antibodies, cytokines, chemokines, and complement, to aid in the war against foreign invaders. Although the induced inflammatory response protects tissues against these insults, the inflammation can itself induce tissue damage and functional disruption as a result of necrosis and fibrosis.

This article will illustrate how the immune response can act as a double-edged sword, both protecting and damaging the host. The first part of the article will show how even small amounts of inflammation in the eye can impair vision and discusses how advances in our understanding of ocular immunology have allowed development of improved therapies for inflammatory eye diseases such as uveitis. The second discusses cytomegalovirus (CMV) retinitis, a blinding complication of severely immunosuppressed patients. The history of this disorder in patients with the acquired immunodeficiency syndrome, before and after the development of highly active antiretroviral therapy (HAART) will illustrate that, despite the induced inflammatory response protects tissues against these insults, the inflammation can itself induce tissue damage and functional disruption as a result of necrosis and fibrosis.

This article will illustrate how the immune response can act as a double-edged sword, both protecting and damaging the host. The first part of the article will show how even small amounts of inflammation in the eye can impair vision and discusses how advances in our understanding of ocular immunology have allowed development of improved therapies for inflammatory eye diseases such as uveitis. The second discusses cytomegalovirus (CMV) retinitis, a blinding complication of severely immunosuppressed patients. The history of this disorder in patients with the acquired immunodeficiency syndrome, before and after the development of highly active antiretroviral therapy (HAART) will illustrate that, despite the problems of ocular inflammation, the eye is far better off with a healthy immune response.

The Ocular Immune Response

The eye is exquisitely sensitive to small alterations in tissue architecture. Cells of the cornea, for example, are highly organized to form a structure with minimal optical distortion. Minimal corneal edema or scarring can severely impair vision. The 10 layers of the retina also have an extremely regimented structure, necessary for visual transduction. Even mild edema in the macula causes metamorphopsia, and cystoid macular edema is one of the major causes of vision loss in patients with uveal inflammatory disease.1

The eye has developed unique constraints on the ocular immune response to moderate tissue damage. Immunologic privilege helps to protect the eye from the deleterious consequences of ocular inflammation. Dooremaal reported in 1879 that implanted pieces of human tumor could grow in the anterior chamber of rabbits, but failed to survive in other parts of the body.2 More recently, Streilein and colleagues have elucidated a number of biological mechanisms and factors that promote immune privilege within the eye.3 Nevertheless, immune privilege is neither complete or insurmountable, and intraocular inflammatory disease remains an important clinical problem.

Inflammatory Eye Disease

Uveitis

Uveitis is a group of disorders characterized by inflammation of the uvea: the iris, ciliary body, and choroid. The disorder accounts for up to 10% of severe vision loss in North America. In the early part of the century, infection was thought to cause most forms of uveitis,4 but today, many causes of the disease are attributed to noninfectious causes of inflammation, including autoimmune. When infection is the underlying cause of uveitis, specific antimicrobial therapy is needed. For most other forms of uveitis, control of intraocular inflammation is paramount for preserving the integrity of the precise architecture of the ocular structures and maintaining vision.

Treatment of Uveitis. Over the last century, advances in our understanding of the immune system have fostered substantial improvements in the treatment of intraocular inflammation. During the first half of the twentieth century, therapy for uveitis was severely limited. Induced hyperpyrexemia, where a patient’s body temperature was increased to 41°C for a period lasting 4 to 6 hours, was a common therapy for acute forms of the disease. This therapeutic approach had some therapeutic efficacy, but was dangerous. Steam baths to raise the body temperature were later replaced by injections with typhoid toxin or milk. Of course the therapy for inflammatory disease was radically altered by the discovery of corticosteroids. In an article published in the Proceedings of the Mayo Clinic, Hench and colleagues described successful treatment of 14 patients with rheumatoid arthritis with 17-hydroxy-11-dehydrocorticosterone.5 The next year, corticosteroids were shown to have a therapeutic effect in uveitis.6,7

Over half a century later, corticosteroids remain the mainstay of therapy for uveitis. Unfortunately, many patients have disease that is resistant to corticosteroid therapy. Others develop severe side effects when receiving corticosteroids. Following from a need for effective immunosuppression for patients receiving organ transplantation, a number of immuno-suppressive agents have been developed. Although these drugs can preserve vision in patients with severe uveitis, they also...
have potential serious side effects, because their mechanisms of action lack specificity and attack the immune system and other tissues at multiple sites. In the war on inflammatory disease, the goal is to specifically target the immunosuppressive attack on disease-causing elements of the immune system while limiting the “friendly fire” that can damage the nonpathogenic parts of the immune system needed to protect the host. Much of my research has focused on elucidating the pathogenesis of ocular inflammatory disease to identify new targets for immunotherapy that will not only improve efficacy but also minimize adverse effects.

