Eight decades ago, a leading authority on uveitis hypothesized that many patients with uveitis suffered from a disease induced by bacterial toxins. Paradoxically, bacterial toxin in the form of endotoxin evolved as a conventional therapy for uveitis. Now the conundrum has come full circle; currently, a subcutaneous or intraperitoneal injection of endotoxin serves as a standard model to induce uveitis in laboratory animals. Cytokines are presumed to be the major mediators of endotoxin-induced inflammation. The simultaneous inflammatory and antiinflammatory ocular effects of endotoxin illustrate the complexity of the actions of cytokines.

DEFINITION AND DIVERSITY. Cytokines are polypeptides that are involved in cell-to-cell communication. These molecules include the expanding list of interleukins, tumor necrosis factors, the interferons, and a host of growth factors including colony-stimulating factors, the fibroblast growth factors, the insulin-like growth factors, the transforming growth factors, the platelet-derived growth factors, epidermal growth factor, and vascular endothelial growth factor. Cytokines are signals for adjacent cells (paracrine stimulation) and sometimes for more remote targets (endocrine stimulation). Cytokines may also feed back on the cell that produces the peptide (autocrine stimulation). In fact, this autostimulatory effect could even occur without secretion of the peptide (intracrine stimulation). Physiologic activities of cytokines include the repair that is critical for tissue homeostasis. Pathophysiologic effects of cytokines include the injury characteristic of inflammation. An understanding of cytokines involves an appreciation of the vast array of different cells that produce these mediators, a knowledge of the dozens of peptides that participate, and a realization that the combinatorial interactions are infinite. Many of these interactions are believed to proceed along organized cascades. Thus, interleukin-1 induces tumor necrosis factor alpha synthesis, which, in turn, induces interleukin-8 and interleukin-6 production.

Within the eye, the importance of cytokines and growth factors has been appreciated. Examples include the contribution of growth factors in corneal wound healing; the appreciation that cytokines can stimulate corneal neovascularization; the vital role of cytokines in any immune-mediated process such as uveitis, keratitis, or corneal graft rejection; the presumed role of growth factors in proliferative diseases, including diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, and fibrosis after filtration surgery for glaucoma. As regulators of cell growth and function, cytokines are candidates to mediate any cellular process including cataractogenesis, macular degeneration, and glaucoma.

EXAMPLES OF PARADOX. Analyzing the activities of a specific cytokine shows the capacity for therapeutic as well as deleterious effects. Consider, for example, the potential importance of transforming growth factor (TGF) beta in the eye. TGF beta is a dimeric peptide with a MW of 24,000. Its multiple functions include acting as a chemotactic, regulating cellular proliferation including angiogenesis, and affecting the synthesis of a variety of other cytokines including interleukin (IL)-1. In tissue culture, TGF beta can either induce cell growth or inhibit it; the effects depend on the cell type and the amount of TGF beta employed. With regard to harmful effects, TGF beta may contribute to fibrosis in wound healing. Increased levels of TGF beta have been
found in the vitreous humor of patients with proliferative vitreoretinopathy. On the positive side, recent reports indicate that local injections of TGF beta may be useful in promoting the healing of full-thickness macular holes. Similar potential for pathology and healing have been described in other organ systems. For example, TGF beta can inhibit joint disease in experimental animals, but it has been implicated as arthritogenic in another animal model.

Other cytokines likewise have paradoxic effects. Interleukin-1 exacerbates experimental autoimmune encephalomyelitis, a model with some resemblance to multiple sclerosis, but IL-1 reduces the inflammation in an experimental model of arthritis. The inhibition of IL-1 is under clinical study to reduce mortality in gram-negative sepsis because of encouraging observations in animal models. However, IL-1 protects granulocytopenic mice from lethal effects of gram-negative infection. Several studies have concluded that the neutralization of tumor necrosis factor improves survival in models of septic shock, but the infusion of tumor necrosis factor is also protective in a model of lethal bacterial infection. Platelet-derived growth factor can accelerate corneal wound healing, but in an artery this process of healing may contribute to atherogenesis.

