Acyclovir
An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy

John J. O'Brien and *Deborah M. Campoli-Richards*

ADIS Drug Information Services, Auckland, New Zealand

Contents

Summary

Synopsis

    Acyclovir (aciclovir) is a nucleoside antiviral drug with antiviral activity in vitro *against members of the herpes group of DNA viruses. As an established treatment of herpes simplex infection, intravenous, oral and to a lesser extent topical formulations of acyclovir provide significant therapeutic benefit in genital herpes simplex and recurrent orofacial herpes simplex. The effect of acyclovir therapy is maximised by early initiation of treatment, especially in non-primary infection which tends to have a less protracted course than the primary episode. Long term prophylactic oral acyclovir, in patients with frequent episodes of genital herpes simplex, totally suppresses recurrences in the majority of subjects; as with other infections responding to acyclovir, viral latency is not eradicated and pretreatment frequencies of recurrence return after discontinuation of treatment. Caution should accom-*

pany the prophylactic use of acyclovir in the general population, due to the theoretical risk of the emergence of viral strains resistant to acyclovir and other agents whose mechanism of action is dependent on viral thymidine kinase. Intravenous acyclovir is the treatment of choice in biopsy-proven herpes simplex encephalitis in adults, and has also been successful in the treatment of disseminated herpes simplex in pregnancy and herpes neonatorium. Intravenous and oral acyclovir protect against dissemination and progression of varicella zoster virus infection, but do not protect against post-herpetic neuralgia. In immunocompromised patients, intravenous, oral and topical acyclovir shorten the clinical course of herpes simplex infections while prophyiaxis with oral or intravenous dosage forms suppresses reactivation of infection during the period of drug administration. Ophthalmic application of 3% acyclovir ointment rapidly heals herpetic dendritic corneal ulcers and superficial herpetic keratitis.

Thus, despite an inability to eradicate latent virus, acyclovir administered in therapeutic or prophylactic fashion is now the standard antiviral therapy in several manifestations of herpes simplex virus infection, and indeed represents a major advance in this regard. With the exception of varicella zoster virus infections, early optimism concerning the use of the drug in diseases due to other herpes viruses has generally not been supported in clinical investigations.

Antiviral Activity

Acyclovir exhibits *in vitro* activity against herpes simplex virus types 1 and 2, varicella zoster virus, Epstein-Barr virus and, to a lesser degree, cytomegalovirus. Although quantitative results vary considerably depending on the viral strain and methodological aspects of the assay system employed, in general herpes simplex virus type 1 is the most susceptible, followed in descending order of susceptibility by herpes simplex type 2, varicella zoster virus, Epstein-Barr virus and cytomegalovirus. Against herpes simplex virus types 1 and 2, acyclovir is generally more potent *in vitro* than the nucleoside analogues idoxuridine, trifluridine or vidarabine, of comparable potency to 2'-fluoro-5-iodoarabinosylcytosine (FIAC) and ganciclovir [DHPG;9-(1,3-dihydroxy-2-propoxymethyl) guanine], and more (herpes simplex type 2) or less (herpes simplex type 1) potent than bromovinyldeoxyuridine. The relative potencies of acyclovir and other antivirals against varicella zoster virus have varied between studies, but the drug is less active *in vitro* against cytomegalovirus than idoxuridine, trifluridine, vidarabine and ganciclovir. Acyclovir appears able to inhibit the productive cycle, but not the latent phase, of Epstein-Barr virus. Depending on the drug concentrations and cell lines involved, combinations of acyclovir plus one of the other nucleoside antivirals or one of the variously derived interferons have generally exhibited additive to synergistic activity against certain herpesviruses, including cytomegalovirus. Replication of herpes simplex virus in explant ganglionic or tissue cultures is readily interrupted during incubation with acyclovir; reversion to latency is noted after several days' exposure to the drug. Acyclovir appears to eradicate part of the latent viral reservoir, as assessed by the reactivation rate after drug removal. Alternate exposure of explant ganglionic cultures to acyclovir-containing and drug-free media has been associated with statistically significant reductions in the proportion of reactivable virus, dependent on the frequency and duration of alternating applications.

The mechanism of action of acyclovir involves highly selective inhibition of herpes virus DNA replication, via enhanced uptake in herpes virus-infected cells and phosphorylation by viral thymidine kinase, and the substrate specificity of acyclovir triphosphate for viral, rather than cellular, DNA polymerase. Epstein-Barr virus and especially cytomegalovirus which does not encode for a thymidine kinase, have reduced susceptibility to acyclovir; the mechanism of action of acyclovir against these viruses may differ from that which operates in herpes simplex.

The antiviral efficacy of acyclovir administered by various routes has been demonstrated in *in vivo* animal models of ocular, cutaneous, genital, CNS and neonatal infections due to herpes simplex viruses. In addition to being influenced by factors such as the animal species, size of viral inoculum, drug dosage, and route and frequency of administration employed, the efficacy of acyclovir treatment correlated closely with the

rapidity of its initiation following viral inoculation. Indeed, initiation of topical or systemic acyclovir within 24 hours of viral challenge has been found to prevent the establishment of viral latency following primary infection, and reductions in the number of reactivable latent herpes simplex foci following acyclovir treatment have been observed in some *in vivo* studies, but acyclovir therapy has not resulted in eradication of established, latent virus from neuronal ganglia. When compared with other antiviral agents in *in vivo* models of herpes simplex virus infections, acyclovir was generally at least as effective as other nucleoside analogues, although research tools such as the newer 2'-fluoropyrimidines and 5'-vinylpyrimidines offered greater protection than acyclovir in certain models, when the agents were administered on an equimolar basis.

Acyclovir-resistant strains of herpes simplex virus and varicella zoster virus arise chiefly from mutations in the genes affecting the production of viral thymidine kinase, and are readily produced *in vitro*. Such strains exhibit variable cross-resistance to other antivirals, depending on the specific mutation(s) conferring resistance and the mechanism of action of the alternative drug. Clinically, acyclovir-resistant strains have been reported very infrequently overall, and usually in association with chronic mucocutaneous lesions in severely immunocompromised patients receiving extended courses of acyclovir. The reduced *in vivo* pathogenicity and ability to establish latency of the vast majority of clinically isolated resistant strains indicates that they are unlikely to cause refractory or aggressive infection in immunocompetent individuals; this supposition has been supported by clinical studies to date. In addition, comparisons of the *in vitro* acyclovir susceptibility of viral isolates from patients receiving chronic oral suppressive acyclovir for several months have not revealed statistically significant reductions in viral susceptibility following treatment; when recurrences did 'break through', they almost always resolved upon administration of therapeutic or increased dosage of acyclovir. However, a recent study reported a correlation between the *in vitro* susceptibility of pretreatment herpes simplex virus isolates and the occurrence of mucocutaneous lesions during prophylactic acyclovir administration. Continued monitoring is required to further define the occurrence and clinical significance of viral resistance to acyclovir.

Pharmacokinetic Studies

Repeated 8-hourly intravenous doses of 2.5 to 15.0 mg/kg provide clinically useful steady-state mean plasma acyclovir concentrations, ranging from 6.7 to 20.6 mg/L, respectively. The bioavailability of oral acyclovir is limited at 15 to 30%. Increasing the contact time of orally administered acyclovir with the absorptive area of the gut, by administering the dose as a direct duodenal infusion over 4 hours, produced a marked increase in bioavailability, indicating that absorption may be capacity-limited, especially at higher dosages. Delivery of topical acyclovir to deeper tissues may be markedly influenced by the formulation vehicle; systemic absorption with topical administration has not been detected. Substantial intraocular penetration is evidenced by a mean acyclovir concentration of 1.7 mg/L in aqueous humour with multidose application of the 3% ointment every 5 hours, and peak concentrations of 6.7 and 5.2 mg/L, respectively, in the aqueous and vitreous humour following a single 25mg subconjunctival injection.

Acyclovir was detected at autopsy in the kidney, lung, nervous tissue, liver and heart of a patient who had received high-dose intravenous therapy with the drug. Cerebrospinal fluid and skin vesicle concentrations following intravenous therapy, and saliva and tear fluid concentrations following oral therapy, were approximately 50%, 100%, 13% and 18% of simultaneous plasma concentrations, respectively. Acyclovir crosses the placenta and accumulates in breast milk such that the milk concentration in a lactating woman was more than 3 times the simultaneous plasma acyclovir concentration. *In vivo* protein binding of acyclovir is low (9 to 24%) and independent of the plasma drug concentration.

Renal excretion is the major route of elimination of acyclovir in subjects with normal renal capacity. Depending on the creatinine clearance, up to 80% of a dose is excreted unchanged in the urine, while the remainder is metabolised to inactive derivatives. The elimination half-life in adults with normal renal function is 2 to 3 hours. As expected, dosage adjustments are required in patients with end-stage renal disease, with the elim-

ination half-life extended in this subgroup to approximately 20 hours, and mean peak plasma concentrations increased approximately 2-fold. Acyclovir is readily haemodialysable, having a dialysis half-life in this situation of about 6 hours. However, continuous ambulatory peritoneal dialysis is much less efficient at removing the drug and the elimination half-life is extended to 14 to 18 hours. Disposition of acyclovir in children is similar to that in adults, but in neonates the relatively underdeveloped renal function results in total body clearance being reduced by two-thirds and the elimination half-life being increased to up to 4 hours.

Therapeutic Trials

Double-blind, placebo-controlled studies in immunocompetent patients have shown intravenous (5 mg/kg 8-hourly), oral (200mg 5 times daily) and, to a lesser extent, topical acyclovir therapy (5% in polyethylene glycol ointment or propylene glycol cream applied 4 to 6 times daily) initiated within 4 days of the first appearance of signs or symptoms to produce significant reductions in the duration of viral shedding and time to complete healing of lesions in initial genital herpes infection. Statistically significant amelioration of the course of infection was most readily demonstrated in the more severe primary initial episode. Pain or dysuria symptoms tended to be less responsive to treatment, especially by topical acyclovir, which was also generally unable to produce statistically significant reductions in new lesion formation. Acyclovir treatment of initial genital herpes did not alter the chronic recurring nature of the infection. However, early, especially patient-initiated, treatment with oral acyclovir at the prodrome of recurrent genital herpes inhibits new lesion formation and viral shedding and reduces episode durations by 1 to 2 days. Nonetheless, due to the shorter duration of recurrent vs initial episodes, the beneficial effects of acyclovir on recurrent episodes are less dramatic. Although results with topical acyclovir in recurrent infection have been somewhat conflicting, the 5% cream has in some placebo-controlled studies exhibited a moderate degree of clinical efficacy, whereas the 5% ointment generally produced only marginal reductions in virological, and little or no amelioration of clinical disease parameters, even with optimal timing of treatment initiation.

Prophylactic oral administration of acyclovir at dosages of 400 to 800 mg/day for 1 to 2 years led to complete suppression of recurrences of genital herpes in approximately 60 to 90% of subjects. Unfortunately recurrence rates returned to pretreatment frequencies after discontinuation of acyclovir. This form of acyclovir therapy was extremely well tolerated and was not associated with the emergence of clinically significant acyclovir resistance.

Acyclovir 5 or 10% ointment has been mostly ineffective for the treatment of recurrent orofacial herpes in immunocompetent patients, although a reduction in healing time of statistical, but limited clinical significance occurred when treatment with the 5% ointment was begun during the prodromal phase. Comparisons of the results obtained in placebo-controlled, double-blind investigations indicate acyclovir 5% cream to be superior to the ointment formulation in treating recurrent orofacial outbreaks, although absolute reductions in symptom duration remain small relative to the duration of a recurrent episode. In contrast, *prophylaxis* with topical (5% cream) and more especially oral (200mg 4 times daily) acyclovir reduces the severity and frequency of recurrences during treatment in patients with a history of frequent outbreaks.

Acyclovir 3% ophthalmic ointment applied 5 times daily cures 95 to 100% of herpetic dentritic corneal ulcers in approximately 5 days, being at least as effective as idoxuridine 0.5 and 1% ointments, trifluridine formulated as a 2% ointment, and vidarabine 3% ointment, and possibly more rapid in effect than these comparative antivirals. The larger geographic corneal ulcers also respond to acyclovir ophthalmic ointment, a double-masked study revealing no difference in efficacy with that of vidarabine in this indication. Several double-masked comparative studies showed that the combination of acyclovir 3% ophthalmic ointment applied 5 times daily plus once daily application of human α-interferon shortens the time to healing of superficial herpetic keratitis (dendritic or geographic ulcers) by approximately 3 days, from 7 to 9 days for acyclovir plus placebo.

Thus, this combination may be a useful advance in the treatment of superficial herpetic keratitis. In contrast, results with the use of systemic (oral) acyclovir 400mg 5 times daily remain equivocal, insufficient duration of therapy being a potentially compromising variable. As might be expected, considering the likely immunological basis of herpetic stromal involvement, acyclovir 3% ophthalmic ointment, applied 5 times daily, is more effective in treating herpetic disciform keratitis (and in a few reported cases, necrotising stromal keratitis) when administered concomitantly with topical corticosteroids. In a double-masked comparison there was no statistically significant difference in the percentage of patients with herpetic disciform keratitis cured, the time to resolution of signs and symptoms, and the time to healing, between patients administered acyclovir or vidarabine ophthalmic ointment 5 times daily, concomitantly with betamethasone 0.1% ophthalmic drops. In herpetic kerato-uveitis, the efficacy of acyclovir 3% ophthalmic ointment applied 5 times daily was not statistically different from that of trifluridine 1% ophthalmic solution applied 6 times daily, although the mean time to healing of corneal ulcers was shorter (p < 0.05) in the trifluridine-treated group; the majority of these patients also received local injection of dexamethasone.

