Herpes simplex keratitis is a leading cause of blindness and disability. Much information has been obtained from recent experimental and clinical observations. These data may ultimately provide insight into more effective methods of therapy.

Key words: herpes simplex virus, herpes keratitis, herpetic keratouveitis, cornea, virus, interferon, immunoglobulins, trifluorothymidine, adenine arabinoside, idoxuridine.

Herpesvirus hominis is a highly successful parasite, having developed a relationship to the host which assures its perpetuation without seriously disturbing the host population. From 50 to 90 per cent of the adult population has neutralizing antibodies to herpes simplex, indicating previous infection, but most of these affected individuals show no clinical manifestation of disease. Ocular herpes may be present either as an initial infection or as a recurrence. The primary lesion of the cornea may be associated with a variety of systemic disturbances, but of more importance is the recurrent or secondary ocular infection which develops in the presence of circulating antibodies. Recurrent herpetic infections have been considered to represent reactivation of endogenously established virus which has persisted within the host in a latent state.

Recent studies have provided some insight into the natural history of herpes simplex infections and have revealed principles which may make it possible to establish more effective control over this infection. Herpesvirus hominis is a small particle, 1,050 Å in diameter, composed of a central core of deoxyribonucleic acid (DNA) covered with protein coats. Upon entry into a suitable host cell on which the virus is completely dependent, cellular function is altered. This redirection of cellular activity by the invading virus leads to destruction of the host cell and formation of many new infective particles.

Two basic groups of herpes simplex virus are known to infect man: Type I and Type II. Type I is generally responsible for recurrent diseases of the eye, lips, and face, while Type II is associated with genital infections but may occasionally cause keratitis in infants.

Significant progress in understanding the pathogenesis of herpes has occurred from the study of dendritic keratitis. Among patients with a first attack of dendritic kera-
titis, there is a 26 per cent recurrence rate in two years, and in those with a second or subsequent episode, the recurrence rate is 43 per cent in two years. Study of patients with recurrent herpetic keratitis has shown persistence of virus in the tear film and virus antigen within lacrimal gland and conjunctiva even between clinical episodes. In fact, when cultures are made of tears or saliva in normal humans, random herpesvirus isolations are made in 5 to 7 per cent of the individuals. This random distribution of herpes isolations is consistent with chronic low-grade infection resulting in intermittent shedding of virus.

Further understanding of herpetic infections has been facilitated by recognition of the fact that the rabbit is an excellent experimental model, not only for primary ocular herpes infection, but for recurrent corneal disease as well.

Review of work done recently in primary herpetic infections in rabbits supports the concept of chronic replication of virus in many tissues. On sequential study following ocular inoculation, herpesvirus was obtained from the tear film, then from the conjunctiva and adnexal tissues, and finally from the cornea. Later in primary infections virus may be recovered from all depths of the cornea and may be identified within the nerves of the corneal stroma. Associated with the acute keratoconjunctivitis of the primary infection is progressive ascending involvement of the central nervous system, with lesions appearing first in the ganglion cells of the ophthalmic branch of the trigeminal nerve, later in the Schwann and satellite cells, and finally in astrocytes and neurons in the descending trigeminal tract. Though herpes has not been isolated from trigeminal nerves in humans, this tissue is capable of harboring viral particles in animals. Thus, the trigeminal nerve and perhaps other portions of the central nervous system must also be considered reservoirs of chronic virus replication.

In chronically infected rabbits, periodic and spontaneous release of virus into the tear film and saliva is noted often, as in humans. Often virus is present in the precorneal tear film several days before the recurrent corneal lesion of herpes appears. Removal of the globe in chronically infected rabbits has no effect on the virus production, further suggesting that the adnexa elaborates infective particles and releases them into the tear film.

Herpes keratitis, as do all other infectious diseases, depends on the balance of virulence of the agent and resistance of the host. Host defenses that have been studied are serum antibody, secretory antibody, interferon, and the inflammatory reaction.

In primary herpetic infection these antibodies assume a maximal level two or three weeks after infection and then drop to lower levels. Local recurrences generally do not affect the serum antibody levels. Conversely, high levels of serum antibodies do not protect against recurrent diseases but probably do play a role in preventing generalized herpes.

More recent studies have defined the unique secretory antibody system which is essentially separate from circulation. The secretory antibody is produced beneath the mucosal surfaces of the body and is secreted into various body fluids, including tears. Secretory antibody in tears can be stimulated by local antigens and local challenge and specific neutralizing antibodies to herpes simplex can be produced.

Immunoglobulin A, the secretory antibody, is a very efficient neutralizer of herpes virus, but, unfortunately, increased production of the antibody does not reduce the incidence of recurrent herpetic keratitis. This paradoxical finding may be explained by the presence of immunoglobulin G, which is present in inflamed eyes and impairs the effectiveness of IgA, perhaps by coating the virus and preventing inactivation by IgA. Thus, recurrent herpes may be a function not only of tissue susceptibility and virus availability, but may also depend on the amount and ratio of antibodies present in the surrounding me-
dium. Altering the ratio of antibodies present in the tear medium may be an important method of controlling recurrences.

