Chemotherapy of herpes keratitis

Herbert E. Kaufman

IDU has been found active in eradicating virus from tissue culture and appears virtually nontoxic in most tissue culture systems. However, conclusions from tissue culture studies can be drawn only with great caution if they are to be applied to in vivo work. More important, IDU is unquestionably active in the treatment of herpetic keratitis in rabbits and monkeys, and appears similarly effective in man. In vivo it is apparently nontoxic, and yet it appears specifically to eradicate virus from the cornea under some circumstances and to permit healing. This is in direct contrast to the damage that can be caused by the use of caustic agents such as iodine, after which there appears to be an extremely high incidence of metaherpetic keratitis.

Although antiviral agents are useful in the treatment of dendritic ulcers and superficial stromal disease, they are not useful in the treatment of irregular corneal defects in which no virus is present (metaherpetic disease), or in the treatment of disciform keratitis, bullous keratopathy, and trits. These latter conditions appear to respond to corticosteroids in combination with antiviral agents, although the duration of therapy is unpredictable. When this combination of agents is used, antiviral agents should be given in the maximum tolerated dose until after the corticosteroids are stopped; they should not be gradually tapered, whereas the corticosteroids should be used in the minimum effective dose and should be decreased as soon as possible. Cytosine arabinoside is an antiviral agent that appears similar to IDU in its activity. Although CA is toxic under some circumstances, there is reason to believe that patients resistant to one agent will be susceptible to the other.

I would like to spend most of our time in a discussion of antiviral therapy in animals and man, but in order to understand these findings I would like to review some of the tissue culture literature.

Antibody and interferon have not been of demonstrable value in the treatment of established viral disease, and they will not be discussed. Antimetabolites, however, do seem useful, and I would like to review briefly their development and some of the potential pitfalls with which the study of these agents is plagued.

Mechanism of action and tissue culture results

For about 15 years antimetabolites have been studied in tissue culture as potentially active antiviral agents. Numerous agents have been found which, administered to cultures at the time of infection or very shortly thereafter, will prevent infection or reduce the titer of infective virus. None of the "antiviral" agents, however, had been found to have any real therapeutic value in vivo. There has been almost no correlation between these in vivo agents preventing infection and the treatment of disease.

In 1961 there appeared a most important

From the Division of Ophthalmology, University of Florida College of Medicine, Gainesville, Fla.

The work was supported in part by United States Public Health Service Grant No. B-3353 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health.
paper by Herrmann. He used a tissue culture system in which cells were treated after infection. These infected cells were covered with agar, and, following this, agents to be tested for antiviral activity were permitted to diffuse through the agar. The inhibition of virus plaques by these agents was quantitated. The importance of this tissue culture technique in which the antiviral agent was applied and diffused to the cells after infection was not obvious at the time, but it has provided a guide to antiviral activity which has correlated with in vivo therapeutic antiviral properties.

One most important aspect of this work is that Herrmann tested many extremely potent inhibitors of DNA in high concentrations, and found that in this system none of these agents except the 5-ido- and bromodeoxyuridines had any activity against herpes simplex and vaccinia virus. These included such potent DNA inhibitors as 5-fluoro-2'-deoxyuridine, and aminopterin which can prevent in vitro infection but has no therapeutic value in vivo. Herrmann also noted the apparent discrepancy between DNA synthesis as measured in standard cell culture systems and antiviral activity. Although it was not clear at the time of this study how well these results would correlate with subsequent in vivo observations, IDU would not have been tested in vivo had some in vitro activity not been detected.

Although IDU had been synthesized some years earlier, and the pharmacologists and biochemists referred to the agent as IUDR, since Herrmann called the agent IDU, we accepted this nomenclature. As Herrmann initially found, the agents which are therapeutically antiviral have unique properties in tissue culture. Under certain circumstances, we find that it is possible to wait until cytopathogenic effect of virus disease is established in culture, and to treat the cultures with IDU even after infection is established. When this is done, both intracellular and extracellular virus titers drop, the rate of fall depending on the concentration of drug (Fig. 1).