Large collaborative studies comparing intravenous treatment using acyclovir and vidarabine have established acyclovir 10 mg/kg 8-hourly, administered for at least 10 days, to be the treatment of choice for biopsy-proven herpes simplex encephalitis. Acyclovir was found to be particularly beneficial in improving overall survival rates and reducing the incidence of serious sequelae to infection. In case reports, intravenous or oral acyclovir therapy of disseminated herpes simplex of various manifestations in near term pregnancy has been followed by survival, without complications, of mothers and infants. Acyclovir and vidarabine appear to be of comparable efficacy in the treatment of neonatal herpes simplex; antiviral prophylaxis of neonates delivered to mothers with active genital lesions is not generally warranted unless additional risk factors are present.

Further case studies have reported the successful treatment with acyclovir of disseminated herpes simplex accompanied by hepatitis, disseminated primary eczema herpeticum, herpes simplex whitlow and herpes simplex-associated erythema multiforme.

Intravenous acyclovir significantly attenuated the development of rash and pain, and protected against ocular involvement in double-blind placebo-controlled studies in immunocompetent patients with acute herpes zoster. Similar benefit with oral therapy usually required higher dosages (600 to 800mg 5 times daily) than are generally used for herpes simplex infections. Therapeutic efficacy was maximised with early initiation of acyclovir treatment, however the drug did not offer protection against post-herpetic neuralgia and was often associated with recurrence of pain soon after withdrawal. A marked reduction (vs placebo) in the incidence of ocular sequelae associated with trigeminal zoster occurred after 1 year's follow-up in patients who received acyclovir 600mg 5 times daily for 10 days during an acute episode. In several case reports, acyclovir treatment of herpes zoster-associated encephalitis, varicella pneumonia, and herpes zoster oticus resulted in rapid resolution of infection.

An unconfirmed potential therapeutic benefit of intravenous acyclovir (10 mg/kg 8-hourly) is suggested by a placebo-controlled study in patients with severe infectious mononucleosis. Acyclovir alone or administered sequentially with human lymphoblastoid interferon appears to offer very limited clinical benefit in chronic active hepatitis B infection, although the latter combination administered concurrently is deserving of further investigation in this indication.

Earlier double-blind, placebo-controlled studies in immunocompromised patients with herpes simplex infections have shown intravenous (250 mg/m^2 8-hourly) acyclovir therapy to dramatically reduce the period of viral shedding, with parallel improvements occurring in healing parameters. Topical application of the 5% ointment was effective with regard to external lesions, but failed to produce a statistically significant reduction in time to healing. More recently, oral administration of 400mg 5 times daily significantly accelerated the resolution of viral shedding and pain, and reduced time to healing by almost two-thirds, in bone marrow transplant recipients.

Perhaps due to ethical difficulties concerning such studies, there remains a lack of controlled or comparative studies of acyclovir treatment of immunocompromised patients with acute varicella zoster infection. Nevertheless, intravenous dosages of 500 mg/m² or 10 mg/kg administered 8-hourly in small numbers of patients have been associated in controlled studies with a protective effect against progression and dissemination of infection, although reductions in time to healing did not generally achieve statistical significance. However, in a comparison with vidarabine, intravenous acyclovir was superior in promoting pain relief and cutaneous healing, in addition to providing significantly better protection against dissemination than the alternative antiviral. A further comparative trial failed to confirm an advantage of acyclovir over vidarabine. Topical acyclovir (5% ointment) also favourably influenced the healing of localised herpes zoster when applied within 3 days of the onset of lesions. Recurrence of varicella zoster infection has been regularly reported after completion of acyclovir therapy in immunocompromised subjects.

Despite transient effects on viraemia and possibly viral titre in the target organ, acyclovir treatment of cytomegaloviral pneumonia in immunocompromised patients has resulted in very little clinical improvement, and has not generally improved survival rates. Similarly, a favourable clinical response to acyclovir therapy of Epstein-Barr virus infections does not usually accompany an antiviral effect of the drug in these patients. However, Epstein-Barr virus-associated oral hairy leucoplakia in patients with human immunodeficiency virus infection responded well to high-dose oral acyclovir in case studies.

Immunologically compromised patients have a predictable pattern of reactivation of latent herpes simplex virus. Thus, in a series of placebo-controlled studies in immunocompromised patients, prophylaxis with intravenous or oral acyclovir for periods of up to 6 months produced virtual complete suppression of clinical herpes simplex infection, while virological results were only slightly less impressive. This protection was confined to the period of drug administration, although in some studies in bone marrow recipients an extension of the median time to first reactivation accompanied an increase in the duration of prophylaxis. Varicella zoster virus infection was also suppressed in seropositive patients during prophylaxis, whereas the effect on cytomegalovirus reactivation was less impressive. However, high-dose (500 mg/m² 8-hourly) acyclovir prophylaxis in immunocompromised individuals led to a statistically significant reduction in the occurrence of invasive cytomegaloviral disease and an associated increase in survival in a controlled study. Nonetheless, prophylaxis against late reactivations of varicella and cytomegalovirus with acyclovir is unlikely to be practical.

Adverse Effects

Acyclovir is generally extremely well tolerated. Ophthalmic administration is only rarely associated with spontaneously reported reactions and the association of these with the drug (as opposed to the disease process) is difficult to discern. Topical therapy is only associated with burning or stinging on application, and a mild erythema or drying in a small proportion of patients. The adverse reactions most frequently reported with intravenous acyclovir are inflammation and phlebitis at the injection site. However, 2 important and serious adverse effects associated with intravenous administration are neurological and/or psychiatric effects (lethargy, tremors, confusion, hallucinations, seizures) and renal precipitation of the drug resulting in renal insufficiency. High peak plasma concentrations have been implicated in both of these problems. In addition, the potential for renal complications may be minimised with slow infusion of doses, adequate hydration, and lower dosages in patients with renal dysfunction. Nausea, vomiting, other gastrointestinal symptoms and lightheadedness have also been associated with high peak acyclovir concentrations following intravenous administration. Short term use of oral acyclovir has most commonly been associated with nausea and vomiting. Long term (1 year) use is equally well tolerated, with nausea, vomiting, diarrhoea, stomach pain, rash and headache occurring at an incidence of less than 5% and in a similar percentage of placebo recipients.

Dosage and Administration   Therapy with acyclovir should be initiated as soon as possible following the onset of signs or symptoms.

The recommended dosage of acyclovir 3% ophthalmic ointment is 5 times daily application into the lower conjunctival sac, continued for at least 3 days after complete healing. Topical 5% acyclovir is recommended in non-life-threatening mucocutaneous herpes simplex infection, applied 5 times daily for 5 to 10 days (cream) or 6 times daily for 7 days (ointment).

For the treatment of herpes simplex infections of the skin and mucous membranes, the recommended oral acyclovir dosage is 200mg 5 times daily for 5 days. Lower oral doses of 200mg may prove effective for chronic suppression of recurrent herpes simplex. The optimum dosage for acute treatment of herpes zoster is 800mg 5 times daily by mouth, for 7 days.

An intravenous dosage of 5 mg/kg (adjusted to 250 mg/m^2 in children under 12 years) infused over 1 hour every 8 hours for 5 days is recommended for the treatment of herpes simplex and varicella zoster infections in the immunocompetent. For immunocompromised patients with varicella zoster, a higher intravenous dosage of 10 mg/kg (500 mg/m^2 in children under 12 years) should be administered 8-hourly for 7 days. Intravenous administration of acyclovir should be gradual (over 1 hour), with adequate hydration maintained to preclude drug precipitation in the renal tubules. Infusion concentrations should not normally exceed 7 mg/ml.

Dosage reductions are necessary in patients with moderate to severe impairment of renal function, dependent on the degree of impairment.

1. Antiviral Activity

Acyclovir (9-[(2-hydroxyethoxy)-methyl]-guanine), an acyclic analogue of the natural nucleoside 2'-deoxyguanosine (fig. 1), selectively inhibits replication of members of the herpes group of DNA viruses, with low host cell toxicity. Prior to its wide clinical application, the antiviral spectrum of acyclovir was the subject of extensive evaluation in both *in vitro* and animal studies. More recent pharmacodynamic studies have focused on the activity of acyclovir in combination with other antivirals and interferons, elucidation of aspects of its mechanism of action, and the monitoring of drug resistance.

1.1 Antiviral Activity *In Vitro*

Detailed coverage of the *in vitro* activity of acyclovir was provided in the previous review in the Journal (Richards et al. 1983), and a more brief treatment is appropriate here. As noted by Richards et al. (1983), it is necessary to emphasise that information obtained from *in vitro* culture systems does not necessarily correlate with the clinical efficacy or toxicity of an antiviral agent. In addition, the immune response is an important variable that is absent in *in vitro* susceptibility testing (Pulliam et al. 1986).

Assay methods used to test the *in vitro* activity of acyclovir have included dye-uptake, plaque reduction, DNA hybridisation, plaque autoradiography and enzyme-linked immunosorbent assay (ELISA) [Barry et al. 1986; Gadler 1983; Martin et al. 1985; van Tiel et al. 1985]. The results of antiviral susceptibility testing are dependent on the assay method, cell type and viral strain employed (Harmenberg et al. 1985b). Thus, in determinations of the acyclovir susceptibility of 10 strains of herpes simplex virus, the drug concentrations required to inhibit viral cytopathic effects by 50% (ID$_{50}$) were 5- to 10-fold higher when using a growth inhibition (dye-uptake) assay than when measured (in the same cell substrate) by a 50% plaque reduction assay (Barry et al. 1986). Unfortunately, a standardised method for determining *in vitro* viral susceptibility to acyclovir does not exist (Dekker et al. 1983), and a definite relationship between *in vitro* viral susceptibility and clinical response does
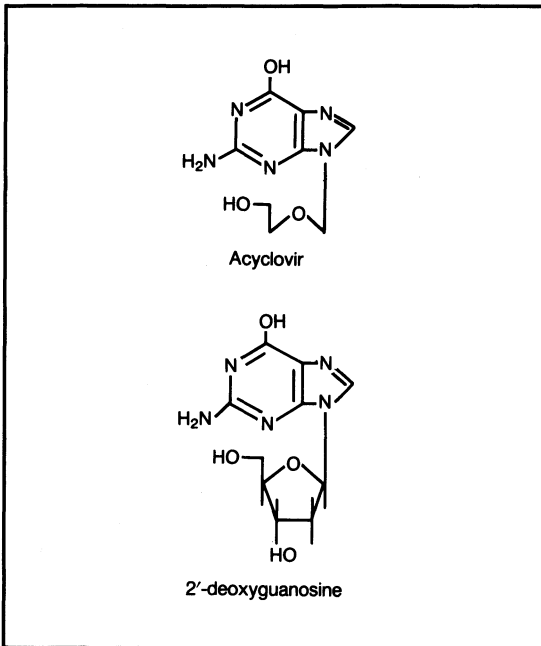
Fig. 1. Chemical structure of acyclovir and its purine nucleoside analogue, 2'-deoxyguanosine.

not always apply (Collins & Oliver 1986; McLaren et al. 1983). Thus, herpes simplex isolates from several immunocompromised patients proved susceptible to acyclovir *in vitro*, yet the infections responded poorly to long term acyclovir therapy (Christophers et al. 1986; Wade et al. 1983). Explanations for this lack of correlation have included difficulty of drug penetration, inactivation at the site of infection, and the effects of viral multiplicity (Harmenberg et al. 1985b). Additionally, such *in vitro* susceptibility may arise if consecutive isolates are not classified according to their restriction enzyme pattern (Schinazi et al. 1986b).

Acyclovir inhibits replication of human herpes viruses in cell culture, with herpes simplex type 1 being the most susceptible, followed in descending order of susceptibility by herpes simplex type 2, varicella zoster virus, Epstein-Barr virus and cytomegalovirus (tables I and II). Acyclovir does not exhibit *in vitro* antiviral activity against viruses outside the herpes group.

1.1.1 Herpes Simplex Virus Types 1 and 2

In general, type 2 strains of herpes simplex virus are less susceptible to acyclovir *in vitro* than type 1 strains, although there has been considerable overlap in the ranges of concentrations reported to inhibit the cytopathic effects of these 2 types of herpes simplex viruses by 50% (ID_{50} as measured by the plaque reduction assay or reduction in viral-induced cytopathogenicity) [table I]. As reviewed by Richards et al. (1983), in most studies ID_{50}s have been in the range 0.01 to 0.7 mg/L for herpes simplex type 1, and 0.01 to 3.2 mg/L for herpes simplex type 2. The 10- to 100-fold reduction in susceptibility of herpes simplex viruses growing in African green monkey kidney (GMK) cells compared with that in human fibroblast cells (Harmenberg et al. 1980) appears to be due, at least in part, to the substantially higher concentrations of thymidine in GMK cells (Harmenberg 1983; Harmenberg et al. 1985a).

Against herpes simplex virus types 1 and 2, acyclovir was less potent *in vitro* than 2'-fluoro-5-iodoarabinosylcytosine (FIAC) and ganciclovir [DHPG;9-(1,3-dihydroxy-2-propoxymethyl) guanine], more potent than idoxuridine and trifluridine, and considerably more potent than vidarabine (table I; Collins 1983; McLaren et al. 1985). While bromovinyldeoxyuridine proved more active than acyclovir against type 1 strains, this situation was reversed in the case of herpes simplex type 2 (Collins 1983).