Pathogenesis of Uveitis. Although the specific etiology of uveitis remains unknown, the initiating stimuli for intraocular inflammation can be divided into two major pathways: an antigen-specific immune-mediated inflammatory response and a nonspecific inflammatory response (Fig. 1).8 Nonspecific ocular inflammatory responses are not antigen-specific and can result from insults including surgery, trauma, and some infections, which cause diffuse tissue destruction. In contrast, autoimmune involving the eye occurs when an antigen-specific immune response is directed against ocular antigens. Interestingly, some cases of idiopathic uveitis may be caused by unrecognized infectious agents, and the infection may lead to secondary autoimmune diseases. The resultant autoimmune disease could be caused by molecular mimicry, an antigen-specific immune response directed against the pathogen that cross-reacts with an antigen in the host tissue. An infection could also induce a secondary immune response by causing tissue destruction and release of sequestered antigens. Importantly, these insights into the pathogenesis of ocular inflammatory disease has allowed investigators to identify new targets for immunomodulation. Two of these new approaches are detailed below.

New Therapeutic Approaches for Uveitis. In both antigen-specific and nonspecific ocular immune responses, damage occurs after inflammatory cells infiltrate the eye and release inflammatory mediators that facilitate destruction. One approach to treating ocular inflammation, therefore, is to inhibit the homing and migration of inflammatory cells to the eye.

Chemoattractant cytokines were previously thought to be the sole choreographer of inflammatory cell migration into inflamed tissues. Chemoattractant cytokines called chemokines have been shown to be involved in the pathogenesis of ocular inflammation in animal models of uveitis.9–11 In addition, levels of chemokines including interleukin (IL) 8, macrophage inflammatory proteins (MIP) 1α and MIP-1β, monocyte chemoattractant protein (MCP) 1, interferon-inducible protein (IP) 10, and RANTES were elevated in the aqueous humor of patients with active stages of anterior uveitis and correlated with the clinical severity of disease.12

More recent data suggest that cell adhesion molecules are critical to the pathogenesis of inflammatory disease. There are 3 major groups of cell adhesion molecules important for inflammatory cell recruitment: the selectins, integrins, and members of the immunoglobulin supergene family. Selectins mediate the initial adhesion of inflammatory cells to the vascular endothelium, causing the cells to crawl along the vascular wall.13 Subsequent interaction of integrins expressed on inflammatory cells then bind with members of the immunoglobulin supergene family to produce a stronger adherence of cells to the vascular endothelium. This binding also promotes transendothelial migration of the inflammatory cells out of the blood vessel and into the inflamed tissue.14

We have investigated the role of cell adhesion molecules in ocular inflammatory disease. We first showed that the expression of specific cell adhesion molecules on ocular tissues is upregulated before inflammatory cell infiltration. In animals injected with Salmonella typhimurium endotoxin, E-selectin is expressed on vascular endothelium in the ciliary body, and intercellular adhesion molecule (ICAM) 1 (CD54) is expressed on ciliary body epithelium before the peak of inflammatory cell infiltration into the eye.15,16 In experimental autoimmune uveitis, ICAM-1 is expressed in the retina several days before the development of intraocular inflammatory disease.17 Importantly, we have shown that monoclonal antibodies directed against a number of cell adhesion molecules, including E-selectin, P-selectin, Mac-1, ICAM-1, and LFA-1, can inhibit the development of uveitis in experimental models.16–19

The transparency of ocular tissues has allowed us to directly view the migration and infiltration of inflammatory cells into the inflamed eye. Becker and colleagues20 have used digital video imaging of rhodamine-labeled cells to study the migration of leukocytes through the microvasculature of the iris during endotoxin-induced uveitis. Preliminary studies show that blocking ICAM-1 and/or LFA-1 has little effect on the initial rolling of leukocytes along the vascular endothelium but does inhibit the firm adhesion of inflammatory cells to the vascular wall and prevent the infiltration of inflammatory cells into the iris tissue. We have also diminished the development of other forms of ocular inflammatory disease by blocking cell adhesion molecules. Experimental allergic conjunctivitis was inhibited with monoclonal antibodies against ICAM-1 and LFA-1.21 Importantly, studies of human ocular tissue have shown that cell adhesion molecule expression is upregulated in the inflamed eye. We have demonstrated that there is increased expression of adhesion molecules in eyes of patients with chronic uveitis and in corneas undergoing graft rejection.22,23 We, therefore, believe that blocking specific adhesion molecules may provide a useful therapeutic approach for a number of ocular inflam-
nflammatory diseases including uveitis, corneal graft rejection, and allergic conjunctivitis.