Another host mechanism which has recently attracted much attention is interferon. Interferon appears to provide a first line of defense against viral disease, being produced early in infection and functioning at the intracellular locus to limit or prevent viral replication and mediating recovery. Interferon occurs naturally and is a species-specific protein exhibiting a broad spectrum of activity against virus, though, in the case of herpes, it is relatively inefficient.

The broad spectrum of activity is in keeping with the mode of action of interferon, which has no effect on the virus itself but prevents the synthesis of the infectious particles. This is accomplished by inducing the cell to form a translational inhibitory protein which prevents the genetic code of the virus from being read by the cell and thereby prevents synthesis of essential viral components. Interferon induction is believed to occur as the result of formation of double-stranded ribonucleic acid (RNA), which the host cell recognizes as foreign and causes the cell to produce interferon. All major groups of virus, and many intracellular parasites, may act as interferon inducers. Many agents including synthetic double-stranded RNAs such as polyinosine polycytosine (Poly I:C) have been found to be potent interferon inducers in some species. Poly I:C has been shown to have some therapeutic effect in herpetic keratitis in rabbits and some prophylactic effect. However, there are limitations. Poly I:C is toxic systemically and the therapeutic effect is slight when compared to specific antiviral drugs. Other disadvantages of interferon induction include fatiguing of its protective effect with time and limited response by primates. At present it seems unlikely that these agents will be of value in treating human disease.

In the treatment of dendritic keratitis, several well-controlled studies have documented the safety and effectiveness of idoxuridine (I.D.U.) against dendritic keratitis. Comparison of debridement versus I.D.U. in treating herpetic epithelial disease has revealed no significant difference between the two modalities in the rate of healing or final visual acuity. In large ulcers and those previously treated with steroids, I.D.U. is clearly superior to cauterization. In addition, comparison of recurrence rates reveals no significant difference between the two means of treatment. Trifluorothymidine, a drug similar in mechanism of action to I.D.U., has been evaluated recently and seems to be somewhat more active than I.D.U. against epithelial herpetic keratitis.

Cryotherapy for epithelial disease is apparently effective in humans, but probably acts as another method of epithelial debridement. However, controlled studies in animals have shown cryotherapy to be ineffective and final opinion must await carefully controlled studies in humans. Stomal disease is a definite contraindication to cryotherapy, as a devastatingly severe anterior inflammation results.

Stomal disease remains a confusing problem, but studies have indicated there are at least two different types. Disciform edema, which appears as a disc-shaped area of gray opalescence of the stroma, usually appears five to ten days after the onset of epithelial disease. In long-standing cases, peripheral and finally central vascularization may occur. Edema is present in all layers of the cornea and various numbers of both lymphocytes and polymorphonuclear cells are present. Herpesvirus cannot be recovered from disciform lesions and this form of stromal disease is considered to be due to a hypersensitivity to virus or viral components or as an autoimmune phenomenon. The hypersensitivity reaction can be mimicked in sensitized experimental animals by injection of purified virus antigen. Prompt clinical improvement is noted when disciform keratitis is treated with corticosteroids. Though some investigators have
indicated that enormous amounts of potent corticosteroids may lessen disability and improve the visual prognosis, it must be remembered that there is a tendency to reactivate epithelial herpes, promote stromal disease, and increase the incidence of superinfection by bacteria and fungi. The antagonism between corticosteroids and I.D.U. lessens the risk of reactivation of epithelial herpes but does not eliminate it.

Less potent corticosteroids such as hydroxymesterone, or very dilute standard corticosteroids such as 0.005 per cent dexamethasone, appear to retain significant antiinflammatory potency and yet do not worsen experimental herpes.

Another form of stromal keratitis appears as heavy, whitish material lying within the corneal stroma. Recent findings implicate direct invasion of the stroma by herpesvirus. Stromal keratitis, however mild, is accompanied by anterior uveitis. This may be secondary to allergic or toxic reactions or by direct invasion of the anterior chamber and iris by virus particles. Immunofluorescence and electron microscopy studies have now identified both free virus particles and intracellular particles within the anterior chamber and the iris of human beings.

Treatment of stromal keratitis and iritis with I.D.U. has been unsatisfactory to date. Experimental trials of other agents such as adenine arabinoside have been promising. The drug is effective when administered subconjunctivally even against herpes infections initiated by injection of virus into the anterior chamber. This agent may be effective in human keratomalacia and is currently under clinical investigation.

In summary, herpes simplex virus appears capable of establishing chronic infection in some species. There is often spontaneous release of virus into various tissues with occasional appearance of clinical disease. Most defense mechanisms are important for the prevention of clinical disease in many instances, and may provide insight into a means of controlling primary and recurrent infections. Newer antiviral agents such a trifluorothymidine and adenine arabinoside are important advances in antiviral therapy, and other more active drugs will soon be available.

REFERENCES

14. Pavan-Langston, D., and Nesburn, A. B.:
chronology of primary herpes simplex infection of the eye and adenval glands, Arch. Ophthal. 80: 258, 1968.