1.1.2 Varicella Zoster Virus, Human Cytomegalovirus and Epstein-Barr Virus

Results from several *in vitro* studies (table II) have demonstrated that acyclovir concentrations varying from 0.3 to 10.8 mg/L are required to inhibit varicella zoster virus by 50%. The limited comparative data available indicate acyclovir to be substantially less potent than bromovinyldeoxyuridine, of similar or slightly greater potency than vidarabine, and of greater potency than ganciclovir and especially phosphonoformic acid (table II).

Human cytomegalovirus has proved relatively resistant to acyclovir in cell culture (table II), with reported 50% inhibitory concentrations ranging

Table I. Summary of the *in vitro* activity of acyclovir, vidarabine, ganciclovir [DHPG;9-(1,3-dihydroxy-2-propoxymethyl)guanine], bromovinyldeoxyuridine (BVDU) and 2'-fluoro-5-iodoarabinosylcytosine (FIAC) against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2)

Reference	Cell culture[a]	Viral assay method	Virus	ID_{50} (mg/L)[b]				
				acyclovir	vidarabine	ganciclovir	BVDU	FIAC
Activity against herpes simplex virus type 1								
De Clercq et al. (1980a,b)	PRK	Cytopathogenicity	HSV-1[c]	0.04	7			
Harmenberg et al. (1980)	HL	Plaque reduction	HSV-1	0.07				
	Sirc	Plaque reduction	HSV-1	0.4				
	Vero	Plaque reduction	HSV-1	1.5				
	GMK (2 cell lines)	Plaque reduction	HSV-1	5.9-13.5				
McLaren et al. (1983)	Vero	Cytopathogenicity	HSV-1[c]	0.13				
Smee et al. (1985)	Vero	Plaque reduction	HSV-1	0.11-0.23		0.045-0.11		0.068-0.11
McLaren et al. (1985)	Vero	Cytopathogenicity	HSV-1[c]	1.3-1.6		0.22-1.8	0.15-1.6	0.38-1.0
Al-Hasani et al. (1986)	Vero	Cytopathogenicity	HSV-1[c]	0.078-1.25				
Pulliam et al. (1986)	Vero	Plaque reduction	HSV-1[c]	0.2-0.6	8.75-20	0.16-0.55	0.15	
Schinazi et al. (1986c)	Vero	Plaque reduction	HSV-1	0.02	7.5			0.005
Activity against herpes simplex virus type 2								
De Clercq et al. (1980a,b)	PRK	Cytopathogenicity	HSV-2[c]	0.04	5			
Harmenberg et al. (1980)	HL	Plaque reduction	HSV-2	0.4				
	GMK	Plaque reduction	HSV-2	9.9				
McLaren et al. (1983)	Vero	Cytopathogenicity	HSV-2[c]	0.27				
Smee et al. (1985)	Vero	Plaque reduction	HSV-2	0.11-0.54		0.068-0.41		0.2-0.48
Al-Hasani et al. (1986)	Vero	Cytopathogenicity	HSV-2[c]	0.24-0.03				
Nusinoff-Lehrman et al. (1986b)	Vero	Cytopathogenicity	HSV-2[c]	0.12-4.39				
Schinazi et al. (1986c)	Vero	Plaque reduction	HSV-2	0.01	11.4			0.02

a   Vero, GMK = 2 strains of green monkey kidney cells; PRK = primary rabbit kidney cells; HL = human fetal lung fibroblasts; Sirc = rabbit cornea cells.

b ID_{50} = concentration inhibiting viral-induced cytopathogenicity or viral plaques by 50%. The range of ID_{50} values is presented where reported, otherwise results are mean or median values. Results reported in μmol/L have been converted to mg/L.

c   Multiple clinical isolates.

from around 2 to more than 50 mg/L. As reported in the review of Richards et al. (1983) and in Cole and Balfour (1987), acyclovir has lower *in vitro* potency than the nucleoside analogues idoxuridine, trifluridine, vidarabine and ganciclovir. However, it is considerably more potent than phosphonoformic acid (Gadler 1983).

The productive cycle of the Epstein-Barr virus

appears to be inhibited by acyclovir, while the latent state remains unaffected. At a concentration of approximately 1.5 mg/L, acyclovir suppressed the reproduction of viral genomes by 50% in superinfected Raji cells and the virus-producing lymphoblastoid cell line P3HR-1. Acyclovir was active only in Raji cells productively infected with Epstein-Barr virus, and latent infection was not eradicated by the drug (Colby et al. 1982; Pagano & Datta 1982).

1.1.3 Activity of Acyclovir Combined with Other Antivirals

Numerous *in vitro* studies have examined the nature of the interaction (e.g. additive, synergistic, antagonistic) between acyclovir and various other purine nucleoside antivirals and interferons. The rationale behind such studies is that combinations of drugs may be found that could inhibit the infectivity and replication of viruses at concentrations that are better tolerated and more easily

Table II. Summary of the *in vitro* activity of acyclovir, vidarabine, ganciclovir [DHPG;9-(1,3-dihydroxy-2-propoxymethyl)guanine] and phosphonoacetic acid (PFA) against varicella zoster virus (VZV), a live attenuated varicella zoster virus vaccine (Oka and KMcC strains) and human cytomegalovirus (CMV)

Reference	Cell culture[a]	Viral assay method	Virus	Results (mg/L)[b]				
				value reported	acyclovir	vidarabine	ganciclovir	PFA
Activity against varicella zoster virus								
Biron & Elion (1980)	HDF	Plaque reduction	VZV[d]	ED$_{50}$	0.46-1.41			
	HDF	Plaque reduction	VZV	ED$_{50}$	1.40	1.41		
De Clercq et al. (1982)	HEF	Cytopathogenicity	VZV	ID$_{50}$[c]	0.4	2.5		
Shigeta et al. (1983)	HEF	Plaque reduction	VZV[d]	ID$_{50}$	1.4-10.8	0.07-3.3		
Larkin & Ogilvie (1983)	HEF	Plaque reduction	VZV[d]	ED$_{50}$	0.91-3.98			
Muto et al. (1984)	HEF	Foci reduction	VZV[d]	ID$_{50}$	1.85-3.98			
Preblud et al. (1984)	HEF	Plaque reduction	Oka	ED$_{50}$	0.90-1.36	0.62-2.10		8.2-13
			KMcC	ED$_{50}$	0.79-1.81	0.80-1.40		12.4-16.4
Cole & Balfour (1986)	HFF	Yield reduction	VZV	ID$_{50}$	0.31-1.15			
	HFF	Yield reduction	VZV[d]	ID$_{50}$	0.17-1.53			
Baba et al. (1986)	HEF	Foci reduction	VZV[d]	ID$_{50}$[c]	2.6	3.5	10.1	27.2
Activity against human cytomegalovirus								
Tyms et al. (1981)	HEF	Plaque reduction	CMV[e]	ED$_{50}$	2.3-17.6			
Plotkin et al. (1982)	HEF	Plaque reduction	CMV[d]	ID$_{50}$	5-25			
Gadler (1983)	HEF	DNA hybridisation	CMV[d]	ID$_{50}$	1.82-56.8	0.91-28.4		3.6-110
Freitas et al. (1985)	HET	Plaque reduction	CMV[f]	ID$_{50}$	12.5, 8.9		1.6, 1.1	
	HEF	Plaque reduction	CMV[f]	ID$_{50}$	21.6, 14.5		1.6, 1.6	
Cole & Balfour (1987)	HFF	Plaque reduction	CMV[d]	ID$_{50}$	3.8-33.3		0.15-1.62	

a   HEF = human embryo fibroblasts; HFF = human foreskin fibroblasts; HET = human embryo tonsil cells.
b   Results reported in μmol/L were converted to mg/L. ID$_{50}$, ED$_{50}$ = concentration inhibiting viral plaques, yield, DNA synthesis or viral-induced cytopathogenicity by 50%.
c   Mean values.
d   Multiple clinical isolates.
e   Four different strains.
f   Two different strains.

achieved *in vivo*. Also, combination therapy employing acyclovir and other selective antiviral agents that act independently of viral thymidine kinase should reduce the incidence of emergence of resistant viral strains (Cheng et al. 1979; Resnick et al. 1986; Schinazi et al. 1982; Schinazi & Nahmias 1982; Smith et al. 1983).

Although the combination of acyclovir 0.45 mg/ L (2.0 μmol/L) plus vidarabine 6.8 mg/L (30 μmol/ L) exerted a less than additive effect on the inhibition of herpes simplex type 1 replication in green monkey kidney cells (Park et al. 1984), the combination of these agents at concentrations of 0.1 and 0.6 mg/L, respectively, exhibited synergistic activity against herpes simplex type 2 in mouse embryo fibroblast culture (Crane et al. 1984; see also the review of Richards et al. 1983). Combinations of acyclovir plus other nucleoside antivirals have usually shown an additive effect against varicella zoster virus (Biron & Elion 1982). The inhibition resulting from acyclovir 4.5 mg/L plus vidarabine 0.25 mg/L was synergistic for 3 of 4 clinical isolates of human cytomegalovirus grown in human embryonic lung fibroblasts using the fractional inhibitory concentration technique, and a fixed vidarabine concentration of 1 mg/L; synergy was found to be most pronounced at acyclovir concentrations of 5.6 to 22.5 mg/L (Spector & Kelley 1985) [fig. 2]. Depending on the method of evaluating synergy, which remains somewhat controversial, antiviral combinations including acyclovir have generally proved additive to synergistic against human cytomegalovirus (Spector & Kelley 1985; Spector et al. 1982b).

Depending on the concentrations employed, human native β-interferon (Kawaguchi et al. 1986; Stanwick et al. 1981), human leucocyte interferon (human α-interferon) [Baba et al. 1984; Hammer et al. 1982; Levin & Leary 1981] and α-hybrid cloned interferons (Crane & Milne 1985) have usually demonstrated synergistic antiviral activity with acyclovir in relation to herpes simplex virus, as measured by plaque reduction and cytopathic effect reduction assay. Combinations of a hybrid interferon [interferon-αA/D (Bgl)] plus acyclovir, vidarabine, or vidarabine-5′-monophosphate, pro-
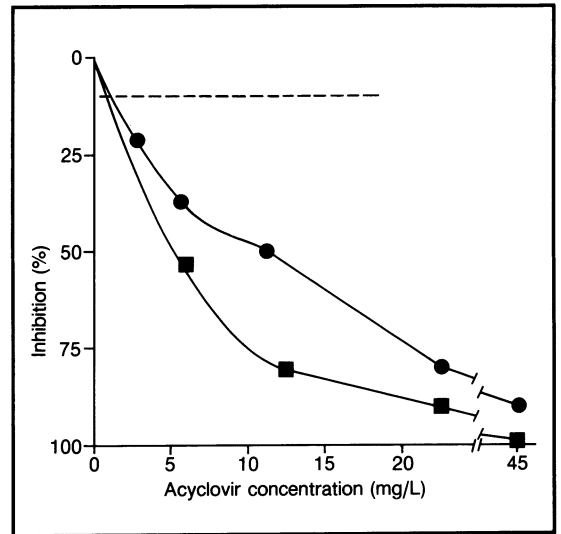
Fig. 2. Inhibition by vidarabine 1 mg/L (–––), acyclovir (●) and acyclovir combined with vidarabine 1 mg/L (■) of a human cytomegalovirus strain isolated from the lung of a bone marrow transplant recipient (after Spector & Kelley 1985).

duced comparable synergistic isobolograms and fractional inhibitory indices in human and murine cell lines, against herpes simplex type 2 (Crane & Milne 1985). The exposure of herpes simplex type 1-infected human lung fibroblast cells to acyclovir 6.8 mg/L (30 μmol/L) plus human leucocyte interferon 125 to 200IU induced viral latency by day 4 of a 7-day exposure, whereas a ganciclovir-interferon combination of identical concentrations failed to inhibit active infection *in vitro* to the same extent. Virus reactivation after removal of inhibitors generally occurred at least 5 days earlier and resulted in a greater production of total virus in cells treated with combined bromovinyldeoxyuridine and interferon than in those treated with acyclovir and human leucocyte interferon (Scheck et al. 1986).

Acyclovir, when combined with human leucocyte interferon, has also exhibited synergy against human cytomegalovirus (Smith et al. 1983) and varicella zoster virus (Baba et al. 1984). In the latter study, the degree of synergism found with acyclovir plus interferon was greater than occurred when interferon was combined with phosphono-

formic acid, vidarabine or bromovinyldeoxyuridine.

A virus-specific ribonucleotide reductase inhibitor (2-acetylpyridine thiosemicarbazone) has recently been shown to potentiate the antiviral activity of acyclovir against herpes simplex virus by approximately 10 times (Karlsson & Harmenberg 1988).

1.1.4 Effects on Latent Herpes Simplex Virus

The characteristic of latency is among the most poorly studied and clinically frustrating aspects of herpesvirus infection. Much remains to be elucidated regarding the state of the viral genome during latency and the factors involved in the induction of and reactivation from the latent state. The inappropriateness to clinical study of the controllable methods of assessing eradication of latent virus, as noted by Richards et al. (1983), led to the focusing of most efforts in the scientific study of herpes simplex virus latency on *in vivo* models (see section 1.2). More recently, explant cultures of murine trigeminal ganglia have been employed as *in vitro* systems for examining the interaction of acyclovir with herpes simplex virus type 1 in the latent state. Millin et al. (1988) suggest the advantages of such a system include the accuracy attainable in the control of the parameters involved in induction and reactivation of latency, and the opportunity afforded for observation of the histology and architecture of latently infected ganglion cells in isolation from the host immune system.