Focusing therapy on disease-causing cytokines is another therapeutic approach for autoimmune disorders. Many forms of ocular inflammation are thought to be caused by an antigen-specific immune response. In some types of uveitis, for example, activated T cells are thought to home and migrate to react against a normally sequestered ocular antigen. Production and expansion of these activated, eye-specific immune cells has been shown to be dependent on cytokines, particularly IL-2. Therefore, another novel approach to treating ocular inflammation would be based on inhibiting this critical cytokine.

Waldmann and colleagues at the National Institutes of Health have developed a monoclonal antibody against the α-chain of the IL-2 receptor (IL-2r). Unlike the β- and γ-chains, the α-chain of the IL-2r is not expressed on the cell surface of resting T cells. However, activated T cells may express up to 50,000 receptors per cell. Therefore this α-chain of the IL-2r is an ideal target for immunotherapy, because it is only present on the activated cells presumably involved in disease pathogenesis.

This antibody against the α-chain of the IL-2 receptor has been humanized to reduce the immunologic response against the molecule and is known as Daclizumab. Robege et al. previously showed that this antibody inhibited the development of experimental autoimmune uveitis. Daclizumab has also significantly decreased rejection in patients receiving renal allografts.

The National Eye Institute studied Daclizumab as potential therapy for uveitis. We assessed the safety and therapeutic activity of Daclizumab in an open-label trial of 10 patients with severe, sight-threatening, intermediate and posterior uveitis. Patients with uveitis requiring at least 20 mg prednisone daily or other systemic immunosuppression were treated with intravenous Daclizumab every 2 to 4 weeks according to a standard schedule. Patients were then tapered off of their baseline immunosuppressive therapy. Over the 1-year study, only two patients had recurrences of significant uveitis after discontinuing their baseline immunosuppressive therapy. Six of 10 patients were able to completely discontinue systemic immunosuppressive medications, and 2 additional patients remained only on small doses of prednisone to treat adrenal insufficiency resulting from long-term corticosteroid use. Only 2 patients had recurrences of significant uveitis off of systemic immunosuppressive therapy. Importantly, adverse events were mild to moderate and did not require discontinuation of therapy. Mild rashes or hives occurred in 6 patients, lower extremity edema in 2, and a limited episode of cutaneous zoster in one patient. These data suggest that anti-IL-2r antibody may be a useful therapeutic approach for severe, sight-threatening uveitis; however, randomized clinical trials are needed to more definitively define safety and efficacy.

Keratoconjunctivitis Sicca
Ocular inflammation is undeniably involved in the pathogenesis of eye disorders such as uveitis. Recent data suggest that the ocular immune response may contribute to the pathogenesis of one of the most common eye diseases, keratoconjunctivitis sicca (KCS) or dry eye. Although previous studies suggested that inflammation caused dry eye in patients with Sjögren’s disease, an autoimmune disorder characterized by destruction of the lacrimal gland, we have demonstrated substantial inflammation in the conjunctiva from patients with non-Sjögren’s KCS. In a study comparing conjunctival biopsies from 15 patients with Sjögren’s KCS to biopsies from 15 patients with non-Sjögren’s KCS, we found substantial conjunctival inflammation in specimens from both groups of patients. Biopsies showed significant T-cell infiltration and expression of HLA class II antigen and ICAM-1. There were no statistically significant differences between the two groups for any marker. These data suggest that inflammation may play an important role in the pathogenesis of both types of dry eye. T-cell infiltration and cytokine production can lead to further irritation of the ocular surface and worsening inflammation. It is not surprising, therefore, that treatment with tear substitutes alone is often insufficient to moderate the disease, and immunomodulatory therapy may be needed to break the inflammatory cycle. Two multicenter, randomized trials showed significant improvement in keratoconjunctivitis sicca in patients receiving topical cyclosporine ophthalmic emulsion.

Cytomegalovirus Retinitis
Much of my clinical practice has been spent on inhibiting the ocular immune response. However, without a healthy immune system, the eye is at tremendous risk of ocular infection and blindness. Nowhere is the double-edged ocular immune response more clearly illustrated than in the eyes of patients with the acquired immune deficiency syndrome (AIDS).

Effect of Highly Active Antiretroviral Therapy. Before the use of HAART, CMV retinitis occurred in up to 40% of patients during their disease. CMV retinitis typically develops when CD4+ cell counts fall below 100 cells/μl and without specific therapy, predictably progresses and can lead to blindness. Even with treatment, the median time to progression of retinitis was as quickly as 2 months. With the widespread use of HAART there has been a striking change in the presentation and course of CMV retinitis.