Similarly, if the infected cells in which virus cytopathogenicity is already established are stained with fluorescent antibody, it is possible to see that at the time drug is added there is considerable specific virus stain. This persists for several days after therapy, but after several days the virus antigen can no longer be found in the culture, although the culture survives intact without apparent toxicity (Figs. 2 to 5). Recent work by Byvoet indicates that when IDU is added to an established infection in tissue culture, the rapid synthesis of viral DNA is not only halted, but the intracellular viral DNA which has been synthesized is eliminated from the cell as fragments. Such a fragmentation of virus DNA has also been found with BDU by Easterbrook, and its rate depends on the concentration of the antiviral agent.

The mechanism of action of IDU and the reason that it is unique in being therapeutically active, whereas other potent DNA inhibitors are inactive, is not clear, but we have postulated one possible mechanism. The excellent studies of Delamore and Prusoff indicate that the action of IDU on the inhibition of DNA synthesis varies widely from cell to cell both in degree and specific metabolic site of inhibition. When a virus infects a cell it is unlikely that it forces the cell into new
Fig. 2. Rabbit kidney tissue cultures stained with fluorescent antibody. Before treatment.

pathways of synthesis of the metabolites already being produced by the cell. It therefore seems unlikely that virus multiplication could be stopped by blocking cellular pathways of nucleotide synthesis without severely damaging the cell. This may be why other DNA inhibiting agents are therapeutically inactive. IDU, however, acts at a metabolic site different from the other antimetabolites tested. It inhibits either the phosphorylation of thymidine or the polymerization of nucleotides, preventing the formation of specific virus DNA molecules. There is evidence that vaccinia virus and perhaps other viruses produce large amounts of kinases and polymerases that may be specific. Although more information is required, the assembly of nucleotides to form the final virus molecule must be unique to the virus, and it may be here that IDU can exert its differential activity. In addition to a possible specific site of action, IDU, in acting at a terminal step in synthesis, blocks all thymidine uptake, even if the thymidine comes from diffusion or from the salvage pathway from breakdown of other DNA. Although only small amounts of thymidine could be present by these mechanisms, the work of Salzman and Shatkin indicates that the virus has "first call" on whatever nucleotide is available, and that even in the presence of small amounts of nucleotide virus synthesis will continue.

Tissue culture studies can be informative, but they can also be extremely misleading. An illustration of this is the data presented by Holmes and more recently by Ey, and one published from our laboratory. In a tissue culture system it is possible, by altering the conditions of the culture, to maximize or minimize toxicity. Holmes and Ey used an immature culture fed with a medium containing 10 per cent calf serum which makes the culture grow at a maximum rate simulating a fetuslike condition. Since some IDU can be incorporated into cellular DNA, the changes in toxicity with rate of multiplication are not only additive but may be cumulative or exponential, and inhibition of DNA synthesis observed in this rapid growth situation is not translatable even to a similar, mature, less rapidly growing tissue of the same type treated for a finite period of time, let alone to other tissues. In addition, these workers, in their unique tissue culture system, found that the concentration of antiviral agent required is higher than that required in the system used by any previous worker. For example, Herrmann found that 1 mcg. of IDU is effective as an antiviral agent against herpes simplex and vaccinia. Loddo and Easterbrook found similar results with vaccinia. Stewart and his coworkers found these low concentrations of IDU effective for preventing herpes simplex and vaccinia. Siminoff found 97 per cent inhibition of virus synthesis with a $10^{-4}$ concentration of drug with no inhibition of cellular DNA synthesis during 2
to 2.5 generations, and results in our laboratory confirm this. For reasons that are not clear, the minimal effective antiviral concentration required in the studies of Ey and Holmes is 50 to 100 times that found necessary by these other workers, and does not appear to correlate with the effective levels found in vivo (Table I).