Latency of herpes simplex virus type 1 resulted when infected murine trigeminal ganglia were incubated for 7 days in media containing 150 mg/L acyclovir. Latency was demonstrated by the presence of ICP-4 (VP 175), an early viral protein found in the nucleus of latently infected ganglia in the absence of late viral proteins or infectious viral particles (Millin et al. 1988). Desuppression of the acyclovir-treated ganglia by cocultivation on Vero cell monolayers led to a 54% spontaneous reactivation of virus after 7 to 21 days. Dunkel et al. (1984) also described an *in vitro* model of acyclovir-induced herpes simplex type 1 latency, utilising

rabbit trigeminal cell monolayers tissue-cultured with neuronal growth factor. After 4 days of incubation with 100 mg/L acyclovir, these cultures demonstrated a 14 to 38% spontaneous and a 42% acetylcholine-induced herpes simplex reactivation, occurring between 4 and 9 days following desuppression (Bean et al. 1986).

As with animal models, *in vitro* systems evaluating latency have provided clear evidence that acyclovir interrupts productive herpes simplex infection, but is unable to eradicate established latent viral foci. However, during incubation with acyclovir, viral reactivation is prevented completely and at least part of the ganglionic viral reservoir eliminated (Klein et al. 1983; Liu et al. 1986; Millin et al. 1988; Park et al. 1982). One explanation for this inability of drug treatment to eradicate latent virus is that reactivation of all latent herpes simplex type 1 does not occur simultaneously. Thus it is difficult to achieve the optimal timing of drug exposure required for successful interaction between antiviral agents and virus-induced enzymes, with part of the viral reservoir remaining to serve as a source for future infectious virions after removal of drug from the medium (Klein et al. 1983; Liu et al. 1986).

The exposure of explant ganglionic cultures alternately to acyclovir-containing and drug-free media has been used in several investigations as a method of improving the conditions for interaction of acyclovir with herpes simplex virus-induced thymidine kinase before mature virus is assembled. The efficiency of virus elimination under these conditions appears to be related to the frequency and duration of the alternating treatment as well as the number of latently infected neurons present (Klein et al. 1981, 1983; Liu et al. 1986; Park et al. 1982).

Increasing the number of cycles of such discontinuous treatment was associated with improved antiviral efficacy, such that when incubation with acyclovir 10 mg/L for periods of 1 to 3 days was alternated 4 times (Klein et al. 1983) or 1 and 3 times (Liu et al. 1986), statistically significant reductions were seen in the proportion of murine trigeminal ganglia containing reactivatable virus. In

neither study, however, was the titre of such virus reduced to zero.

1.2 Activity *In Vivo* Against Herpes Simplex Virus Types 1 and 2

As expected, animal models were well utilised during the preclinical and early clinical phases of the study of the antiviral effects of acyclovir. The most important findings from *in vivo* studies of acyclovir are presented below, mainly in overview since it is the intention of this updated review to place most emphasis on the growing body of clinical data for this now well-established antiviral agent. More detailed reviews of animal data are presented by Collins (1983) and Richards et al. (1983). Direct extrapolation of *in vivo* results to the clinical situation is inappropriate; these data are of tentative predictive value only as regards antiviral efficacy in humans. Several methodological variables, for example animal species, virus strain, size of inoculum, drug dosage and route of administration, and rapidity with which therapy is initiated, influence the outcome of antiviral therapy with acyclovir to a greater or lesser degree. Moreover, investigations of acyclovir therapy in comparison to, or in various combinations with, other antivirals in individual infection models have varied with regard to factors such as dosing interval, route, size of viral inoculum, and statistical calculations, making interstudy comparisons difficult. Animal models of herpesvirus infections other than herpes simplex, such as murine cytomegalovirus infection, are of very limited usefulness as predictors of clinical efficacy against the corresponding human infections (Collins 1983) and are not considered below.

Except where otherwise noted, the data are derived from the previous review in this journal (Richards et al. 1983).

1.2.1 Ocular Infections

In numerous open and placebo-comparative investigations, acyclovir has produced healing or suppressed the development of experimental epithelial corneal lesions of herpes simplex type 1 keratitis in the rabbit eye. Acyclovir 3% ophthalmic ointment applied up to 5 times daily was of at least similar antiviral efficacy as the intravenously administered drug at a dosage of 50 mg/kg/day, with curing of lesions generally seen after 4 days of treatment. Several comparative studies indicated 3% acyclovir ointment to be at least as effective as idoxuridine 0.5% and trifluridine 3% ophthalmic ointments, and more effective than vidarabine 3% ophthalmic ointment. In addition, Pavan-Langston et al. (1978) found that acyclovir proved significantly (p < 0.05) more effective than idoxuridine 0.5% ointment or vidarabine 3% ointment in the treatment of experimental iritis (antiviral therapy was applied 5 times daily for 6 days). However, Maudgal et al. (1985) reported that stromal keratitis and associated iritis induced by intrastromal inoculation of rabbits' eyes with herpes simplex type 1 was suppressed to a significantly greater degree by an ointment containing trifluridine 2% and neomycin sulphate 1% than by acyclovir 3% ointment, when the agents were applied 5 times daily for 5 days beginning 1 day postinfection.

1.2.2 Cutaneous Infections

Various reports document the treatment of cutaneous herpes simplex infection in the mouse model with topical (3 or 5% gel, ointment or dimethylsulphoxide solution), subcutaneous (40 to 60 mg/kg/day) or intraperitoneal (20 or 50 mg/kg/day) acyclovir initiated within 1 to 2 days of inoculation; the drug has generally decreased the severity of infection as assessed by mortality rates and by the development, duration and extent of viral shedding from lesions. Overall, therapy of lumbosacral or orofacial infection with topical acyclovir proved less effective than with phosphonoacetic acid, equally effective as bromovinyldeoxyuridine, and more effective than vidarabine, cytarabine or idoxuridine in respect of decreasing lesions and mortality rates and prolonging animal survival (Deschamps et al. 1979; Park et al. 1979, 1984). Acyclovir in combination with vidarabine administered topically (4 times daily in concentrations of 5 and 10%, respectively), and intravenously (twice daily at doses of 50 and 100 mg/kg/

day, respectively) was significantly ($p < 0.05$) more effective than identical doses of the individual agents in groups of 16 hairless mice, with the combination therapy preventing ulceration completely and leading to zero mortality after 2 weeks (Park et al. 1984).

Compared with collateral application of the vehicle alone, topical acyclovir 1, 3 or 5% in polyethylene glycol has demonstrated dose-related improved lesion healing and decreased virus titres when treatment was begun up to 2 days after dorsal herpes simplex type 1 inoculation in guinea-pigs. When topical treatments were compared in these animals, acyclovir 5% was less effective than phosphonoformic acid 3% and edoxudine (5-ethyl-2'-deoxyuridine) 3%, but more effective than recombinant interferon α (30×10^6 U/ml) [Collins & Oliver 1982; Freeman & Spruance 1984; Park et al. 1980; Spruance et al. 1984b, 1985]. It is likely that the efficacy of topical acyclovir formulations is limited by low percutaneous drug delivery from the polyethylene glycol vehicle, since superior antiviral results have been achieved when the barrier-altering solvent dimethylsulphoxide (fig. 3), and to a lesser extent when modified aqueous cream, was employed as the vehicle (Collins & Oliver 1982; Freeman & Spruance 1986; Spruance et al. 1984b, 1985).

1.2.3 Genital Infections

Statistically significant reductions in mortality rates from those of control groups occurred in the murine model of genital herpes type 2 infection, following both twice-daily intravaginal administration of 2 or 5% acyclovir aqueous solution and oral administration of an approximately 400 mg/kg/day dose, each for 4 days. Similarly effective, as assessed by viral titres, were intravaginally applied acyclovir 1 and 5% ointments initiated up to 72 hours after inoculation, and 15.6 to 125 mg/kg/day administered orally beginning 24 hours after infection (Kern 1982; Pancic et al. 1981).

In vivo synergy was observed when combinations of acyclovir, vidarabine and low-dose polyriboinosinic-polyribocytidylic acid (poly-L-lysine) carboxymethylcellulose complex [poly IC(LC)], an
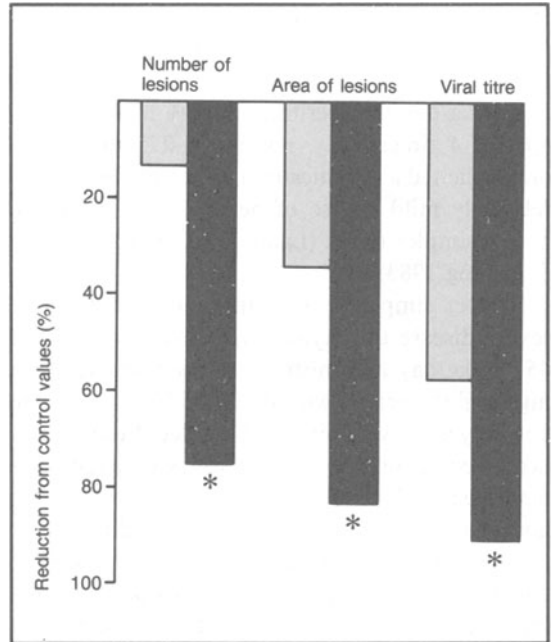
Fig. 3. Effects of topical acyclovir 5% formulated in dimethylsulphoxide 95% (■) or polyethylene glycol (□) used 4 times daily for 3 days beginning 24 hours postinoculation for the treatment of dorsal cutaneous herpes simplex type 1 infection in guinea-pigs. ✳ = significantly ($p < 0.05$) different from control (vehicle alone) values (after Freeman & Spruance 1986).

interferon inducer, were administered intraperitoneally 2 days after mouse inoculation (Crane et al. 1984). In this study, higher doses of acyclovir (50 mg/kg/day for 4 days) combined with vidarabine (125 mg/kg/day for 6 days) completely prevented paralysis and death after 4 weeks. However, toxicity was seen with combinations of either nucleoside analogue in these doses and poly IC(LC) 5 mg/kg administered on 4 alternate days. With regard to protection against symptom onset and death, monotherapy with acyclovir was superior to that with either vidarabine or poly IC(LC).

Compared with saline infusion, continuous subcutaneous infusion of acyclovir 92 mg/kg/day for 7 days beginning 1 day prior to herpes simplex type 1 intravaginal inoculation markedly reduced the severity of genital lesions and the incidence of neurological sequellae such as loss of bladder or rectal control in the guinea-pig (Myerson & Hsiung 1983).

However, when the initiation of acyclovir treatment was delayed until 72 hours postinfection, neither continuous subcutaneous infusion (as above), 50 mg/kg/day intraperitoneally, 5% topical cream applied 4 times daily, nor 90 to 225 mg/kg/day orally elicited a statistically significant effect on the relatively mild course of herpes genitalis due to herpes simplex type 1 (Landry et al. 1982; Myerson & Hsiung 1983).

Herpes simplex type 2 appears to cause more severe disease than type 1 virus. Acyclovir 15 or 45 mg/kg/day administered intramuscularly, 125 mg/kg given orally twice daily, or 5% acyclovir in polyethylene glycol ointment applied 4 times daily decreased the severity of infection with herpes simplex type 2 when therapy was initiated within 48 hours of inoculation (Kern 1982). Additionally, acyclovir at a concentration of 5 mg/L added to the animals' drinking water 12 hours postinfection (mean serum level 1.2 mg/L) was associated with milder disease than placebo in guinea-pigs, as measured by lesion severity scores and frequency of neurological sequellae (Bernstein et al. 1986); 50 or 100 mg/kg injected intraperitoneally daily beginning 72 hours postinfection decreased the incidence of paralysis and death, and healed lesions more rapidly than placebo in guinea-pigs with herpes simplex type 2 genital infection (Landry et al. 1982).

In comparisons employing the guinea-pig model of herpes simplex type 2 genital infection, topical 5% acyclovir was as effective as 5% ganciclovir if initiated within 48 hours of virus inoculation (Smee et al. 1985), while acyclovir 50 and 100 mg/kg daily was less effective than the fluoropyrimidines 2'-fluoro-5-iodoarabinosylcytosine (FIAC), 2'-fluoro-5-iodoarabinosyluracil (FIAU) and 2'-fluoro-5-methylarabinosyluracil (FMAU) in daily doses of 50 mg/kg, when these agents were injected intraperitoneally for 3 days (Mayo & Hsiung 1983).

1.2.4 Encephalitis and Disseminated Infections

Intraperitoneal, subcutaneous and oral administration of acyclovir to mice inoculated intracerebrally with herpes simplex virus types 1 or 2 has been shown in several studies to decrease mortality rates and usually increase mean survival times from those of placebo-treated controls, provided therapy was initiated within 24 hours of inoculation. Additionally, the drug proved highly effective in either eliminating mortality or preventing signs of central nervous system involvement when used to treat various animal models of secondary encephalitis, in which the initial site of herpes simplex infection was ocular, genital or cutaneous (see Richards et al. 1983).