HAART, which usually includes a protease inhibitor and at least two reverse transcriptase inhibitors, has led to decreased HIV replication, elevations in CD4+ cell counts, and reduced mortality. The study of CMV retinitis in patients on HAART has allowed us to clinically assess the effects of this immune recovery on a major opportunistic infection. In 1997 we reported four patients receiving HAART with inactive CMV retinitis despite no maintenance anti-CMV therapy. We have now reported 28 patients with stable CMV retinitis who did not progress without maintenance anti-CMV therapy; 3 of whom never received treatment for their retinitis. To date, 65 patients with CMV retinitis who have experienced immune recovery while receiving HAART but not receiving specific anti-CMV therapy have been followed for a median of 5 to 16.4 months (Table 1). Only one of these patients had a reactivation of retinitis, which occurred after the CD4+ count decreased below 50 cells/μl.

The clinical benefit of immune recovery on HAART is also illustrated by a decrease in the incidence of CMV retinitis. Because of the use of HAART, the number of new cases of CMV retinitis has decreased dramatically. In a study of 1255 patients, each of whom had at least a single CD4+ cell count below 100 cells/μl, the incidence of any of 3 major opportunistic infections, including CMV retinitis, declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years in 1997.

The CD4+ count appears to be a better predictor of an
significant increase in eyes with CMV retinitis. We previously showed that anterior chamber flare measured by laser flare photometry was significantly increased in eyes with CMV retinitis. This compromise of the blood-ocular barrier allows proteins and cells into the eye. In addition, this breakdown in the blood-ocular barrier may permit CMV antigen to leak out of the eye and give the antigen access to lymphoid organs. This exposure of CMV may partly explain the frequent occurrence of immune recovery uveitis in our studies.

Importantly, we do not know whether this immune recovery uveitis is related to subclinical viral replication. It is unclear whether stopping treatment with specific anti-CMV medications exacerbates the ocular inflammatory disease. However, immune recovery uveitis does develop in eyes with CMV retinitis, despite treatment with anti-CMV medications.

Immune recovery has lead to inflammatory disease associated with other opportunistic infections. Patients with subclinical Mycobacterium avium complex infection can develop leukocytosis, fever, and lymphadenitis following HAART. Patients with latent cryptococcal central nervous system infection can develop a meningitis on HAART. Similar to patients with CMV retinitis, these patients have also had dramatic improvements in the underlying opportunistic infection.

There was initially concern that because many of these opportunistic infections develop at extremely low CD41 counts, patients may have lost the clones of cells that could functionally respond to the invading organisms. These studies provide clinical evidence that this is not the case and that immune recovery in patients receiving HAART is effective in controlling opportunistic infections, even in patients with a history of severe immunosuppression.

Despite the development of immune recovery inflammation in some patients with opportunistic infections on HAART, it is clear that the benefits of a rejuvenated immune response greatly outweigh the risks. HAART has led not only to increased survival and lower rates of opportunistic infections, but to improved quality of life. The immune system does a much better job controlling CMV retinitis than any available drug therapy. When in balance, the ocular immune response performs a formidable task, defending the eye against insults while preserving tissue architecture and visual function. Although the ocular immune response is double-edged, the eye is clearly better off with an intact immune defense.

I was fortunate to have the opportunity to discuss the pathogenesis of immune-mediated ocular disease with Dr. Cogan. It was particularly rewarding to examine patients with

### Table 1. Reported Cases of Inactive CMV Retinitis without Specific Anti-CMV Therapy

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients*</th>
<th>Median Time not Receiving Therapy (mo)†</th>
<th>No. of Patients with Reactivation</th>
<th>CD4+ Cell Count when Therapy Stopped (cells/μl)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitcup et al.41</td>
<td>4 (1)</td>
<td>6 (4–12)</td>
<td>0</td>
<td>24–28</td>
</tr>
<tr>
<td>Reed et al.55</td>
<td>4 (4)</td>
<td>5 (4–7)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Tural et al.46</td>
<td>7 (0)</td>
<td>9 (9–12)</td>
<td>0</td>
<td>18–52</td>
</tr>
<tr>
<td>Macdonald et al.47</td>
<td>11 (0)</td>
<td>5 (3–18.5)</td>
<td>0</td>
<td>6–41</td>
</tr>
<tr>
<td>Vrabec et al.42</td>
<td>8 (0)</td>
<td>13.5 (3–16)</td>
<td>0</td>
<td>9–24</td>
</tr>
<tr>
<td>Whitcup et al.43</td>
<td>2 (2)</td>
<td>9.5 (7–12)</td>
<td>1</td>
<td>6–11</td>
</tr>
<tr>
<td>Jabs et al.48</td>
<td>15 (0)</td>
<td>8 (3–16)</td>
<td>0</td>
<td>9–65</td>
</tr>
<tr>
<td>Whitcup et al.44</td>
<td>14 (0)</td>
<td>16.4 (8–22)</td>
<td>0</td>
<td>8–130</td>
</tr>
</tbody>
</table>

NA, not available.

