As we enter the year 2000, we are asked to consider what advances may occur in the field of ocular inflammatory disease in the next 50 to 100 years. This is a daunting and probably unwise endeavor, but an extremely interesting one.

The diagnosis and treatment of ocular inflammatory disease began as a scientific discipline in the 17th century, with the recognition of infectious diseases, such as gonorrhea, that can affect the eye.1 Thereafter, for the better part of the next 2 centuries, most all ocular inflammatory diseases were considered infectious in nature, with syphilis and tuberculosis believed to be the primary culprits. As such, demonstration of the efficacy of antibiotics in treating such infections was a major medical milestone of the 20th century. However, not all cases of ocular inflammation responded to antibiotics, and theories began to appear suggesting that “autoimmunity” may also be playing a role in some forms of ocular inflammation. For example, experiments in as early as the first decade of this century showed that lens antigens could induce anaphylaxis in guinea pigs,2 and that ocular tissues injected into rabbits and guinea pigs could cause endophthalmitis.3

Accordingly, current practice emphasizes the importance of differentiating between infectious and noninfectious intraocular inflammation.4 However, in many cases this is difficult and since the exact etiology or pathogenesis of these immune-

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mediated diseases is largely unknown, our efforts in treating them remain limited to the use of non-specific agents such as corticosteroids or immunosuppressive drugs. Therefore, in the new millennium, we might look forward to advances in our understanding of pathogenic mechanisms, using new techniques of immunologic and genetic research, to guide us toward better therapeutic modalities. This article will consider first future directions in pathogenesis and diagnostics, then briefly introduce therapies that are likely to emerge for the clinician in the new millennium.

ADVANCES IN PATHOGENIC MECHANISMS AND DIAGNOSTIC TECHNIQUES

Most of our understanding of the pathogenesis of intraocular inflammation has come from infectious and noninfectious experimental models of disease. It is likely that we will gain greater understanding of specifically which cells are responsible for ocular tissue damage, how they are activated, how they gain access to the eye, and how they are down-regulated. In particular, this last element will direct us toward therapies that may enhance natural tolerizing mechanisms that the body engages to reestablish a noninflammatory state of homeostasis.

RECOGNITION OF OCULAR DISEASES CAUSED BY NEW INFECTIOUS AGENTS

Like human immunodeficiency virus in promoting infection by cytomegalovirus (causing retinitis in patients with acquired immunodeficiency syndrome) and human T-cell lymphotropic virus 1 (HTLV-1) (causing intermediate uveitis, adult T-cell leukemia, and myelopathy), new microorganisms have emerged or have been recognized to directly or indirectly cause ocular inflammatory diseases over the last few decades. Other examples of microbes newly identified to cause intraocular inflammation include *Borrelia burgdorferi* (Lyme disease), *Bartonella henselae* (cat-scratch disease), *Tropheryma whippelli* (Whipple disease), and *Brucella* species (brucellosis). It is easy to imagine other new infectious agents wreaking inflammatory havoc for the eye in the future. Mankind’s continual manipulation of the environment gives ample opportunity for new microbes to evolve in nature, or for an already existing microbe to jump from an animal species to an unsuspecting human being. Of course, a prime recent example is the trans-species movement of spongiform encephalopathy in cows (mad cow disease) and the neurologic disease scrapie in sheep to Creutzfeld-Jakob disease in humans. Although mostly of concern to neurologists, there does exist a risk that prion disease can be transmitted to humans via ocular donor tissue transplantation. Furthermore, it has been shown in experimental animals that mere conjunctival instillation of scrapie can cause neural infection in mice, and that photoreceptor degeneration occurs with scrapie infection in hamsters.

**BLURRING OF THE DISTINCTION BETWEEN INFECTIOUS AND NONINFECTIOUS FORMS OF OCULAR INFLAMMATORY DISEASE**

Even the view that ocular inflammation is either infectious or non-infectious has come under scrutiny in recent years. For example, inflammatory cells observed in the uveitis associated with HTLV-1 are believed to be HTLV-1-infected T cells that have crossed the blood-ocular barrier and selectively accumulated in the eye, rather than the result of direct infection by the virus of ocular cells. The fact that the treatment for HTLV-1-associated uveitis is corticosteroids also underscores the immune-mediated “by-stander” damage that is caused by viral infection of T cells. As an example of possible induction of immune-mediated disease by bacteria, the shared amino acid sequences between HLA-B27 and *Klebsiella pneumonieae* nitorgenase have led many investigators to suspect that antigenic mimicry is responsible for HLA-B27–associated spondyloarthropathies, and therefore also for HLA-B27–associated uveitides. In the future, as we learn more about the immune response to foreign as well as self-antigens, we may find that many conditions start out as infections, or become exacerbated by secondary infections, and later are perpetuated by dysregulated immunological processes. Indeed, while we have become relatively successful at managing virulent bacterial and viral infections, we may be less equipped to deal with “stealth” microorganisms that subvert the immune system to survive without necessarily causing death of the host. With better diagnostic techniques we hope to be able to select specific antimicrobial therapy to challenge these agents.

**NEW INVESTIGATIVE TOOLS**

Experimental studies will provide a lead for clinical studies that will take advantage of the vast amounts of information emanating from the Human Genome Project. Apart from providing us with information on genes for disease susceptibility and disease protection, the Human Genome Project may offer the opportunity to furnish every individual with “smart card” genetic information indicating to them the risks of specific diseases. In view of the many associations of intraocular inflammation with intercurrent systemic disease, especially infections, even if mediated by “autoimmune” mechanisms, it may be possible for individual patients to take prophylaxis against recrudescence of inflammation using this kind of “bar code” information.