Studies comparing acyclovir with various antiviral agents in the mouse model of herpes simplex encephalitis have usually revealed variations in potency rather than clear differences in efficacy between agents. Toxic effects in these studies were not reported in detail. Against central infection with herpes simplex type 1, acyclovir was less potent than both ganciclovir and 2'-fluoro-5-methylarabinosyluracil (FMAU) following subcutaneous administration of these drugs for 5 days beginning 24 hours postinoculation (Smee et al. 1985), and less effective (p < 0.05) than equimolar doses of 5-vinyl-1-β-D-arabinofuranosyluracil (Vara U) and (E)-5-(2-bromovinyl)-1-β-D-arabinofuranosyluracil (BrVaraU) by the intraperitoneal route (Reefschläger et al. 1986). In the latter study, however, protection of mice from encephalitis and death due to intracerebral infection was similar among the antiviral agents when acyclovir 100 mg/kg/day was compared with VaraU and BrVaraU in doses of 100 and 200 mg/kg/day, respectively, after twice-daily treatment for 5 days. In the treatment of herpes simplex type 2 central infection, acyclovir was of similar potency to vidarabine but less potent than 2'-fluoro-5-iodoarabinosylcytosine (FIAC) and especially FMAU (Schinazi et al. 1983), superior to VaraU with intraperitoneal dosage 3 times daily for 5 days, and superior to VaraU and phosphonoformic acid when each was administered in the animals' drinking water for 5 days (Reefschläger et al. 1987). Schinazi et al. (1986a) delayed treatment until 72 hours postinfection and reported a similar overall effect of acyclovir, vidarabine and FIAC with respect to mortality rates and survival times, but a much greater protective effect from FMAU.

With the aim of identifying synergistic combinations which may prove valuable when extrapolated to the clinical situation, the *in vivo* activity of acyclovir combined with other antiviral agents has been investigated in the mouse model (Schinazi et al. 1983, 1986a). Marked synergy against herpes simplex type 2 encephalitis resulted from intraperitoneal coadministration of acyclovir plus vidarabine, FIAC or FMAU in molar ratios of 1 : 1, 1 : 1 and 1 : 8, respectively (Schinazi et al. 1986a). Analysis by both the median effect and isobologram methods indicated the combination of acyclovir and FIAC to be the most highly synergistic as well as the least toxic. The combination of acyclovir plus passive immunisation with human immune globulin produced a synergistic antiviral effect in immunocompetent and, to a lesser extent, immunocompromised mice (Cho & Feng 1980; Yamamoto et al. 1985). This presumably reflects the importance of cellular immunity in the control of herpes simplex infections (Hilfenhaus et al. 1987). Treatment of herpes simplex type 1-infected mice with acyclovir 40 mg/kg/day for 5 days plus a single dose of human immune globulin 50mg resulted in a synergistic effect on survival after 100 days, but only when the immunotherapy was initiated early (4 hours postinfection). Synergism was evident from the survival rate at 20 days postinfection when immune globulin had been administered as late as 2 or 3 days postinfection. Early immunotherapy prevented seroconversion in most animals, thus the protection afforded by this regimen was probably a result of complete elimination of the viral challenge (Hilfenhaus et al. 1987).

1.2.5 Neonatal Infections

Newborn or weanling mice infected intranasally with a lethal inoculum of herpes simplex type 2 virus provide an experimental model that closely resembles the pathogenesis of human neonatal herpes virus infection (Kern et al. 1986). In this model (Crane & Sunstrom 1988; Karim et al. 1985; Kern et al. 1986; Overall et al. 1980) and in neonatal rabbits inoculated subcutaneously with herpes simplex virus type 2 (Sicher & Oh 1981), intraperitoneal acyclovir 50 to 120 mg/kg/day for 5 to 10 days has generally produced a statistically significant reduction in mortality rate or increase in the median time to death when treatment was initiated up to 2 days after viral challenge. In these models, successful acyclovir treatment has been associated with the inhibition of viral replication in several tissues, including the central nervous system (Kern et al. 1986; Sicher & Oh 1981).

Acyclovir treatment has been associated with a higher survival rate than vidarabine therapy in the mouse model, usually by around 20%, and a longer median survival time (Crane & Sunstrum 1988; Karim et al. 1985; Overall et al. 1980). A synergistic decrease in mortality rate was observed with the combination of acyclovir 80 mg/kg/day plus vidarabine 125 mg/kg/day in intranasally infected mice, when drug administration was begun 30 hours postinfection (Karim et al. 1985). Addition of herpes simplex type 2 specific antiserum to this treatment regimen did not increase the protection conferred. Similarly, Crane and Sunstrum (1988) administered intraperitoneal combinations of acyclovir plus vidarabine or vidarabine-5'-monophosphate, observing additive reductions in mortality when treatment was begun 2 hours following viral inoculation. The combination of acyclovir and recombinant α-interferon (γ HuIFN-αA/D) 1×10^5 IU/day was consistently toxic to mice in this study, a similar finding to that of Connell et al. (1985).

1.2.6 Latency

Since the publication of the previous acyclovir review in this journal (Richards et al. 1983), there have been few additional published investigations of the effects of acyclovir in the prevention, suppression or eradication of latent herpes simplex virus in animal models. Several earlier studies found oral, intraperitoneal, subcutaneous or topical acyclovir therapy of experimentally induced herpes simplex infection to reduce in frequency or prevent the establishment of neuronal latency provided the drug was administered within 24 hours of viral inoculation. The animal models involved included mice with cutaneous herpes simplex type 1 or 2 infections or ocular herpetic disease, guinea-pigs with herpes simplex type 2 genital infections,

and the rabbit eye model of herpes simplex type 1 ocular infection. Acyclovir prophylaxis has completely suppressed disease recurrence and viral shedding in various animals with established latent herpes simplex infection, for the duration of treatment. In some cases a reduction in the number of reactivatable latent foci was observed, however a more recent study (Demangone et al. 1987) confirms the earlier conclusion that acyclovir therapy does not result in eradication of latent virus from neuronal ganglia.

1.3 Mechanism of Action

The mechanism of action of acyclovir has been the subject of detailed investigation. As described in the review by Richards et al. (1983), the antiviral effect of acyclovir on herpes simplex viruses and varicella zoster virus has been found to result from its interference with DNA synthesis (fig. 4). The following discussion is based on the above review. The exact mechanisms of acyclovir in other susceptible viruses have not been fully elucidated.

Acyclovir exhibits a selective inhibition of herpesvirus replication, with extremely low toxicity towards uninfected host cells. This selectivity derives from the specific, sequential phosphorylation of acyclovir by herpesvirus-coded thymidine kinase. Thus intracellular activation of the drug to acyclovir triphosphate is a principal requirement for antiviral activity *in vitro*.

The initial selective phosphorylation, to acyclovir monophosphate, is catalysed by virus-coded thymidine kinase. Acyclovir monophosphate is subsequently converted to the diphosphate via cellular guanylate kinase, and then to the triphosphate via other host cell enzymes. Acyclovir triphosphate is the active metabolite and functions as both a substrate for and preferential inhibitor of viral DNA polymerase. In competition with the natural nucleoside, deoxyguanosine triphosphate, acyclovir triphosphate binds to herpes simplex DNA polymerase and is incorporated into a DNA primer-template, thus preventing further elongation of the DNA chain. Acyclovir triphosphate has thus been termed a 'suicide inactivator' of viral DNA poly-
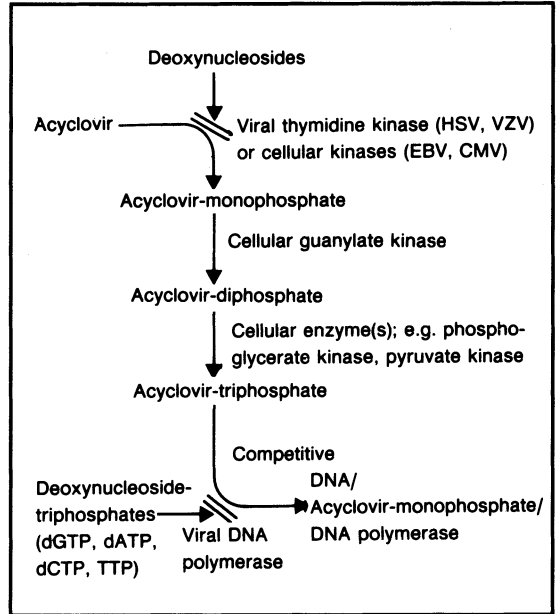
Fig. 4. Acyclovir inhibition of viral DNA synthesis. Acyclovir competes with deoxyribonucleosides for viral thymidine kinase, or cellular kinases. In addition to competitively inhibiting the association of deoxynucleoside triphosphates with viral DNA polymerase, acyclovir triphosphate incorporates into the growing viral DNA chain, leading to the termination of DNA synthesis because of its lack of a 3′-hydroxyl moiety. Acyclovir monophosphate is not excised from the primer template by the 3′,5′ exonuclease activity of viral DNA polymerase, but binds strongly to inactivate the polymerase (from Richards et al. 1983). *Abbreviations:* HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein-Barr virus; CMV = cytomegalovirus.

merase (Furman et al. 1984). *In vitro* study has revealed small virus-derived DNA fragments in herpes simplex virus-infected cells exposed to acyclovir, findings consistent with chain termination of viral DNA (McGuirt et al. 1984). The selective action of acyclovir is evidenced by the minimal phosphorylation to the monophosphate effected by cellular enzymes and by the much greater sensitivity of viral DNA polymerase, compared with the host cell enzyme, to inhibition by acyclovir triphosphate. The uptake of acyclovir into uninfected cells is poor (Elion 1984).

The monophosphorylation of acyclovir occurs poorly in cells infected with thymidine kinase-negative herpes simplex mutants, with Epstein-Barr

virus, although the latter virus appears to have some degree of thymidine kinase activity (Littler et al. 1986), and with cytomegalovirus, which does not code for a thymidine kinase. The relatively high susceptibility of Epstein-Barr virus DNA polymerase to inhibition by acyclovir triphosphate (formed via cellular enzymes) is responsible for the significant antiviral activity seen (Datta & Pagano 1983), while the lesser susceptibility of cytomegalovirus DNA polymerase, combined with low substrate concentrations, results in minimal susceptibility of this virus to acyclovir. Although the initial quantitative step in the antiviral mechanism of acyclovir is impeded in these viruses, at the DNA polymerase level a similar action to that in herpes simplex virus appears to operate.

1.4 Viral Resistance to Acyclovir

1.4.1 Characteristics of Resistant Strains

It is well established that herpes simplex virus can be made less susceptible to acyclovir by serial passage *in vitro* in the presence of subinhibitory concentrations of the drug (Richards et al. 1983). Resistant strains presumably emerge by 'selection' of naturally occurring viruses with relatively low susceptibility to acyclovir. Such strains have been reported in pre-therapy isolates from several clinical studies (Dekker et al. 1983; McLaren et al. 1983; Parris & Harrington 1982; Straus et al. 1984a).

Viral thymidine kinase catalyses the monophosphorylation of acyclovir to a greater extent than do cellular enzymes, and triphosphorylated acyclovir is more specific for viral DNA polymerase than for cellular DNA polymerases (see section 1.3). Resistance to acyclovir develops through mutations in the thymidine kinase and/or DNA polymerase genes of herpes simplex virus.

Two resistance mechanisms involving viral thymidine kinase have been described. These are: (a) selection of thymidine-kinase-deficient mutants that induce very little enzyme activity after infection, and (b) selection of mutants possessing a thymidine kinase of altered substrate specificity that is able to phosphorylate thymidine but not acyclovir. The vast majority of mutants arising *in vitro* are

of the thymidine kinase-deficient type, because as noted by Richards et al. (1983) viral thymidine kinase is not necessary for viral reproduction in these rapidly dividing cell cultures containing a large pool of monophosphorylated nucleotides. Varicella zoster virus appears to manifest resistance to acyclovir via mechanisms similar to those seen in herpes simplex virus (Cole & Balfour 1986).

Resistance involving herpes simplex DNA polymerase is due to selection of mutants encoding an altered enzyme, which is resistant to inactivation by acyclovir triphosphate. DNA polymerase mutants may also be resistant to antiviral agents unrelated to acyclovir, such as phosphonoformic acid, which acts directly on the viral DNA polymerase (Furman et al. 1984). However, polymerase mutants resistant to acyclovir or phosphonoformic acid were found to be susceptible to the acyclovir analogue ganciclovir (Cheng et al. 1983).

The genetic locus in which a change occurs to produce drug resistance may be important clinically, since thymidine-kinase-deficient strains of herpes simplex virus have greatly reduced infectivity, pathogenicity and likelihood of inducing latency in a variety of animals (Ellis & Barry 1985; Tenser & Dunstan 1979) and in man (Straus et al. 1984a), while acyclovir-resistant DNA polymerase mutants appear to retain the virulence of their wild-type parents (see Richards et al. 1983). Generally thymidine kinase-deficient virus cannot be recovered from ganglia (Price & Khan 1981), although 20% of trigeminal ganglia were found to be infected following ocular inoculation of mice with such a strain (Tenser et al. 1979). The pathogenicity of a thymidine-kinase-deficient acyclovir-resistant strain of herpes simplex virus isolated from the cerebrospinal fluid of an immunocompromised child treated with acyclovir was analysed in mice (Sibrack et al. 1982). An absence of inflammation or perivascular infiltration was noted in the child, and intracerebral inoculation of mice was associated with a 1,000-fold decrease in neurovirulence and death due to encephalitis (*vs* wild-type). Nonetheless, cutaneous lesions induced by the resistant mutant proved slow to heal, and chronic infection resulted; while some lesions eventually healed,

others tended to persist for long periods, resulting in the ultimate death of the mouse. Certain thymidine-kinase-deficient acyclovir-resistant herpes simplex type 2 clones retain their virulence in the mouse model of herpes simplex encephalitis, although the pathogenesis of such variants in mice may be significantly different from that seen in humans (Schinazi 1987).