It is possible, therefore, to find a tissue culture system which will magnify toxicity and, if these authors are correct, which will minimize the antiviral effect of IDU in a way different from that found in other systems. In the same tissue under more stable conditions, Stewart found that the concentration of IDU required to produce toxicity in rabbit kidney tissue culture is 1,024 times as high as the concentration necessary effectively to prevent virus infection by 100 TCID₅₀ of herpes simplex. This is an enormous therapeutic index, but it should be obvious that the effect of antiviral agents differs so widely from tissue to tissue even within a single host, as well as from culture to culture, that quantitative relationships in tissue culture cannot freely be transferred to in vivo studies, and any implication that this is possible is likely to be misleading.

It is significant that these authors found 17 patients virus positive. Of these, 11 (65 per cent) were virus negative within 2 days of IDU therapy. Thirteen (76 per cent) were negative in 4 days and 15 (88 per cent) were culture negative within 6 days. This is extremely impressive especially since, as Gundersen points out, the incidence of culture positivity does not

Fig. 3. Rabbit kidney tissue cultures stained with fluorescent antibody. Treated one day with IDU.
decrease with time. The reversion from culture positivity to negativity in man after IDU therapy compares favorably with that found in experimental keratitis. In vivo, no definite toxicity of these agents has been documented in the eye in doses that are effectively antiviral to the cornea. In fact, Calabresi and Welch have found that sufficient drug can be given systemically to prevent vaccinia infection, and these authors suggest the possibility of systemic administration for the treatment of smallpox and other conditions.

In our laboratory, similar errors have occurred from extrapolating tissue culture data to in vivo situations. We found that the aging of IDU, or small amounts of the breakdown product of IDU, would inhibit the cure of established virus infection in the specific tissue culture system which we were studying. Since we had the clinical impression that old IDU might be less effective therapeutically than fresh material, we took this tissue culture data in our particular system as evidence to support this contention. At the time of the presentation of these results, Braley and Leopold both cautioned as to the errors inherent in reasoning from tissue culture to in vivo situations, and subsequent evidence has shown that they appear to be correct. Stewart pointed out that this inhibition does not occur in a system similar to that used by Herrmann, or in other tissue culture systems. Subsequently, studies by us in rabbits and monkeys have demonstrated no inhibition of antiviral activity by the breakdown products of these agents. Recent studies in man similarly indicate that old material is active, although quantitation is not possible.

We must now conclude that there is no good evidence that stability is a crucial factor in IDU therapy.

Fig. 4. Rabbit kidney tissue cultures stained with fluorescent antibody. Treated 3 days with IDU. The specific staining, although much less than before therapy, is still present.
Experimental herpes simplex keratitis

There is no question but that IDU is effective in the treatment of herpes simplex keratitis in the rabbit and in the monkey. The details of the results of treatment of experimental keratitis, however, vary to some extent from investigator to investigator. It appears that when the infection does not cause encephalitis or widespread systemic disease, a large proportion of clinical cures result from IDU treatment. This has been the experience of many of our studies, Corwin’s study, Laibson’s study, and some of Furgiuele’s series. In infections which tend to cause encephalitis or widespread systemic disease, the proportion of cures drops, although the disease is benefited, at least temporarily. In infections which tend to cause encephalitis, it appears that stromal involvement is much more common with virus deep in the stroma where the concentration of IDU is minimal (Table 1). In addition, in this type of infection there is a severe blepharoconjunctivitis so that the cornea, even if cured by the IDU, must be constantly bathed in new virus from the lids and conjunctiva which is not eradicated by IDU. This possibility of reinfection by blepharoconjunctivitis was suggested by Hogan some years ago, and has been confirmed experimentally. In encephalatogenic infections we have bathed the conjunctiva in silver nitrate and excised pieces of conjunctiva. Although silver nitrate, even in miniscule quantities, is so poisonous that it tends to kill tissue culture cells, nevertheless it was possible to demonstrate herpes virus in the conjunctiva in this type of infection. It is possible that virus from blepharoconjunctivitis rather than from the cornea contributes to the finding of positive cultures and to the apparent presence of virus in some corneas which appear to be clinically cured.

