Herpetic keratitis
Proctor Lecture
Herbert E. Kaufman

My selection as Proctor Lecturer is one of the greatest honors of my life. This lecture seems especially appropriate in topic since Dr. Proctor, who founded this award, was himself primarily interested in ocular infections, and it has been more than 25 years since any Proctor Award recipient has addressed himself to this subject. The work cited represents the synthesis of the efforts of many people, and I must acknowledge their efforts.

Herpes simplex infection typically begins as an epithelial ulcer that looks like a branching tree (Fig. 1). This dendritic lesion may expand so that it becomes geographic in character (Fig. 2) or may invade the stroma, damaging the collagen lamellae and causing stromal scarring and haze (Fig. 3). Once someone has had more than one attack of herpes, the chances are almost 50% that he will have another occurrence within 2 years. This disease, then, which tends to begin early in life, may keep recurring, and even though the initial attack can be suppressed, continued morbidity over the years and the likelihood of eventual visual damage are real. If one considers that there appear to be somewhere between 300 and 500,000 cases of corneal herpes a year and that very significant morbidity is associated with these attacks, it is easy to understand why both NEI Corneal Task Forces have considered it a primary corneal problem. Even if the resulting corneal scar can be removed with keratoplasty, a real risk remains that recurrences will occur in the transplant (Fig. 4). The terrible problems that such patients have had with their disease drove me to search for some better treatment for it.

When I first began the search for drugs that might be active in the treatment of herpes keratitis, things were even more confused than they are now. The literature contained hundreds of articles on drugs which were "antiviral" in tissue culture, but these had no activity in vivo. It appeared that many drugs which interfered with cell membranes or cell metabolism in any way could make cells more difficult to infect and reduce the titer of virus produced by these cells, but these in vitro effects had no meaning in vivo.

Similarly, a number of antimetabolites had been used in an attempt to inhibit viral multiplication, but it appeared to me that virtually all of these inhibited normal cellular synthetic processes rather than any specifically virus-encoded enzymatic step (Fig. 5). When cellular synthetic processes were inhibited and the raw materials of DNA were scarce, the evidence indicated that the virus could multiply more readily than the cell, and this therefore did not appear to be a useful approach to virus chemotherapy.

In my search for an effective antiviral agent, I looked toward the only enzyme system which at that time was known to be necessary for viral DNA synthesis and yet was known to be coded by the virus genome. This was the DNA polymerase system. The only drug in the world at that time known to
specifically inhibit DNA polymerase and be incorporated into DNA was iododeoxyuridine (IDU) and its close relatives chlorodeoxyuridine and bromodeoxyuridine. These drugs had been synthesized for cancer chemotherapy 3 years before by Prusoff in the Department of Pharmacology at Yale and were available for trial. In fact, even though there was no evidence that the selective toxicity would be adequate for effective virus chemotherapy, they were the only drugs available at that time acting on the DNA.
Fig. 3. Stromal invasion can result in stromal necrosis and scarring.

Fig. 4. Recurrences may occur in the transplant, and certain ones occur in areas not adjacent to previously infected tissue.

polymerase step for which some selectivity could be hoped.

Somewhat to my surprise, IDU was very active therapeutically in rabbits with herpes keratitis\textsuperscript{1,3} and in people.\textsuperscript{9} Table I is a summary of the double-blind studies of IDU. In spite of these encouraging results, however, it was clear that it was not an ideal drug. It was quite insoluble, and the total amount of antiviral activity which could be obtained was limited. In addition, there was some toxicity and allergy resulting from it.
Fig. 5. Drugs such as fluorodeoxyuridine, which inhibit cellular thymidine synthesis, are not effective antivirals in vivo. Drugs like iododeoxyuridine, which do not inhibit this normal cellular synthetic step but rather inhibit final assembly of virus or are incorporated into virus at its terminal synthesis step, effectively inhibit virus multiplication in vivo.