DNA polymerase variants have also on occasion exhibited diminished neurovirulence *in vivo* (Field & Coen 1986; Larder & Darby 1985; Larder et al. 1986) although a high frequency of cataracts was found in mice surviving intra-cerebral inoculation with drug-resistant herpes simplex type 1 DNA polymerase mutants (Field & Coen 1986). A DNA polymerase mutant strain of acyclovir-resistant herpes simplex type 1 isolated by Parker et al. (1987) from a patient with chronic myelogenous leukaemia retained the ability to infect murine ganglia (Collins 1988). However, unlike wild-type virus, the resistant strain failed to invade the central nervous system of mice after peripheral inoculation.

Viruses expressing thymidine kinases of altered substrate specificity have been studied less extensively, but seem to have a normal or only somewhat diminished capacity to infect, cause disease and establish ganglionic latency in animals (Boisjoly et al. 1983; Darby et al. 1984a; Tenser et al. 1985).

1.4.2 Cross-Resistance with Other Antivirals In Vitro

The occurrence of cross-resistance in acyclovir-resistant mutants is dependent on the nature of the mutations conferring resistance. The extent of *in vitro* cross-resistance to other antivirals is of major clinical importance since it provides information which may aid the design of suitable therapeutic regimens for infections caused by acyclovir-resistant strains (Schinazi 1987). Suitable drug combinations may minimise the frequency of appearance of resistant isolates.

Herpes simplex virus mutants which are resistant to acyclovir due to an absence of viral thymidine kinase are cross-resistant to other agents which are phosphorylated by herpesvirus thymidine kinase, such as bromovinyldeoxyuridine, idoxuridine, ganciclovir and the 2'-fluoropyrimidine nucleosides 2'-fluoro-5-iodoarabinosylcytosine (FIAC), 2'-fluoro-5-iodoarabinosyluracil (FIAU) and 2'-fluoro-5-methyliodoarabinosyluracil (FMAU) [Darby et al. 1984a; McLaren et al. 1985; Richards et al. 1983]. These mutants retain susceptibility to agents such as vidarabine, phosphonacetic acid, phosphonoformic acid and the newly synthesised phosphonate derivative (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine which either require no phosphorylation or can be phosphorylated by cellular enzymes and consequently act independently of viral thymidine kinase (De Clercq 1987; Larder & Darby 1986; Schinazi 1987; Vinckier et al. 1987).

Genetic variants which retain the ability to express thymidine kinase while manifesting acyclovir resistance via altered substrate specificity of this enzyme or alterations to the viral DNA polymerase are more difficult to generate *in vitro* and hence less information is available regarding their cross-resistance patterns. Mutants of herpes simplex having altered substrate specificity are generally as susceptible as wild-type strains to drugs whose action is independent of viral thymidine kinase, but may display cross-resistance to other nucleoside antivirals, such as ganciclovir and bromovinyldeoxyuridine (Larder & Darby 1986; Richards et al. 1983). However, such strains will have variable cross-resistance patterns depending on the precise location of the mutation conferring resistance (Darby et al. 1984b). A laboratory acyclovir-resistant herpes simplex type 1 mutant which retained intermediate (69% of wild type) thymidine kinase activity demonstrated significant *in vivo* and *in vitro* susceptibility to both vidarabine and bromovinyldeoxyuridine. The resistant strain was less virulent than the wild-type parent, producing significantly (p < 0.05) less severe ocular keratouveitis in rabbits on days 4 to 7 postinoculation (Boisjoly et al. 1983).

DNA polymerase mutants of herpes simplex tend to possess more complex resistance patterns. Larder and Darby (1986) found all acyclovir-re-

sistant DNA polymerase mutants of herpes simplex type 1 studied to be susceptible to bromovinyldeoxyuridine and relatively susceptible to idoxuridine and ganciclovir. Each of these mutants responded similarly to phosphonoacetic acid, phosphonoformic acid and vidarabine but, among the 7 mutants, significant increases in susceptibility to these agents were observed with approximately equal frequency to decreases in susceptibility. The response of each variant to aphidicolin was usually the inverse of its response to these other 3 drugs. The DNA polymerase mutant isolated from an immunocompromised patient after extended acyclovir therapy proved to be 10 times less sensitive to acyclovir and 3 to 4 times less sensitive to phosphonoacetic acid (Parker et al. 1987).

In studying the *in vitro* susceptibilities to acyclovir of herpes simplex type 1 isolates from several immunocompromised patients, McLaren et al. (1985) concluded that patterns of drug cross-resistance in the clinical setting may result from a variable combination of altered amount and substrate affinity of the viral thymidine kinase. Thus, an isolate expressing thymidine kinase having a 50% reduction in acyclovir affinity proved cross-resistant to ganciclovir and bromovinyldeoxyuridine but susceptible to the experimental nucleosides FIAU, FIAC and FMAU. A second isolate with a thymidine kinase affinity for acyclovir of just 1% of the pretherapy isolate was cross-resistant to each of these agents. Susceptibility to FMAU, but to none of the other nucleoside analogues tested, occurred with an isolate expressing thymidine kinase with a slightly altered substrate specificity but which was present in only 6% of the amount of the pretherapy strain. All isolates retained susceptibility to phosphonoformic acid, as expected.

1.4.3 Resistance in Human Viral Infection

The emergence of viral strains exhibiting resistance or reduced susceptibility to acyclovir in the clinical setting is a matter of concern which has been addressed in studies examining clinical isolates from several hundred patients. These have usually involved comparisons of *in vitro* susceptibility between pre- and post-therapy isolates, in normal and immunocompromised patients receiving intravenous, oral or topical acyclovir therapy for primary or recurrent herpes simplex virus infection. Assessment of the problem of clinical resistance is still hampered by the relative novelty of this area of research, as evidenced by the absence of a standardised assay and a lack of consensus as to what constitutes a resistant strain. In this regard, more simple, direct and accurate methods of determining viral susceptibility are needed (Crumpacker 1983).

As noted by Richards et al. (1983), and confirmed in more recent reports (Barry et al. 1985; Nusinoff-Lehrman et al. 1986b; Svennerholm et al. 1985; Wade et al. 1983; Vinckier et al. 1987), in almost all cases of clinical resistance of herpes simplex virus to acyclovir, the mechanism has been via selection of mutants lacking or deficient in thymidine kinase activity, indicating that mutation at the DNA polymerase locus is a rare event in the natural setting. However, Parker et al. (1987) have recently reported an immunosuppressed bone marrow transplant recipient who yielded herpes simplex isolates resistant to acyclovir over several months of treatment with the drug. Resistance was found to be due to an altered viral DNA polymerase, with no evidence of any alteration or deficiency in virally induced thymidine kinase.

The demonstration of mixed populations of acyclovir-resistant and susceptible strains of herpes simplex virus obtained from patients who have not been exposed to acyclovir suggests that natural mutation of the thymidine kinase gene is relatively frequent. Such mutant viruses might be expected to undergo selection during acyclovir treatment, especially with long term oral therapy, when acyclovir plasma concentrations are significantly lower than those resulting from intravenous administration. In clinical trials, however, oral administration of acyclovir to immunocompetent patients has not been associated with the frequent emergence of *in vitro* viral resistance (Collins & Oliver 1986; Dekker et al. 1983; Svennerholm et al. 1985). Indeed, the range of herpesvirus susceptibilities was often similar in acyclovir-treated patients and those receiving placebo (Dekker et al. 1983; McLaren et al.

1983; Nusinoff-Lehrman et al. 1986a). Among patients whose herpetic lesions were treated with acyclovir 5% cream or acyclovir 5% or 10% in a polyethylene glycol ointment, comparisons of the pre- and post-therapy viral susceptibilities revealed no major differences (Collins & Oliver 1986; Marlowe et al. 1984), suggesting that development of resistance is not associated with topical therapy. Nevertheless, in view of the limited value of topical therapy and the finite risk of its association with resistant virus production, a cautious rational approach to its use appears the most appropriate (Raab & Lorincz 1983).

Acyclovir-resistant strains are also uncommon in immunocompetent patients receiving long term prophylactic (suppressive) treatment for recurrent genital herpes (Al-Hasani et al. 1986; Nusinoff-Lehrman et al. 1985, 1986b). Nusinoff-Lehrman et al. (1986a) evaluated the *in vitro* susceptibilities of 183 herpes simplex virus isolates from 107 patients, obtained before, during and after acyclovir administration. The use of daily acyclovir for up to 4 months was not associated with a significant change in mean susceptibility, as assessed by dye uptake assay. Furthermore, in this study all 6 isolates of herpes simplex from patients with breakthrough recurrences showed no change in susceptibility. However, in a smaller study employing a more sensitive plaque reduction viral assay to confirm the results of dye uptake testing, resistant herpes simplex virus was shed by 3 patients who had breakthrough recurrences during acyclovir prophylaxis. Two of these responded favourably to continued acyclovir treatment and after acyclovir was discontinued, all 3 patients shed acyclovir-susceptible virus in the following recurrent episode of genital disease. Smith and Goodwin (1988) noted significant correlation between *in vitro* susceptibility of preprophylaxis herpes simplex isolates and the occurrence of breakthrough attacks, in 20 patients receiving suppressive acyclovir 400 to 600mg daily for frequently recurring mucocutaneous infection. The mean ID_{50} ($p < 0.05$), ID_{90} and ID_{99} ($p < 0.005$ for each) values determined by plaque reduction were significantly higher for isolates associated with subsequent breakthrough in-

fections. These and other authors (Barry et al. 1986) have suggested that ID_{90} and ID_{99} values are likely to be better predictors of clinical response to prophylaxis than the ID_{50}, because the higher inhibitory concentrations better reflect the presence of viral strains with reduced susceptibility which seem more likely to be responsible for recurrences.

Patients with normal immunity from whom herpes simplex virus having reduced susceptibility to acyclovir has been recovered either before, during or after therapy, have usually responded well clinically to acyclovir treatment (Collins & Oliver 1986; Dekker et al. 1983; Nusinoff-Lehrman et al. 1986a). However, there have been several reports of a lack of response to therapy associated with acyclovir-resistant herpes simplex virus exhibiting defective thymidine kinase activity in severely immunocompromised patients who have received prolonged or repeated courses of acyclovir (Barry & Nusinoff-Lehrman 1985; Christophers & Sutton 1987; Dekker et al. 1983; McLaren et al. 1983; Wade et al. 1983; Vinckier et al. 1987; see also the review of Richards et al. 1983). As discussed above, these viral strains tend to be debilitated in their ability to infect and to cause disease or latency. While in the individual having normal immunity such virus would be eradicated by the immune system, in the immunocompromised patient (especially bone marrow transplant recipients) it is sometimes associated with stabilisation of previously resolving disease and persistence of chronic lesions (Nusinoff-Lehrman et al. 1986a,b; Svennerholm et al. 1985). Many immunocompromised patients regarded as treatment failures have shed acyclovir-susceptible virus, and it is likely that these individuals were simply unable to clear their infections (Barry et al. 1985). The most severe clinical consequences to be associated with acyclovir-resistant herpes simplex virus have been observed in immunocompromised patients. These have included refractory cases of chronic mucocutaneous infection (Westheim et al. 1987) and extensive genital herpes that failed to heal after prolonged acyclovir treatment (Schinazi et al. 1986b; Svennerholm et al. 1985). Schinazi et al. (1986b) found that the variants exhibiting *in vitro* resistance were also

resistant *in vivo* to high doses of systemic acyclovir, but responded to a combination of acyclovir and vidarabine.

Limited clinical investigation has revealed no evidence of a significant change in *in vivo* susceptibility of varicella zoster virus with acyclovir therapy (Cole & Balfour 1986), although resistant mutants of this virus can be isolated *in vitro* in a manner analogous to herpes simplex virus (Biron et al. 1982; Preblud et al. 1984). Analysis of 20 paired clinical isolates from patients who received oral acyclovir or placebo for acute zoster led Cole and Balfour (1986) to conclude that *in vivo* emergence of resistant varicella zoster virus appears to occur very infrequently.

Because the frequency of *in vitro* resistance to acyclovir is relatively low before and after therapy, further studies examining many isolates from a large number of patients with compromised immune function are required to accurately assess and more cleary define the clinical implications of reduced *in vitro* susceptibility to acyclovir (Nusinoff-Lehrman et al. 1986b). In its clinical use thus far, viral resistance to acyclovir leading to infection refractory to the drug has been rare, particularly in immunocompetent patients in whom to date no significant clinical ramifications have resulted from herpesvirus of altered acyclovir sensitivity. Certain patient groups, such as the severely immunocompromised and those undergoing chronic suppressive regimens have been identified as being most frequently associated with the emergence of resistant herpes simplex strains, which may or may not accompany a poor response to the drug. Susceptibility monitoring of clinical isolates from these patients remains an important therapeutic requirement.