Fig. 5. Rabbit kidney tissue cultures stained with fluorescent antibody. All specific staining is gone after 5 days of therapy.
Table I. Preliminary study of the penetration of I-125 IDU* into the rabbit eye

<table>
<thead>
<tr>
<th></th>
<th>Immediately after instillation of drug</th>
<th>4 Hours after instillation of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 IDU/Gm. tissue</td>
<td>Standard error</td>
</tr>
<tr>
<td>Epithelium</td>
<td>6.5</td>
<td>±0.10</td>
</tr>
<tr>
<td>Stroma</td>
<td>2.2</td>
<td>±0.04</td>
</tr>
<tr>
<td>Aqueous</td>
<td>0.8</td>
<td>±0.02</td>
</tr>
<tr>
<td>Iris</td>
<td>1.0</td>
<td>±0.0</td>
</tr>
<tr>
<td>Lens</td>
<td>0.1</td>
<td>±0.0</td>
</tr>
<tr>
<td>Vitreous</td>
<td>0.2</td>
<td>±0.0</td>
</tr>
</tbody>
</table>

*These figures are total I-125 counted above. Method: Eyes treated for 24 hours with a total of 50 μc of labeled compound in an 0.1 per cent IDU solution administered every 2 hours as drugs.
studying the cornea become available, some minimal alteration in corneal healing or regeneration may be found, but even if this should be the case, it must be slight since with doses of drug that eliminate virus no definite change in the host has been found to date.

**Factors in clinical virus therapy**

A proper evaluation of the therapy of herpes simplex keratitis in man must await the results of the double-blind studies now in progress. A certain amount of information has been gathered, however, and I would like to summarize our impressions to date. The experience indicates that IDU has not eliminated the problem of herpes simplex keratitis and has not provided all the answers to this disease, but does appear to be an agent that is useful. In uncontrolled studies of approximately 5,000 cases, about 80 per cent of the patients with dendritic keratitis appear to have good to excellent responses within a week. Although these results must be validated against controlled series, this agent appears effective in the treatment of acute superficial herpetic disease.

When in considering the therapy of herpetic keratitis, it becomes crucial to define the pathogenesis of the various stages of the disease.

**Epithelial virus ulcers.** Acute virus infection results in a dendritic ulcer. Sometimes acute and primary infection also causes an epithelial keratitis, epithelial vacuoles, and a keratoconjunctivitis. Later, as the dendritic ulcer progresses, it can widen, invade stroma, and assume a geographic pattern. In these conditions the multiplication of virus appears to cause the tissue damage and antiviral agents appear useful.

**Metaherpetic nonvirus ulcers.** Often after the dendritic phase, a nondescript corneal ulcer may occur, usually with stromal edema. This lesion, called “metaherpetic” by Gundersen and “geographic” by Thygeson, is referred to as “metaherpetic” in the following discussion. It does not contain virus, and a misunderstanding of its pathogenesis is responsible for much of the clinical frustration caused by this disease.

Experience with several hundred cases has convinced me that metaherpetic epithelial defects result from an edematous and unhealthy stroma. Frequently, patients with this syndrome complain of pain on arising which becomes less during the day. Therapeutically many of them respond to a bland ointment administered at night. In every way this syndrome is similar to a recurrent erosion such as is seen after trauma. The essential ingredient is damage to the stroma and Bowman’s membrane, and it matters little whether this damage be caused by a foreign body, virus infection, or caustic chemicals. Since virus multiplication does not cause the condition, antivirals are not of benefit.

Metaherpetic keratitis appears much less frequently than it did when iodine scrub was more commonly used. Iodine, phenol, or any caustic agent can damage Bowman’s membrane and the corneal stroma, and can produce either an ulcer which does not heal, or an opacification of the stroma. We have seen it in patients with typical adenovirus infection and other nonherpetic corneal disease after scrub. When iodine or other denaturing agents contact the corneal stroma of man or animals, severe tissue necrosis, corneal scarring, and blindness can result. In man, an intact Bowman’s membrane generally protects the stroma from these protoplasmic poisons and their use does not generally cause harm. When Bowman’s membrane has been damaged by a virus infection which invades the stroma, iodine and similar poisons are contraindicated and should not be used. When one sees many cases of herpes, he is impressed by the difficulty in being certain that any given patient does not have some defect in Bowman’s membrane which would permit these agents to precipitate corneal stroma and result in scarring, and it was common to see patients who were “scrubbed” return...
with appreciable corneal scarring. Often the dendritic lesion was gone, but a nondescript epithelial defect persisted which was very slow to heal. The dendritic had now become metaherpetic. When the corneal epithelium is gently removed from these lesions (as is done to take virus cultures) the epithelium rapidly regrows, indicating that the epithelium is capable of dividing, but the healing is often stopped so that a defect identical to the original remains. Cautery of such lesions generally makes them worse.