Fig. 6. Dose-response curves obtained by probit analysis with normal isolation, IDU-sensitive virus. BDU, Bromodeoxyuridine; CA, cytosine arabinoside; F3TDR, trifluorothymidine.

In order to find superior drugs, it was necessary to develop animal models which were more reliable than those in general use at the time. At that time, it was common to use Draize scores and other multivariant assays. These would give a certain number of points for the healing of the corneal ulcer, a certain amount for the intensity of iritis, some for redness of the conjunctiva, and so on. This kind of scoring did not prove to be useful and was not predictive. The real clinical problem is the corneal ulcer, and in the animal models, considering this parameter as an isolated parameter proved to be most reliable. We used a scoring system in which 0 was a healed cornea, 1+ a fourth of the cornea involved by ulcer, 2+ a half, 3+ three fourths, and 4+ virtually the whole cornea. We took elaborate steps to mask the study so that in evaluating these animals the scorer had no knowledge of the treatment. This even in-
volved mixing the animals up within the animal room so that all of those treated with a given drug were not examined at the same time. Even factors such as treating all right eyes and keeping all left eyes as controls have entered bias into the scoring in the past and rendered the results valueless from a quantitative point of view. However, when all these precautions were taken, rather precise, reproducible drug effects could be obtained.8

Dose-response curves could be plotted, ED50’s could be obtained, and relative potencies of drugs could be estimated (Fig. 6). With such a system, cross-resistance was easy to test (Fig. 7), as were drug effect in terms of additivity or synergism and rate-limiting metabolic steps in terms of competitive or noncompetitive reversal of drug effects by inhibited metabolites.

With this kind of a predictive animal system, a large number of drugs have been tested in both animals and man (Fig. 8). These include IDU and bromodeoxyuridine,
which were similar although bromodeoxyuridine was somewhat more toxic. Cytosine arabinoside in rabbit keratitis had approximately the same potency as IDU but was more soluble (Fig. 6). Its increased concentration could not be used, however, because it was more toxic than IDU in both rabbits and man. Adenine arabinoside (Ara-A) in rabbits was about equal to IDU but was important as an alternative to IDU because it had the potential for systemic activity as well as topical activity; trifluorothymidine in rabbits was clearly superior to IDU and Ara-A in experimental keratitis.
TRIFLUOROTHYMIDINE THERAPY

Fig. 12. Cumulative frequency distribution graph of days required for ulcers to heal with F₃T (trifluorothymidine) or IDU. (From Wellings, P. C., Awdry, P. N., Bors, P. H., Jones, B. R., Brown, D. C., and Kaufman, H. E.: Am. J. Ophthalmol. 73:932, 1972.)

In man, the next drug to be used was Ara-A (Fig. 9). Whereas IDU had its primary effect by incorporation into replicating DNA, Ara-A seemed to act primarily as a terminator of the DNA chain. The arabinose sugar appeared to prevent the 3:5 bond that would continue the sugar backbone of the DNA helix. It was most important for systemic use because it did not inhibit hematopoiesis and depress blood elements. It had one other vital property for a systemically active drug. Studies from our laboratory and Steele et al. indicated that in full systemic antiviral doses, it did not depress the host's cell-mediated immunity. These effects, however, had little to do with its topical activity. In rabbits, this was approximately the same as in man, and in the large-scale double-blind studies in man, both the effectiveness and the acute toxicity were similar to those of IDU (Figs. 10 and 11).

Trifluorothymidine (Fig. 6) in rabbit studies seemed to be a far more effective drug for topical use, although its rapid hydrolysis in the bloodstream increased its safety as a topical drug on the one hand but on the other reduced the likelihood of its being particularly useful in systemic therapy. Some slight incorporation into DNA occurs with trifluorothymidine, but there is marked inhibition of DNA polymerase and an additional inhibition of thymidylic synthetase.