2. Pharmacokinetic Studies

The fundamental pharmacokinetic properties of acyclovir were fairly well established at the time of the previous review in the Journal (Richards et al. 1983). Further detailed reviews of this subject have been provided by Brigden and Whiteman (1985), de Miranda and Blum (1983) and Laskin (1983).

This update presents an overview of the pharmacokinetics of acyclovir as reported by Richards et al. (1983), incorporating the findings of more recent studies where these provide significant additional information.

Acyclovir concentrations in body fluids have been determined accurately and sensitively by methods including radioimmunoassay, reverse-phase high performance liquid chromatography and virus inhibition bioassay. With a sensitivity limit of 0.01 mg/L, the radioimmunoassay technique is approximately 20-fold more sensitive than either high performance liquid chromatography or bioassay methods (Laskin 1983). A competitive enzyme-linked immunosorbent assay utilising anti-acyclovir monoclonal antibody and of similar sensitivity to radioimmunoassay has also been described (Tadepalli et al. 1986).

2.1 Absorption and Plasma Concentrations

2.1.1 Intravenous Administration

The pharmacokinetics of intravenously administered acyclovir have been best described by a 2-compartment open model, regardless of the intravenous input method (de Miranda & Blum 1983; Laskin 1983). Additionally, dose over the range 2.5 to 15.0 mg/kg, length of infusion and single- *versus* multiple-dose administration do not appear to influence the pharmacokinetic disposition of acyclovir (de Miranda & Blum 1983). Mean peak acyclovir concentrations after 1-hour infusions vary in a fairly linear fashion with the dose administered. The finding that steady-state peak plasma concentrations achieved with 8-hourly multiple doses of the drug (6.7, 9.7, 20.0 and 20.6 mg/L, respectively, at 2.5, 5.0, 10.0 and 15.0 mg/kg dosages) are similar to those seen after equivalent single doses, indicates that acyclovir accumulation is unlikely with 8-hourly administration in patients without serious renal dysfunction (Whitley et al. 1982).

2.1.2 Oral Administration

Absorption of orally administered acyclovir is slow, variable and incomplete, with mean peak plasma concentrations usually occurring 1.5 to 2.5

hours postdose. The oral bioavailability is approximately 15 to 30% (de Miranda & Blum 1983).

There are conflicting reports regarding the effects of dose size on the extent of oral absorption. Brigden et al. (1980) reported that the percentage of an oral dose recoverable in the urine decreased from 13.2% of a 100mg dose to 6% of a 600mg dose, and that mean peak plasma concentrations occurring with a single 600mg dose (0.58 mg/L) varied little from that with a 200mg dose (0.50 mg/L), suggesting that absorption of acyclovir from the gastrointestinal tract may be a saturable, dose-dependent process. In contrast, de Miranda et al. (1982c) found a doubling of steady-state peak and trough concentrations and AUC with an acyclovir dosage of 400mg 4-hourly, compared with 200mg 4-hourly; among subjects receiving 200, 400 or 600mg every 4 hours, a relative constancy was seen in urinary recovery of unchanged drug and in bioavailability calculated from urinary excretion data. The authors concluded that in the 200 to 600mg dose range, the net absorption of acyclovir is nearly proportional to the dose. More recent data support capacity-limited absorption. When a 400mg dose was administered either as tablets or as a 500ml duodenal infusion over 4 hours, AUC with the infusion was almost double that with the tablets, presumably as a result of the increased contact time of the solution with the absorptive area of the gut (Lewis et al. 1986).

Since the publication of the review of Richards et al. (1983), A515U (6-deoxyacyclovir; desciclovir), a prodrug of acyclovir, has been investigated clinically. In providing greatly improved acyclovir bioavailability after oral administration, the compound is a useful research tool.

A515U is devoid of antiviral activity *in vitro*, but undergoes conversion to acyclovir *in vivo* by xanthine oxidase (Jones et al. 1987; Krasny & Krenitsky 1986). It is well tolerated with excellent oral absorption, and with oral administration yields plasma acyclovir concentrations comparable to those attained via the intravenous route (Selby et al. 1984).

2.1.3 Topical and Intraocular Administration

Transcutaneous penetration of acyclovir after topical administration can be markedly influenced by the formulation used. Freeman et al. (1986) investigated the effect of vehicle choice on the drug flux through excised human skin from 5% acyclovir formulations. Modified aqueous cream and 95% dimethyl sulphoxide were associated with 8-fold and 10-fold increases in acyclovir flux, respectively, compared with the polyethylene glycol vehicle.

Although some systemic absorption of acyclovir may occur through damaged skin, this appears to be limited. Indeed, in patients with herpes genitalis, acyclovir was undetectable in plasma (< 0.023 mg/L) during therapy with topical 5% acyclovir in polyethylene glycol applied 4 to 6 times daily for 5 to 7 days (Corey et al. 1982b).

When 3% acyclovir ointment was applied to the inferior cul-de-sac of 25 eyes every 5 hours for 4 to 6 doses prior to cataract extraction (last dose 5 minutes prior to surgery), the mean acyclovir concentration in aqueous humour was 1.7 mg/L, indicating a relatively high level of penetration (Poirier et al. 1982).

Substantial intraocular penetration of acyclovir also occurs following subconjunctival injection, although intraocular use of the intravenous formulation is not recommended by the manufacturer. A 25mg injection produced aqueous and vitreous concentrations of 1.15 to 6.66 and 0.65 to 5.20 mg/L, respectively, in 5 patients undergoing enucleation. The highest acyclovir blood concentration was 0.12 mg/L 2 hours after injection, which had declined to 0.05 mg/L by 7 hours postinjection (Schulman et al. 1987).

2.2 Distribution

Information on the distribution of acyclovir in human tissues and biological fluids is limited. The drug appears to penetrate into cerebrospinal fluid, producing concentrations approximately 50% of those in plasma. Autopsy on a patient who had received multiple-dose intravenous therapy with acyclovir 400 to 1200 mg/m^2 8-hourly revealed that

concentrations of drug in the kidney, nervous tissue (brain and spinal cord) and lung were 1000%, 25 to 70% and 131% of the corresponding plasma concentrations, respectively; drug concentrations in the liver and heart were similar to those in the lung (Wade et al. 1982).

Distribution into the aqueous humour after oral administration has been demonstrated in patients who received 5 doses of acyclovir 400mg in the 24 hours prior to cataract extraction (Hung et al. 1984b). Acyclovir concentrations in aqueous humour were approximately 30 to 50% of corresponding plasma concentrations, and approximately half as great as those found in aqueous humour by Poirier et al. (1982) after topical administration using acyclovir ointment. A mean tear fluid concentration of 0.64 μmol/L was achieved among 12 patients with superficial herpetic dendritic corneal ulceration administered oral acyclovir 400mg 5 times daily; this represented 18% of the mean concomitant plasma concentrations (Collum et al. 1985b).

Vesicular drug concentrations in varicella zoster patients were approximately equivalent to plasma concentrations after intravenous infusion (7.2 to 43.2 mg/kg/day) [Spector et al. 1982a] and oral administration (200 to 400mg 4-hourly) [Van Dyke et al. 1982b]. Following oral administration acyclovir has been detected in saliva at a concentration of 13% of that in plasma, and in vaginal secretions at variable concentrations (Van Dyke et al. 1982a).

The transplacental passage of acyclovir was demonstrated in women prescribed the drug during the first, second or third trimester for life-threatening complications of severe herpesvirus infections (Greffe et al. 1986; Haddad et al. 1987; Leen et al. 1987). In 13 such pregnancies, the acyclovir concentration in cord blood ranged from < 0.11 to 0.56 mg/L (< 0.5 to 2.5 μmol/L) while amniotic fluid samples contained < 0.11 to 1.2 mg/L (< 0.5 to 5.5 μmol/L) [Kingsley 1986].

As acyclovir is well distributed in the tissues and has low protein binding, it might be expected to accumulate in breast milk. A course of oral acyclovir 200mg 5 times daily in a lactating woman

led to such accumulation (Lau et al. 1987). The acyclovir concentration in breast milk exceeded that in maternal plasma at all times except that of minimal plasma concentration, indicating secretion by an active or facilitated transport process. Meyer et al. (1988) assayed for acyclovir in the serum and milk of a lactating woman who was treated with oral acyclovir 200mg 5 times daily, for herpes zoster. Daily sampling revealed acyclovir milk concentrations on average 3.24-fold higher than corresponding serum concentrations (1.06 vs 0.33 mg/L); the elimination half-life from milk was 2.8 hours. The data suggested infant exposure in this situation to be < 1 mg/day and hence of low theoretical risk.

The mean volume of distribution of acyclovir at steady-state, calculated from combined data (6 studies), was 48 L/1.73m^2 (range 22.5 to 101) [Blum et al. 1982]. In vitro plasma protein binding of 22 and 33% was observed when 4.0 and 0.4 mg/L solutions of ^{14}C-acyclovir, respectively, were incubated with normal human plasma (de Miranda et al. 1979). In 4 patients who had received an infusion of ^{14}C-acyclovir the degree of binding (range 9 to 24%; mean 15.4%) was independent of plasma acyclovir concentration, over the range 0.4 to 5.1 mg/L (de Miranda et al. 1982a).

2.3 Metabolism and Elimination

The only significant metabolite of acyclovir is 9-carboxymethoxymethyl guanine, an inactive metabolite which accounts for up to 14% of a dose in persons with normal renal function. A minor metabolite which accounts for less than 0.2% of a dose appears to be 8-hydroxy-9-(2-hydroxyethoxy-methyl) guanine (de Miranda et al. 1979, 1982b) [fig. 5].

As noted in the review of Richards et al. (1983), renal excretion is the major route of elimination of acyclovir in subjects with normal renal function. The mean percentage of a dose recovered unchanged in the urine ranged from 45 to 79% in several studies, and decreased with decreasing creatinine clearance. In studies examining a dosage range of 0.5 to 15 mg/kg administered intraven-
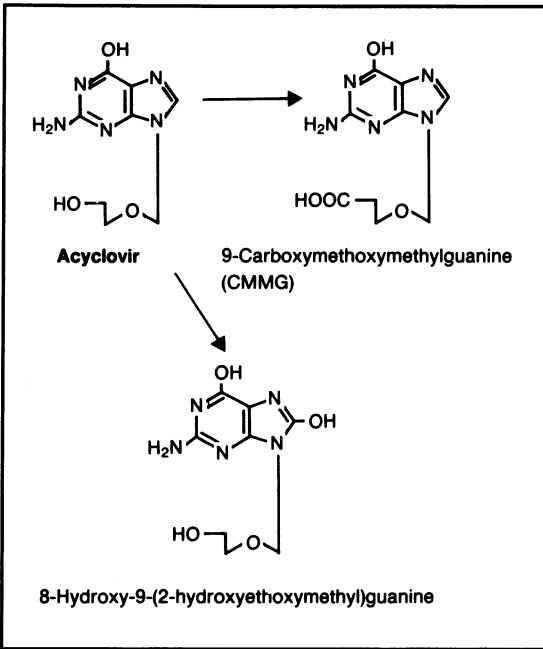
Fig. 5. Chemical structures of the metabolites of acyclovir.

ously to patients with normal renal function, the elimination half-life was 2 to 3 hours. As renal clearance accounts for approximately 75 to 80% of the total body clearance of acyclovir, it is substantially greater than estimated creatinine clearance, indicating that renal tubular secretion as well as glomerular filtration plays a role in the elimination of acyclovir (Laskin 1983).

2.4 Pharmacokinetics in Neonatal and Paediatric Patients

Mean peak plasma concentrations of acyclovir in neonates following 1-hour infusions of 5, 10, and 15 mg/kg were 6.8, 13.8 and 19.4 mg/L, respectively, showing a direct relationship between dose and peak plasma concentration (Hintz et al. 1982). Similarly, mean peak plasma concentration and AUC were proportionate to dose in infants and children receiving 300 or 600 mg/m^2 doses of acyclovir as an oral suspension (Sullender et al. 1987). At 2.5 to 4.0 hours, the elimination half-life in neonates is slightly longer than in adults (Hintz et al. 1982).

The total body clearance of acyclovir in neonates up to 3 months old ranged from 105 to 122 ml/min/1.73m^2 (6.3 to 7.3 L/h) [Laskin 1983] and is approximately one-third that of adults with normal renal function. This finding is consistent with changes that occur in the kidney during the first year of life. Thus, with multiple-doses of oral acyclovir 300 mg/m^2, 3 infants less than 2 months old achieved mean peak plasma concentrations which were greater than twice those in 2 patients aged 1.5 and 1.8 years (Sullender et al. 1987).

The disposition of acyclovir in children 1 year of age and older is generally comparable to that seen in adults (Laskin 1983).

2.5 Pharmacokinetics in Patients With Renal Function Impairment

In patients with end-stage renal disease, acyclovir is slowly eliminated; mean peak plasma concentrations are nearly double those seen in patients with normal renal function, the mean elimination half-life is extended to approximately 20 hours, and the mean total body clearance is decreased 10-fold (Richards et al. 1983). Mean peak and trough plasma acyclovir concentrations appear to be inversely related to creatinine clearance. When patients from several studies were stratified according to their creatinine clearance values, there was little variation in mean volumes of distribution at steady-state and elimination half-lives between patients with creatinine clearances of greater than 80 ml/min/m^2 and those with creatinine clearance in the range 15 to 50 ml/min/m^2, but mean total body clearance and mean renal clearance were decreased by 41% and 50%, respectively, in the latter group (Blum et al. 1982). Such relative constancy in both volume of distribution and elimination half-life with changed total body clearance is theoretically unlikely, and may reflect a lack of statistical power in the treatment of these latter findings.