Although the mechanical removal of diseased epithelium can be of benefit in treating dendritic disease, the use of denaturing agents has never been shown to increase this benefit and sometimes appears to be harmful.

It is illustrative in considering this possibility to examine the data on iodine scrub presented by Gundersen. In his study, 53 patients received no treatment. Of these, 9 developed metaherpetic disease. Thus, 17 per cent of untreated herpes simplex was followed by metaherpetic keratitis. In addition, 1 of these patients developed a disciform keratitis, and 1 a hypopyon ulcer. As iodine was used, the incidence of metaherpetic keratitis increased. Eighty-seven patients received local iodine treatment, and, of these, approximately 26 per cent developed metaherpetic keratitis (20 per cent of all attacks were followed by metaherpetic keratitis). Here, too, 2 patients were found to have hypopyon keratitis and 2 developed a disciform keratitis. When iodine was used to treat the whole cornea, the incidence of metaherpetic keratitis increased further. Approximately one out of every three attacks treated (33 per cent of attacks) was followed by metaherpetic keratitis. The average duration of corneal staining in this phase of the disease was 33 days in one group and 35 days in the other. Although the groups were not well controlled, the incidence of metaherpetic keratitis in the group treated with iodine scrub of the whole cornea was approximately double that of the untreated controls. This data suggest that although iodine scrub may have made those patients who would recover spontaneously achieve this condition more rapidly, it may have increased the severity and disability of the disease in the remaining. In this study, one third of all patients with dendritic keratitis treated by chemical cautery developed metaherpetic disease. Despite these appalling figures, this treatment, which may make some heal more promptly but may make others much worse, has never been subjected to an impartial study with comparable groups that can be compared and evaluated. It is interesting, however, that even at the time of Gundersen’s presentation of this data, Dr. Gore mentioned the importance of avoiding injury to Bowman’s membrane, and Dr. Friedenwald suggested that bile might be an excellent therapeutic agent since it might remove the corneal epithelium without producing injury to the corneal stroma.

At the Massachusetts Eye and Ear Infirmary, many physicians were sufficiently impressed by the harm done by iodine that, before IDU or any other specific agent was available, a double-blind clinical study of herpes simplex keratitis was undertaken to compare simple curettage with iodine scrub. This study was abandoned for the testing of specific antiviral drugs, but the desire to minimize the harmful effects of caustics has motivated further experimental work on this problem.

Stromal disease. Stromal disease may be of three general types:

1. We have already discussed iatrogenic stromal scars.
2. Virus may multiply in the stroma causing localized, white, cheeselike lesions. These lesions appear to respond, though slowly, to antiviral agents and may occur along with disciform lesions.
3. Disciform keratitis begins as an edematous patch of cornea occurring over an area of folds in Descemet’s membrane. It is usually accompanied by some iritis and may result from a primary damage
to the endothelium as a result of a toxic or allergic response to the virus. Usually the involved area of cornea is central, but it may be eccentric and the whole cornea may be involved in a bullous keratitis. In its pure form, this condition and herpetic iritis are not helped by antivirals. Steroids, although dangerous if virus persists in the epithelium, do benefit the disciform lesion and the iritis.33

In evaluating the results of any therapy, it is not strictly correct or scientifically acceptable to compare untreated patients from another area and time with those treated in the study. A precise evaluation of antiviral therapy, therefore, must await the many excellent double-blind studies now in progress. In reports of the results of treatment, however, it appears that some investigators are impressed by the occasional case that does not respond, and it seems that they may have an unrealistic picture of the natural course of the disease. For example, some authors appear surprised by the fact that a slight stromal haze sometimes remains behind the healing dendritic.10 It is common, however, to see patients treated before the advent of specific antivirals who have considerable stromal haze and in whom the outline of the previous dendritic ulcers is clearly visible in the stroma years after their initial attack. Jones16 also comments on the stromal haze sometimes seen after either mechanical curettage or IDU therapy.