We first discovered the antiviral effect of trifluorothymidine and its usefulness in herpes keratitis 14 years ago. Although everything suggested that this would be a superior
AVERAGE RATE OF HEALING  
EXCLUDING FAILURES  
(in mm²/day)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Moorfields Series</th>
<th>Gainesville Series</th>
<th>Total (both centers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₃T</td>
<td>9.42 (0.01-3.88)</td>
<td>0.56 (0.1-1.5)</td>
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</tr>
<tr>
<td>IDU</td>
<td>0.13 (0.02-0.41)</td>
<td>0.21 (0.15-0.41)</td>
<td>0.17</td>
</tr>
</tbody>
</table>


drug to those otherwise available, the initial expense of the drug and the expense involved in FDA clearance kept it from being made generally available. Initial studies by our group and by Barry Jones’ group at Moorfield's confirmed the superiority of trifluorothymidine (Figs. 12 and 13). More recently, excellent clinical studies have been done, primarily by Pavan-Langston and Foster and Laibson, and these studies also confirm that this drug causes lesions to heal much more reliably than previously available drugs (Figs. 14 to 17).

The finding of drugs active against viral multiplication provided effective agents to treat superficial herpes, but the problems in deep stromal disease remain. Although the pathogenesis of the different stages of the disease was not clear, it seemed that systemically active drugs would be needed to treat stromal necrosis and iritis. This requirement for systemically active compounds stressed the need for more selective drug effects and the elimination of toxicity to the host.

Ara-A was the first practical systemically active drug that did not greatly inhibit the bone marrow system or the host’s own cell-mediated immunity. Double-masked studies with this drug used intravenously indicated that there could be some effect on deep stromal disease and iritis (Fig. 18), and later studies with herpes encephalitis showed that the drug could treat this terrible fatal and debilitating disease. Ara-A also was effective in treating zoster (especially disseminating herpes zoster in immunosuppressed hosts), cytomegalovirus, and some kinds of hepatitis. Even so, there was a great deal of confusion in its early use in terms of both its systemic and its topical activity. This was because the Ara-A was rapidly deaminated to hypoxanthine arabinoside, which also had some antiviral activity (Fig. 9). When Ara-A and the hypoxanthine were compared with each other by putting each drug in a tissue culture and comparing antiviral effect, the hypoxanthine was found to have about one fifth of the activity of Ara-A. Chemical analysis of drug concentration therefore predicted very potent effects after topical application and other kinds of use. Unfortunately, because the Ara-A in tissue culture was rapidly deaminated, the comparison was really between hypoxanthine and itself, and only when deamination was inhibited or cultures were used that did not cause drug deamination was it found that the hypoxanthine was far less active than Ara-A (probably about a log unit less than anticipated). The real problem, however, is that although Ara-A is the safest of the systemic antiviral drugs, it is not truly selective. The possibility remains that host DNA can be altered, and the worry over mutagenesis and teratogenesis remains.

New kinds of drugs were needed, and these have been assiduously sought. Our first experience in attempting to find truly selective antiviral drugs on the basis of the biochemistry of virus metabolism involved a series of drugs initially studied by Sheldon Greer and his group in Miami. Briefly, bromodeoxycytidine is not active as the cytidine but must be deaminated to bromodeoxyuridine before it can interfere with DNA synthesis (Fig. 19). Herpes simplex virus induces a deaminase which can make bromodeoxycytidine active and is not inhibited by tetrahydrouridine. Normal cellular deaminase is inhibited by tetrahydrouridine. The addition, then, of tetrahydrouridine to bromodeoxycytidine prevents toxicity to normal cells and permits inhibition of viral DNA synthesis. Although this was our first
step along the lines of selective viral inhibition, the combination for many reasons was clumsy to use, and the antiviral effect was not as great as we thought would be needed.

Over the years, there have been a number of studies which generally involve the use of normal unaltered purines and pyrimidines that have sugars or sugarlike substances which are abnormal attached to them. These compounds, when properly selected, can be phosphorylated by virus-induced thymidine kinase, whereas they are not phosphorylated by the normal cellular thymidine kinase, which appears to be more fastidious (Figs. 20 and 21). For any of these drugs to be incorporated into the DNA chain or interfere with DNA synthesis, phosphorylation is a necessity. The property of the drugs which permits them to be phosphorylated only by virus-infected cells and viral-induced thymidine kinase, then, provides a distinct biochemical mechanism for selective antiviral toxicity.