* Values in parentheses are the number of patients who never received specific anti-CMV therapy.

† Values in parentheses are the range.

The exact mechanism of immune recovery uveitis is also unknown; however, the finding that the inflammation is limited to eyes with CMV retinitis may give us insight into the pathogenesis of this disorder. CMV retinitis could induce inflammation in patients with immune recovery through a number of effects. First, CMV retinitis leads to a breakdown in the blood-ocular barrier. We previously showed that anterior chamber flare measured by laser flare photometry was significantly increased in eyes with CMV retinitis. This compromise of the blood-ocular barrier allows proteins and cells into the eye. In addition, this breakdown in the blood-ocular barrier may permit CMV antigen to leak out of the eye and give the antigen access to lymphoid organs. This exposure of CMV antigen to the lymphoid system could stimulate an antigen-specific immune response against CMV that could overwhelm immune privilege. Interestingly, one patient with CMV retinitis but no uveitis had a very small area of retinal involvement. Low amounts of available CMV antigen and minimal breakdown in the blood-ocular barrier may limit the development of immune recovery uveitis. The amount of CMV antigen in the eye could also be related to anti-CMV treatment. The sustained-release intravitreal ganciclovir implant, for example, could minimize CMV antigen in the eye by delivering higher levels of drug to the eye. In addition, the degree of immune reconstitution may also influence the resultant inflammatory response. Our patients had fairly dramatic immune recovery on HAART, with some CD4+ counts higher than 1000 cells/μl, and this may partly explain the frequent occurrence of immune recovery uveitis in our studies.

### Immune Recovery Uveitis

Although the rejuvenated immune response in patients on HAART can effectively control CMV retinitis, we are now seeing significant intraocular inflammation in some patients. This immune recovery uveitis is characterized by a number of inflammatory signs including vitritis, retinal edema, epiretinal membrane, anterior uveitis, and cataract. Some patients with immune recovery uveitis develop substantial visual loss, predominantly from macular edema. Treatment with corticosteroids has lead to improvements in the underlying opportunistic infection. Patients with CMV retinitis, despite treatment with anti-CMV medications.

Immune recovery has lead to inflammatory disease associated with other opportunistic infections. Patients with subclinical Mycobacterium avium complex infection can develop leukocytosis, fever, and lymphadenitis following HAART. Patients with latent cryptococcal central nervous system infection can develop a meningitis on HAART. Similar to patients with CMV retinitis, these patients have also had dramatic improvements in the underlying opportunistic infection.

There was initially concern that because many of these opportunistic infections develop at extremely low CD4+ counts, patients may have lost the clones of cells that could functionally respond to the invading organisms. These studies provide clinical evidence that this is not the case and that immune recovery in patients receiving HAART is effective in controlling opportunistic infections, even in patients with a history of severe immunosuppression.

Despite the development of immune recovery inflammation in some patients with opportunistic infections on HAART, it is clear that the benefits of a rejuvenated immune response greatly outweigh the risks. HAART has led not only to increased survival and lower rates of opportunistic infections, but to improved quality of life. The immune system does a much better job controlling CMV retinitis than any available drug therapy. When in balance, the ocular immune response performs a formidable task, defending the eye against insults while preserving tissue architecture and visual function. Although the ocular immune response is double-edged, the eye is clearly better off with an intact immune defense.

I was fortunate to have the opportunity to discuss the pathogenesis of immune-mediated ocular disease with Dr. Cogan. It was particularly rewarding to examine patients with
Cogan’s disease with the person for whom the disease is named after. It is therefore a special and personal honor to receive this year’s Cogan Award. All of us in the field of ophthalmology owe a great deal to the work of Dr. Cogan. In an interview in 1989, Dr. Sally S. Hughes asked Dr. Cogan what was the most important knowledge he imparted to others? Dr. Cogan replied, “To transit some of my enthusiasm for the esthetic, scientific, and humanistic possibilities in the study of the eye and its connections to the brain. I guess I would leave it at that.”

References