Although many patients reported upon by Gundersen did very badly, these studies were done some time ago. Dr. Thygeson,14 however, reported on 200 patients seen 7 years ago:

"Since the majority of our cases were referred to us for consultation, and so could not be followed over any considerable period, it was impossible to make a statistical analysis of visual loss for the series as a whole. We are able to say, however, that major temporary diminution of vision was the rule, and we feel that permanent diminution of vision probably obtained in the majority of cases because of the almost invariable involvement of the pupillary area. The globes were lost in three cases, and in an appreciable number of the disciform cases vision was reduced to light perception only. On the other hand, we were struck by the fact that, in a considerable number of dendritic cases with pupillary involvement, vision temporarily diminished gradually returned over a period of months or years. Unfortunately, recurrent attacks tended to neutralize such improvement and we must conclude that in our experience herpetic keratitis in the United States leads to more reduced vision than any other corneal disease.

"We were impressed by the great economic cost of this disease, that is apparent not only in the lost or diminished vision known to have been caused by it but in the work-time lost during the all too frequently recurring attacks. A number of our patients have been unable to hold steady jobs because of the frequency of the recurrences."*

Therapeutic regimen

To date we have reported on more than 200 patients treated at the Massachusetts Eye and Ear Infirmary and the University of Florida Teaching Hospital with IDU.29,33 It would serve little purpose to summarize our additional experience with treatment, or to summarize in detail the other uncontrolled series which have been reported. It is impossible to be absolutely certain that herpes simplex keratitis has not become a more mild disease in the last several years than it was previously, and only the double-blind studies in progress at present will permit a true assessment of the value of antiviral agents. To date, case report forms on approximately 5,000 patients indicate that between 80 and 85 percent of patients with dendritic ulcers respond promptly to IDU.24-27 Our results

have been somewhat better, and although this may be because we are more fastidious in diagnosing cases of atypical or meta-
herpetic disease, and because we pursue the therapy more vigorously, it may also be due to some unconscious bias. In man as well as animals, however, IDU appears to be a useful antiviral without documented toxic effects on the cornea, and yet with a specific ability to eradicate virus in at least some cases in humans and to promote healing of the cornea. There is no question that, despite this agent, herpes simplex remains a problem, and more information is necessary to understand the details of this disease and its treatment. On the basis of the limited knowledge available to date, however, I would like to outline the present therapy used in our clinic and its rationale.

**Dendritic ulcers.** When IDU drops were used they were administered every hour during the day and every 2 hours at night until the lesion was nearly healed. When only minimal punctate staining remained, the frequency of the drops was decreased to every 2 hours during the day only, but the drops were continued for several more days at 2 hour intervals during the day only. Now IDU ointment 0.5 per cent (“Stoxil” ointment) is generally used. When ointment is administered 5 times a day, nocturnal administration of the medication seems unnecessary, and therapeutic response seems to be at least as good as with drops.

Some cases of dendritic disease are resistant to IDU, and when some improvement has not taken place in 4 or 5 days, our previous therapy was to gently debride the cornea with a scalpel and to continue the IDU. Since the discovery of the new antiviral, cytosine arabinoside (CA), resistant cases have been treated with 1 per cent CA ointment 4 times a day and the patients have responded promptly. Previous studies on DNA synthesis suggest that resistance to IDU and resistance to CA are separate and that cross resistance should not occur. Our brief experience with this agent in man would suggest that this is the case. Whichever ointment is used, treatment is continued for several days after the apparent cure of the dendritic lesion.