Thymidine kinase has been known for some time as an important enzyme in the action of all DNA inhibitors. Bromodeoxyuridine and IDU, for example, have some antitumor effect. Tumor cells, however, can become resistant to these drugs simply by dropping out thymidine kinase from their cellular enzymes and obliterating the drug effect. Centifanto and Kaufman studied the possibility of thymidine kinase alterations in the virus being responsible for viral resistance to IDU. They found, however, that with this relatively new, selective drug, if either cellular or viral-induced thymidine kinase was present, the drug could be active. When no thymidine kinase was present and no phosphorylation of the IDU took place, there was no antiviral effect (Fig. 22).

At present, potency is a limiting factor in the thymidine kinase–selective drugs, although a new one called acycloguanosine or BW248U appears to be the most potent by far (Figs. 23 and 24). In topical administration against herpes keratitis in the rabbit, it seems as active as most other compounds available (Figs. 25 to 28) and more active than AIU, another thymidine kinase–selective drug studied by Puliafito et al. It is effective
against herpetic iritis when given systemically and subconjunctivally and appears to have a large margin of safety when given systemically. This opens up a whole new era of truly selective virus chemotherapy that offers great promise.

In the treatment of virus disease, however, drugs are not enough, and a real understanding of the mechanism of action of damage caused by the virus is required. For example, more than 10 years ago, I concluded that the major mechanism of human defects of corneal ulcers, as well as the mechanism by which ulcers could develop after herpes infection without the presence of live virus in the lesions, was a failure of adhesion between the epithelium and its basement membrane.30 Hemidesmosomes (Fig. 29) or adhesion complexes bind the epithelium to its base, and even after virus or other damaging agents are gone, if these have been damaged, healing does not take place, or else the cornea heals and then breaks down again. This may seem like a small point; nevertheless, it was clinically vital to recognize, since the treatment for such an adhesion defect is patching the eye or putting a soft contact lens over the epithelium to protect it from the rubbing action of the lids, which would take off the nonadherent cells. Opening the eye to put in frequent drops and putting in agents that might be irritating are in fact the worst things possible for this kind of disease. Exposure and drying problems are also common in desensitized corneas after herpes infections.

Even disease directly attributable to the virus is not necessarily due to viral multiplication. Some years ago, for example, we showed that there could be a delayed hypersensitivity to viral antigens in the cornea.36 Although the models were by no means exact, in some ways the disciform edema could be mimicked by such a delayed hypersensitivity.37 Metcalf and Kaufman,38 working in my laboratory, used the technique of Henson et al.39 for showing modification of
Herpetic keratitis

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<tr>
<th>Type of Lesion</th>
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<th>Percent</th>
<th>IDU No. (N = 52)</th>
<th>Percent</th>
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<td>Dendritic</td>
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<td>80.00</td>
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<td>Total No. of Patients Healed</td>
<td>76</td>
<td>93.83</td>
<td>47</td>
<td>73.44</td>
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Fig. 17. Cumulative frequency of patients healed by therapy and type of ulcer.

**TABLE 1. Clinical evaluation of keratouveitis**

<table>
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<tr>
<th>Parameter</th>
<th>Double-blind study</th>
<th>Ara-A A (8 patients)</th>
<th>Placebo (10 patients)</th>
<th>Ara-A open (4 patients)</th>
<th>Placebo (8 patients)</th>
<th>Ara-A after placebo (8 patients)</th>
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<td>Discomfort</td>
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<td>I S W</td>
<td>I S W</td>
<td>I S W</td>
<td>I S W</td>
<td>I S W</td>
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<tr>
<td>Injection</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>3</td>
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<tr>
<td>Corneal edema</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Anterior chamber activity</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>7</td>
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</table>

I, improved; S, same; W, worse.