The mechanisms that resolve these conflicting observations are unknown. Possible explanations include dose dependence of effects, differing activities depending on administration route, indirect interactions with other cytokines, and regulation at a receptor level.

The subtle difference between physiology and pathophysiology can also be demonstrated on a molecular level. The regulation of interleukin-1 serves as a paradigm. IL-1 alpha and beta are multipotent cytokines whose activities include induction of fever, stimulation of the acute-phase response, bone marrow stimulation, bone remodeling, cellular recruitment, and lymphocyte activation. The activity of IL-1 appears to be regulated by a naturally occurring peptide that competes with IL-1 for receptor binding. The retinal pigment epithelium synthesizes an intracellular form of this inhibitory peptide. As yet, no agonist effects have been described for the IL-1 receptor antagonist peptide. However, a single amino acid change in this peptide converts it from an antagonist to an agonist. Conversely, a single amino acid change in IL-1 converts it from an agonist to an antagonist.

The challenges in determining the importance of cytokines in eye disease are immense. In vitro studies may produce results that are not physiologically important, and in vivo studies are also fraught with limitations. First, the presence of the mediator in an ocular fluid does not guarantee its physiologic importance. An inhibitor, for example, could neutralize potential biologic effects. Conversely, the absence of the peptide does not exclude its possible importance because some of the cytokines are rapidly metabolized. Second, studies in which cytokines are pharmacologically inhibited are beset with problems in interpretation. If no biologic response is achieved, did the inhibitor reach adequate biodistribution in the critical microenvironment that determines the cytokine’s effect? If the inhibitor does alter the pathology, was the inhibitor truly specific in its action? Finally, studies that examine the effect of direct injection of cytokines produce interesting pathologic effects. IL-1, IL-2, IL-6, IL-8, tumor necrosis factor, granulocyte-macrophage colony stimulating factor, and gamma interferon are among the cytokines whose ocular activities have been studied by direct injection. However, the results of such experiments are hardly physiologic. The absence of response could result from rapid metabolism before the peptide reaches its site of action or from downregulation of receptors. The presence of a response may simply reflect supra-physiologic concentrations. Finally, one should not assume that the role of a cytokine in an organ such as the skin or joint is comparable to the importance of that cytokine in the eye.

**THE CHALLENGE FOR PHARMACOTHERAPY.** The biologic functions of cytokines and their ubiquitous nature are such that it is inconceivable to think that cytokines are unimportant in any organ system. Exciting and novel strategies are evolving to understand the physiologic importance of cytokines and ultimately to have pharmacologic tools to alter their role. These strategies include the use of naturally occurring substances such as decorin to inhibit TGF beta or the IL-1 receptor antagonist peptide to inhibit IL-1 effects; the use of neutralizing antibodies directed against either the peptide or its receptor; the use of soluble receptors to act as a “sponge” that competes with the cell-associated receptor for ligand binding; the use of “antisense” nucleotides that block peptide expression by interfering with the translation of RNA; and the use of peptides that are modified by genetic engineering, some of which bind to the receptor without triggering the intracellular events that normally result after a cytokine finds its cellular receptor. If the biodistribution and half-life of an inhibitor are such that it could be useful in the treatment of eye disease, how could the therapy be targeted to the eye? For most cytokines, their putative pathogenic role in one site is balanced by an important physiologic role in another. Is TGF beta or interferon gamma or IL-1 solely pathogenic, or does each play a homeostatic role such that inhibitors may have paradoxic effects?

We have entered an era in which it is possible to produce large quantities of peptides with high purity. In the case of hemopoietic growth factors, these peptides are demonstrating tremendous clinical usefulness. In other instances, such as the antitumor effects of interleukin-2, we have found that the beneficial effects are limited by the multifunctionality of the peptide, which results in toxic effects. Conversely, it is now possible to target and neutralize a host of cytokines whose roles in some settings and concentrations appear harmful. Endotoxin, transforming growth factor beta, interleukin-1, and tumor necrosis factor illustrate the paradox that a single substance can be both therapeutic and pathogenic. The cytokine network is immensely complex with limitless interactions and counter-regulatory effects. Their biology is certain to be immensely important in the eye.

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**References**

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