In addition, to determine which of the 100 000 or so human genes are activated in a patient, small samples of cells or tissue may be tested by highly sophisticated techniques such as the “Affymetrix” and serial analysis of gene expression (SAGE) technology, with or without proteomics (study of the function of gene products). These data can then be used to specifically modulate gene activity with appropriate therapies such as DNA vaccines (see below). Moreover, as genetic information becomes available on more and more microorganisms, it will be possible to run a full screening on blood or tissue samples using customized oligonucleotide probes to determine which, if any, microor-
ganism might have played a part in the induction or reactivation of inflammation.

Whether such genetic information can be used will depend on many factors, not least of which is whether the treatment will cause more damage than the disease. Clearly, it is preferable to remove damaged cells and dead microorganisms by mechanisms involving apoptosis rather than necrosis, and this will require development of highly selective treatments and a highly sophisticated understanding of the pathogenesis of various diseases. Moreover, the advent of readily available genetic information in the form of “smart cards” and easy genetic testing will also require concomitant advances in our management of patient privacy and other ethical and medicolegal issues. Discussion regarding how to handle such potent information has already begun among the experts; however, society-at-large has yet to comprehend the issues surrounding availability of such information.

ADVANCES IN THERAPEUTIC MODALITIES

Advances in the understanding of pathogenesis and in diagnostic techniques will serve as a driving force for new therapies. In the new millennium, we can expect breakthroughs in our day-to-day treatment of ocular inflammation, especially of what has been considered noninfectious inflammation, which has up until now been treated mostly nonspecifically with immunosuppressive agents. Three examples of possible new approaches to therapy of intraocular inflammatory disease are presented here but many more possibilities exist.

Gene Therapy for Ocular Inflammatory Disease

Gene therapy for various ocular diseases, mainly for hereditary retinal diseases and intraocular malignancies but also for ocular inflammation, is an obvious choice and one that has been considered in several recent reviews.13-15 The eye, through its exposed anterior surface, is ideal for the possibility of gene therapy. Furthermore, since the effects of gene therapy to somatic cells may be short-lived, the treatment of active ocular inflammation with, for example, the transient expression of certain cytokines, is an appealing idea. A gene that encodes for a protein for which expression is desired may be transferred to cells at the surface of the eye (with topical application) or to cells within the eye (with intraocular injection) by using a viral vector such as retrovirus or adenovirus, or by using nonviral liposomes.13,14 Candidates for expression to suppress ocular inflammation would include naturally occurring anti-inflammatory cytokines such as transforming growth factor β, and interleukin 10, as well as posttranscriptional factors that regulate both proinflammatory and anti-inflammatory cytokine production. However, unlike hereditary disorders in which one defective gene might be replaced, ocular inflammation involves the interplay of multiple gene products, and thus knowledge of which proinflammatory genes are overactive or which anti-inflammatory genes are underactive in individual patients will be important to help modulate the disease. It is also important to remember that not all inflammation is “bad” and that the regulation of this process will involve very careful modulation of endogenous as well as exogenous gene function. Indeed, it may be better to attempt to “switch on” endogenous genes that are not functioning effectively in the inflammatory situation, particularly in chronic disease.

Monoclonal Antibody Technology for Ocular Inflammatory Disease

New approaches to the therapy of ocular inflammatory disease often evolve from advances in other fields. For example, phage technology has made possible customized, fully human monoclonal antibodies, such as anti–tumor necrosis factor α antibody, which is currently in phase 3 clinical trials for the treatment of rheumatoid arthritis. Since experimental evidence supports the use of such antibodies for treatment of uveitis, they would be ideally suited to this category of disorders. Monoclonal antibodies to other proinflammatory cytokines, for instance, interleukin 15, would also be possible. According to pharmaceutical companies that manufacture these antibodies, several billion human antibodies have already been characterized using this technology and await extraction and bulk manufacture as required.

Antigen-Specific Tolerizing Therapy

If a single foreign antigen or autoantigen is responsible for ocular inflammation, or if persistence of an antigen is important in the perpetuation and increasing severity of disease, antigen-specific therapy that eliminated or at least disabled the antigen would clearly be advantageous. Procedures that induce tolerance to antigens have been recognized for nearly a century and are currently being evaluated in clinical practice. For example, a randomized, masked study is under way investigating the efficacy of inducing oral tolerance by feeding retinal soluble antigen (S antigen) to patients with refractory uveitis. However, much needs to be learned regarding dosage, mode of delivery, form of the antigen, and other factors if we wish to avoid sensitization while inducing tolerance to that antigen.

BEYOND OUR WILDEST DREAMS?

Of course there are many other developments that may soon influence the diagnosis and/or therapy of ocular inflammatory disease. In particular, one major focus of research in coming years will be the development of cell or tissue-seeking techniques to deliver drugs or express genes only within the target site, to minimize the side effects of therapy. Advances such as these will continue to refine our understanding and treatment of ocular inflammation in the future. It is almost certain that many of the advances that will emerge in the new millennium are beyond our imagination at present, just as some of those de-
scribed herein were undreamed of 50 or 100 years ago.

Accepted for publication September 10, 1999.

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A look at the past...

Absolute glaucoma following tuberculosis of the interior of the eye is an extremely rare condition, and although the literature of ocular tuberculosis is particularly rich, there is very little in regard to glaucoma in connection with tuberculosis, and I was able to find only three cases in which there was increased intraocular tension, hypotony being the rule. These cases, however, differ from mine in that the increased tension was not a prominent symptom and the glaucoma did not mask every sign of tuberculosis, as in my case. The case, therefore, seems worth reporting and the more so on account of the peculiar extension of the tuberculous process in the ball.