Fig. 18. Effect of intravenous Ara-A and placebo on herpetic iritis with some stromal disease. (From Abel, R., Jr., Kaufman, H. E., and Sugar, J.: Am. J. Ophthalmol. 78:659, 1975.)

Fig. 19. In a normal cell, tetrahydroxuridine (THU) prevents the deamination of bromodeoxycytidine (BrdC) and the ultimate incorporation into DNA (Pathway A). A virus-infected cell (Pathway B) possesses the enzymes necessary for the deamination and phosphorylation of BrdC and results in the incorporation into its DNA, providing a selective toxicity to infected cells.
POSSIBLE SITES OF INHIBITION OF DNA SYNTHESIS

<table>
<thead>
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<th>Inhibitors</th>
<th>Steps in DNA Synthesis</th>
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<tbody>
<tr>
<td>5-Iodo-2'-deoxyuridine (IUDR)</td>
<td>Thymidine (TDR)</td>
</tr>
<tr>
<td>IUDR-monophosphate</td>
<td>Thymidine monophosphate (TMP)</td>
</tr>
<tr>
<td>IUDR-triphosphate</td>
<td>Thymidine triphosphate (TTP)</td>
</tr>
<tr>
<td>Iodo-DNA</td>
<td>DNA</td>
</tr>
<tr>
<td></td>
<td>Reproduction</td>
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</table>

Fig. 20. For nucleotide analogs to effect DNA synthesis they must be phosphorylated.

pathogenesis of stromal disease might be on a largely hypersensitivity basis. In fact, when we titered corneas from rabbits inoculated intrastromally, virus multiplication occurred shortly after infection, but infectious virus had largely disappeared by the time clinical disease began.

Clinically, there is a counterpart of this kind of model in that disciform edema responds exquisitely to corticosteroids. After
IDU ANTIVIRAL ACTIVITY

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>TK⁻</th>
<th>TK⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELL TK⁻</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>TK⁺</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Fig. 22. If either virus or cell contain thymidine kinase (TK), IDU can be phosphorylated and active. Similarly, IDU-resistant virus was found by Centifanto to have thymidine kinase–inducing ability.

![Diagram](https://via.placeholder.com/150)

Fig. 23. Structure of acycloguanosine (BW248U).

Fig. 24. Acycloguanosine is selectively phosphorylated by viral-infected cells but not by normal cells, and therefore it selectively inhibits virus multiplication.

Fig. 25. Severity of experimental herpetic keratitis in the rabbit. Treatment with acycloguanosine or IDU produces rapid healing.

the initial control, often as little as a drop of corticosteroid a day or less will completely suppress the disease and keep the patient asymptomatic. Corticosteroids can potentiate the ability of herpes virus to infect the surface, so I initially suggested the use of combined corticosteroids (for therapeutic efficacy) and antivirals (for greater safety), and the value of this combination has been confirmed by double-blind studies by Jones and others. We still need to characterize the nature of the cell membrane antigens involved and determine whether some better antagonist than the potentially dangerous corticosteroids can be found, but at least we are making progress in understanding the problem.

Recurrences of herpes remain a major clinical problem. Laibson and Kibrick and Nesburn et al. developed an excellent animal model for recurrences, in which rabbits are initially infected with selected strains and then develop recurrences after the lesion has been healed for several weeks. Most of what we know about recurrent ocular herpes is due to the work of Nesburn et al., as well as that of Stevens et al. and others. Virus appears to become latent in the trigeminal ganglion and perhaps also in the sympathetic and parasympathetic ganglia in between at-
TOPICAL TREATMENT

- 3% ACYCLOGUANOSINE
- 0.5% IDU
- 3% TFT
- 10% AIU
- PLACEBO

Fig. 26. Topical treatment of herpetic keratitis in the rabbit showing similar effects of acycloguanosine, trifluorothymidine (TFT), and IDU.

attacks. It can appear in tears, and the lacrimal virus may be a primary mechanism through which corneal infection takes place, but the mechanism by which virus gets into the ganglion and out remains unclear. Present drugs have not been able to eradicate virus from the ganglion.