**Metaherpetic ulcers.** Metaherpetic disease is not treated with antiviral agents. In general, the application of a bland ointment at bedtime as done in recurrent erosions will result in rather prompt amelioration of symptoms and healing. Sometimes stromal edema and stromal damage are so extensive that IDU and corticosteroids are used together. The corticosteroids minimize the stromal edema and permit the epithelium to heal.

**Stromal disease and corticosteroid therapy.** Stromal disease characterized by dense, white, cheezy opacities appears to respond, although slowly, to antiviral agents. Disciform keratitis, as signaled by edema of the cornea with folds in Descemet’s membrane and some iritis, does not respond to antiviral agents alone. This condition, as well as the iritis, will respond to corticosteroid therapy, however. It has been well documented that the virus of herpes simplex can persist in cases of disciform keratitis, and that corticosteroids alone can result in the recurrence of dendritic ulcers and in perforations of the cornea when used to treat disciform or metaherpetic keratitis. There is little question, however, that the administration of antiviral agents in both experimental animals and in man minimizes, although it does not completely abolish the deleterious effects of corticosteroids on this virus, and occasionally dendritic lesions develop even with combined therapy. It has frequently been possible to study patients who have recurrent dendritic ulcers following steroid therapy of disciform lesions. In these patients, the addition of antiviral agents generally results in the complete disappearance of the dendritic lesion, even though the steroid regimen is continued. Similarly, the discontinuation of antiviral agents during such treatment has frequently resulted in the appearance of dendritic lesions. Changing the dosage can
permit or cure the ulcers. A common difficulty in the combined use of antiviral agents and corticosteroids results from a misunderstanding of the mechanism of action of antivirals.

Corticosteroids minimize the corneal edema in cases of disciform keratitis and quiet an iritis. In the case of disciform keratitis, we feel strongly that the corneal scarring and long-term visual disability are markedly reduced by the use of anti-inflammatory agents. Corticosteroids, however, make superficial herpes keratitis worse. It is not uncommon for recurrences of dendritic ulcers to develop in patients with disciform keratitis or metaherpetic keratitis who are treated with steroids, and instances of perforation of the cornea have been documented in such patients. In man, as in animals, antiviral agents appear to competitively reverse the untoward effects of corticosteroids on herpes simplex keratitis. These agents do not make corticosteroids completely harmless, and in occasional patients, dendritic ulcers can recur during treatment with corticosteroids even in the face of concomitant antiviral therapy. When antivirals are used frequently, however, and corticosteroids are used sparingly, the corticosteroid effect appears markedly ameliorated. We therefore endeavor to maintain a maximum therapeutic regimen of antiviral agent and a minimum dose of corticosteroid. When IDU drops are used, we employ them every 2 hours during the day, and use corticosteroids no more often than 3 or 4 times a day. The duration of therapy that will be necessary is unpredictable and can be determined only by attempting to withdraw the corticosteroids. In some patients, corticosteroids can be withdrawn within 2 to 3 weeks, and then antivirals are stopped. In very severe cases, months of therapy may be required, but since this involves the instillation of medication only during the day, patients appear to tolerate this well and we are convinced that long-term visual disability is minimized. When treating this disease, although we attempt to gradually decrease the steroid dose, we do not taper the antiviral regimen. Antivirals are continued in this maximum dosage until the steroids are completely stopped. Patients have frequently been referred to us after improving from the combination of corticosteroids and antivirals because their physicians decreased the administration of both agents simultaneously. This not uncommonly results in the recurrence of dendritic keratitis and the frustration of the physician. If antiviral agents are continued in their full dosage until the corticosteroids have been completely stopped, recurrences of dendritic lesions are rare.

Although other forms of therapy may be available for dendritic disease and may provide some benefit, there is no question in our minds that the combined use of corticosteroids and antiviral agents is the treatment of choice for disciform keratitis and herpetic iritis. The antivirals do not make corticosteroids completely harmless, but certainly reduce the danger of the agents to levels at which they are not only acceptable, but appear to be indicated in the treatment of disciform keratitis and iritis.