In the absence of definitive elimination of sources of viral latency, other approaches to the prevention of recurrent herpes have been investigated. We have shown in rabbits that although interferon is a weak therapeutic agent, it is extremely potent in preventing recurrent herpes. In fact, the antimetabolite drugs, when given chronically, result in recurrences that are very small and disappear very rapidly, but they do not totally prevent recurrences, whereas interferon does. Interferon is really a series of proteins made by infected cells, which can travel to uninfected cells and protect them from viral infection. This mechanism of protection seems to be primarily through the prevention of translation or transcription of viral DNA messengers.

Human interferon is now obtained from Finnish blood donors. Their white cells are separated and stimulated by Sendai virus, and the resultant substance is subsequently purified. Because of the difficulty in obtaining human interferon, we first turned to the use of artificially synthesized, readily available inducers that stimulate interferon so well in rabbits and mice. We found that there are major species differences in responses to interferon inducers and that both large- and small-molecular-weight inducers active in rodents have little or no effect in man.

Human interferon has been shown to be able to prevent the recrudescences of epithelial herpes which come when an initial dendritic lesion is wiped off. Higher-titer interferon is necessary for this, however, and a definitive study of spontaneous recurrences has not yet been done. A recent workshop on interferon at the National Institute of Allergy and Infectious Diseases has concluded that additional human studies with higher titer interferon are indicated. If these are effective, then new sources of the drug and new inducers effective in man will be sought.

The problems of recurrent herpes and stromal disease persist. It is possible that some people develop stromal disease not only because of differences in host susceptibility but because of differences in viral biochemistry and virulence as well. Studies are necessary to determine whether the development of this devastating clinical complication is due to viral factors or host factors and, if so, whether they can be modified.

Centifanto et al. have shown that patients who get recurrent herpes are different from those who have been infected by the herpes virus and have never developed disease. They compared a group of patients who regularly got recurrent herpes keratitis with a group of age-, sex-, and race-matched controls who had antibody to the herpes virus but had never developed obvious clinical disease. The disease-negative, antibody-positive controls had, in 20% of the cases, significant cell-mediated immunity as measured by leukocyte-migration inhibitory factor stimulated by herpes virus antigen. None of the patients who got recurrences had cell-mediated im-
Fig. 27. Acycloguanosine is effective for treating herpetic iritis in the rabbit when administered either intravenously (50 mg/kg B.I.D., days 1 to 8) or subconjunctivally (10 mg B.I.D., one eye only, days 1 to 4).

Fig. 28. Comparison of in vitro effects of antiviral agents against two strains of herpes virus.

Fig. 29. Electron micrograph of corneal epithelium showing hemidesmosomes (arrow). The epithelium is above and the basement membrane below.
high degree of reliability, clearly predict the way. We now have effective topical antiviral drugs. We have animal models which, with a high degree of reliability, clearly predict the effect to be expected clinically in man, as well as the toxicity. We have systemically active drugs and the potential of getting highly active, potent, completely selective drugs, with the possibility that perhaps the source of viral reinfec tion can be eradicated. The biology of recurrent herpes and stromal disease is gradually being understood, and this understanding may result in new and better therapy of this devastating clinical disease.

Summary

Although much needs to be learned about the serious clinical problem of herpes infection of the cornea, we have come a long way. We now have effective topical antiviral drugs. We have animal models which, with a high degree of reliability, clearly predict the effect to be expected clinically in man, as well as the toxicity. We have systemically active drugs and the potential of getting highly active, potent, completely selective drugs, with the possibility that perhaps the source of viral reinfec tion can be eradicated. The biology of recurrent herpes and stromal disease is gradually being understood, and this understanding may result in new and better therapy of this devastating clinical disease.

REFERENCES
24. Laibson, P. R.: Personal communication.