Cytosine arabinoside, a new antiviral

In addition to the IDU ointments now available, the discovery of cytosine arabinoside is a significant advance in the treatment of this disease. This agent appears to act in tissue culture and in experimental studies in a manner generally similar to that of IDU, except that it is considerably more soluble and acts to inhibit DNA at a different site. Because of its solubility when it is administered in ointment form, it is likely that there is, transiently, a very high concentration of agent on the cornea (perhaps as high as 30 per cent), but then the concentration decreases, whereas IDU is sufficiently insoluble that a stable low concentration appears to be provided by the ointments. In any case, cytosine arabinoside is a useful agent.
certain DNA-synthesizing systems, cytosine arabinoside may, in some systems, interfere with respiration and may be concentrated within cells. In tissue culture CA appears toxic in some situations where IDU is nontoxic, and in high concentrations in normal subjects similar toxicity appears. When a solution of 5 per cent drops was used 6 times a day for 7 days, all 5 normal subjects developed a severe keratitis characterized by vacuoles and inclusions in the epithelium, pain, and, in some cases, iritis. This cleared over a period of about 2 weeks. When 1 per cent solution was used 6 times a day for a week, no such toxicity was observed. Similarly, when a micropulverized ointment was applied (1 per cent ointment) 6 times a day, 1 normal patient out of 8 in the study developed some vacuoles and staining of the epithelium, but this was transient even though the drug was continued. Three of the 8 taking this crystalline ointment experienced discomfort at the time of administration of the ointment. When a soluble ointment was used (1 per cent) 6 times a day, no toxicity was apparent. When CA ointment 1 per cent is used 4 times a day as we have done clinically, it may be present in higher concentrations than IDU and appears similarly effective, but long-term toxicity must be studied. At present, there is no evidence that this agent is in any way superior to IDU, however, there is reason to believe, from experimental data and from our present experience with approximately 25 patients treated with this agent, that patients resistant to IDU will not be resistant to CA, and presumably the reverse will also be true.

Summary

Although some information has been obtained from tissue culture studies on the basic mechanism of action of antiviral agents, the correlation between activity in tissue culture and activity in vivo is exceedingly poor, and conclusions from tissue culture studies can be drawn only with great caution if they are to be applied to in vivo work. IDU has been found active in eradicating virus from tissue culture and appears virtually nontoxic in most tissue culture systems. More important, it is unquestionably active in the treatment of herpetic keratitis in rabbits, monkeys, and other species, and appears similarly effective in man. In vivo there is no definite evidence of any toxicity, and yet it appears to specifically eradicate virus from the cornea under some circumstances and to permit healing of the cornea. The apparent harmlessness of this agent is in direct contrast to the damage that can be caused by the use of caustic agents such as iodine in the treatment of corneal disease. After the use of caustics there appears to be an extremely high incidence of metaherpetic keratitis.

Although antiviral agents are useful in the treatment of dendritic ulcers and superficial stromal disease, they are not useful in the treatment of irregular corneal defects in which no virus is present (metaherpetic disease) or in the treatment of disciform keratitis, bullous keratopathy, and iritis. These latter conditions appear to respond to corticosteroids in combination with antiviral agents, although the duration of therapy that will be required is unpredictable. When this combination of agents is used, antiviral agents should be given in the maximum tolerated dose until after the corticosteroids are stopped; they should not be gradually tapered, whereas the corticosteroids should be used in the minimum effective dose and should be decreased as soon as possible. Cytosine arabinoside (CA) is a new potent antiviral agent that appears generally similar to IDU in its activity. Although CA is toxic under some circumstances, there appears reason to believe that patients resistant to one agent will be susceptible to the other.

The laboratory studies referred to in this section were done with Mrs. Emily Maloney and clinical studies were done with Drs. Claes Dohlman and Eeva-Liisa Martola. These workers contributed both concepts and effort to this study.
REFERENCES


23. Lathson, P. R., and Leopold, I.: Treatment of herpetic keratitis with 5-ido-2'-deoxyuridine (5-IDU), A. M. A. Arch. Ophth. (In press.)


32. Sory, T. W., and Furgiuele, F. P.: The