Acyclovir is readily haemodialysable. A single 6-hour course of haemodialysis reduced the acyclovir plasma concentration by 60%, the dialysis

elimination half-life being 5.7 hours and the dialysis clearance 82 ml/min (Laskin et al. 1982).

In the small number of patients studied, continuous ambulatory peritoneal dialysis (CAPD) has proven much less efficient than haemodialysis in removing acyclovir from plasma, with the elimination half-life usually being 14 to 18 hours and the dialysis clearance approximately 4 ml/min (0.24 L/h) [Brundage et al. 1985; Seth et al. 1985; Shah et al. 1986]. In 6 non-infected subjects receiving CAPD, Boelaert et al. (1987) found the pharmacokinetics of acyclovir to be described by a 3-compartment model, comprising plasma, peripheral and peritoneal compartments. The contribution of peritoneal-dialysate clearance to total body clearance depends on the frequency of fluid changes but is usually less than 10% (Boelaert et al. 1987; Seth et al. 1985; Shah et al. 1986).

3. Therapeutic Trials in Immunologically Competent Patients

In the intervening years since the publication of the previous review of acyclovir in the Journal, additional well-designed clinical trials have been conducted which further elucidate the therapeutic role of this now well-established antiviral agent. The wider clinical availability of the oral formulation of acyclovir has occurred together with the publication of studies documenting the high efficacy and safety of chronic suppressive oral regimens for the prevention of recurrent genital herpes. Oral acyclovir administration also offers the benefits of outpatient systemic treatment for recurrences of mucocutaneous herpes simplex, which would be expected to be optimised in well-informed patients who are aware of the need to initiate the drug as early as possible in the course of an episode. Specific guidelines for the use of suppressive treatment in genital herpes have been proposed for use in high risk patients (Gold & Corey 1987).

3.1 Herpes Simplex Virus Infections

3.1.1 Genital

Genital herpes continues to be a disease of increasing incidence, with major social ramifications. First (initial) clinical episodes of genital herpes in-

fection are termed primary when serological testing at the time of presentation fails to reveal antibodies specific for herpes simplex virus, in patients with no previous history of genital sores. Initial non-primary infections are first episodes in those whose sera are positive for herpes simplex antibodies; these infections are normally less severe than true primary episodes. In addition, the disease is characterised by recurrences, which are generally milder and of shorter duration than the initial episode (Nilsen 1985).

Genital herpes is usually caused by herpes simplex type 2, although type 1 virus was found to be the causative agent in 10 to 40% of cases of primary infection, depending on the geographic area (Sacks 1987). In a primary infection, the incubation period is about 6 days and viral shedding persists for 11 to 12 days, with mucocutaneous lesions requiring 2 to 3 weeks or longer to fully heal. The milder recurrent episode, while running a similar course to the primary outbreak, has a mean pain duration of 4 to 6 days, virus shedding time of 4 to 5 days, and a healing time of around 10 days (Mindel & Sutherland 1983) [fig. 6].

As reviewed by Richards et al. (1983), the efficacy of acyclovir in ameliorating the symptoms of initial genital herpes has been well established in comparative studies with placebo. More recently, the effects of the drug on recurrence patterns, and indications for the use of long term suppressive and prophylactic acyclovir regimens, have received most attention in the literature. Perhaps because there are few antivirals currently under study which confer benefit comparable to that of acyclovir in this therapeutic area, acyclovir has undergone very few comparisons with other agents in patients with genital herpes. It is of value to note that, as discussed by Richards et al. (1983), a striking characteristic of genital herpes is its variability of expression; thus meaningful data will only be supplied by well-designed, controlled studies.

Initial Episodes

Intravenous, oral and topical administration of acyclovir in patients with a mean duration of symptoms of 3 to 4 days has been shown in pla-
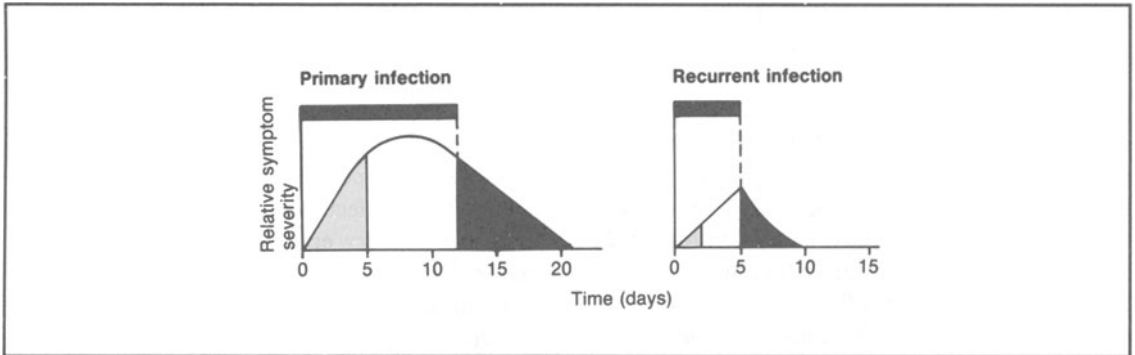
Fig. 6. Natural history of vesicles (▨), ulcers (□), crusting (■) and duration of viral shedding (■) in primary and recurrent genital herpes (after Mindel & Sutherland 1983; reproduced with permission).

cebo-controlled studies to significantly attenuate the course of the initial episode of genital herpes (table III). Systemic treatment for 5 to 10 days has produced the most dramatic and consistent results, while the effects of acyclovir 5% cream and particularly ointment (polyethylene glycol base) have generally been less impressive. A direct comparison of the efficacy of acyclovir administered by the oral and intravenous routes may be inappropriate, since trials with the intravenous drug have involved hospitalised patients with severe infection (Mertz et al. 1984).

In several of the double-blind comparisons with placebo listed in table III, oral and topical acyclovir markedly reduced the duration of viral shedding from a median of 5 to 13 days with placebo to 1 to 4 days with acyclovir, in patients with primary and/or non-primary initial episodes. Cervical viral shedding has also been rapidly reduced by treatment with acyclovir (Corey et al. 1983b; Mertz et al. 1984), although this parameter has been reported only infrequently. In cross-trial comparisons, systemic acyclovir reduced the duration of viral shedding to a significantly ($p < 0.001$) greater degree than did topical therapy (Corey et al. 1983b), and a similar but non-significant trend occurred when the results of 2 multicentre double-blind studies involving intravenous, oral and topical (cream and ointment) acyclovir were analysed (Fiddian et al. 1983a). Kinghorn et al. (1986b) found the antiviral effect of oral acyclovir to be much

more pronounced than that of the topical formulation; the median duration of viral shedding during oral treatment was 2 days compared to 4 days with topical acyclovir in a previous study (Kinghorn et al. 1983).

Acyclovir treatment of primary genital herpes infection results in an approximate halving of the duration of pain, time to healing, time to crusting and duration of systemic manifestations, from that seen with placebo treatment. In several placebo-controlled studies, intravenous, oral or topical acyclovir significantly shortened the time to complete healing of lesions from a median of 11 to 21 days with placebo to 6 to 12 days (Corey et al. 1983a,b; Fiddian et al. 1983a; Kinghorn et al. 1983; Lacey et al. 1985; Mertz et al. 1984). Nevertheless, the effect of treatment has often been inconsistent over the various parameters studied. Thus, impressive reductions in duration of viral shedding and time to complete healing with various formulations have accompanied non-significant changes (statistically) in duration of pain and combined symptoms (Lacey et al. 1985), constitutional symptoms (Mertz et al. 1984), and dysuria (Corey et al. 1983b). As noted in the review of Richards et al. (1983) and confirmed more recently, studies which have stratified patients according to whether the treated episode was primary or non-primary have generally determined a more marked benefit in those with primary episodes. In the study of Mertz et al. (1984) acyclovir therapy significantly ($p < 0.001$) de-

Table III. Summary of double-blind studies comparing acyclovir (A) with placebo (P) in patients with initial episodes (primary and non-primary) of genital herpes

Reference	No. of patients (% with primary infection/% female)	Daily dosage and route (duration)	Infection[a]	Duration of symptoms pretreatment (days) A	Duration of symptoms pretreatment (days) P	Results[b] viral shedding duration	crusting time	healing time	pain duration	new lesion formation; % A pts vs % P pts
Systemic acyclovir therapy										
Bryson et al. (1983)	48 (48/65)	200mg × 5 oral (10d)	Primary Initial	3.4	3.6	A < P A ≤ P (m) A < P (w)	A < P A ≤ P (m) A < P (w)	A < P A ≤ P (m) A < P (w)	A < P (m) A ≤ P (w)	A < P; 4 vs 44
Corey et al. (1983b)	31 (severe) (87/87)	5 mg/kg × 3 IV (5d)	Primary Initial	3.8 3.7	4.0 3.6	A < P A < P	A < P A < P	A < P A < P	A < P A < P	
Mertz et al. (1982)	111 (-/65)	200mg × 5 oral (10d)	Primary		3.7[c]	A < P	A < P (m)	A < P (m) A = P (w)		A < P; 13 vs 61
Mertz et al. (1984)	150 (79/63)	200mg × 5 oral (10d)	Primary Non-primary		4.0[c]	A < P A < P	A < P A = P	A < P A = P	A < P A = P	A < P; 18 vs 62 A = P; 33 vs 32
Nilsen et al. (1982)	31 (68/55)	200mg × 5 oral (5d)	NS	2.8	2.6	A < P	A ≤ P (m) A < P (w)	A < P	A < P	A < P; 0 vs 43
Peacock et al. (1984)	82 (54/71)	5 mg/kg × 3 IV (5d)	Primary Initial	NS	NS	A < P	A < P	A < P	A < P	A < P; 26 vs 50
Topical acyclovir therapy										
Corey et al. (1982b)	69 (74/64)	5% ointment 4-6 times/day (7d)	Primary Non-primary	4.3 3.5	4.7 2.8	A < P A = P	A < P A = P	A < P A = P	A < P A = P	A = P; 81 vs 83 A = P; 42 vs 63
Corey et al. (1982a)	77 (64/68)	5% ointment 4 times/day (7d)	Primary Non-primary	4.0 4.2	4.0 3.5	A < P A < P	A ≤ P A = P	A ≤ P A = P	A = P	
Fiddian et al. (1983a)	101 (-/62)	5% cream 5 times/day (10d)	Initial	3.2	3.4	A ≤ P (m) A < P (w)	A = P (m) A < P (w)	A < P	A = P (m) A < P (w)	A < P; 35 vs 55
Lacey et al. (1985)	30 (-/66)	5% ointment 5 times/day (10d)	NS	2.8	3.6	A < P	A = P	A < P	A = P	A = P; 19 vs 21
Thin et al. (1983)	40 (-/62)	5% ointment 5 times/day	NS	3.3	3.3	A < P[d]	A < P A = P (w)	A < P	A < P A ≤ P (w)	A < P; 6 vs 45

a Initial includes patients with either primary or non-primary infections.
b < indicates statistically significant difference between treatment groups; ≤ indicates a non-significant tendency; = indicates similar results for both groups. Results are specified for men (m) and women (w) where this information was provided. Where sex is not specified results are from men and women.
c Median for all patients.
d In women the duration of viral shedding was significantly shorter for external genital lesions only.
Abbreviation: NS = not specified.

creased the duration of viral shedding in those with non-primary episodes, but not the time to crusting or healing, new lesion formation, or the duration of symptoms. This differential effect may be a result of the shorter natural history of the non-primary outbreak of genital herpes.

Topical acyclovir has generally failed to reduce the rate of new external genital lesion formation to a statistically significant extent compared with placebo treatment (table III). Corey et al. (1983b) reported new crops of lesions during therapy in 20% and 13% of those receiving intravenous and oral acyclovir, respectively, while the figure was 69% in patients treated topically. The symptoms of dysuria (related to herpes simplex virus urethritis) and viral shedding from the cervix have also responded poorly to topical acyclovir, in contrast to systemic treatment (Corey et al. 1983b; Lacey et al. 1985; Mertz et al. 1984; see also the review of Richards et al. 1983).

Sexual differences in the response to acyclovir therapy of initial genital herpes have been variable, and often unevaluable due to a lack of patient numbers. Also, such differences are not unexpected, since the incidence and severity of various symptoms tend to vary between the sexes.

Concomitant topical treatment with 5% acyclovir cream appears to confer no advantages to patients receiving the drug orally for this condition (Kinghorn et al. 1986a).

Acyclovir has been compared with co-trimoxazole (trimethoprim plus sulphamethoxazole) alone or administered in combination with acyclovir (Kinghorn et al. 1986b), and with inosine pranobex, in double-dummy fashion (Mindel et al. 1987). In both studies acyclovir treatment was associated with statistically significant reductions in the duration of viral shedding and time to healing compared with the alternative antimicrobial. Additionally, the combination of acyclovir plus cotrimoxazole produced a significantly (p < 0.01) shorter time to lesion healing than did acyclovir alone, although patient numbers were small.

Treatment of the initial episode of genital herpes with acyclovir does not alter the chronic, recurring nature of the infection. Time to first recurrence and

frequency of recurrences during follow-up have been similar in acyclovir and placebo recipients. Several studies have identified the prognostic significance of typing the causative virus isolate, recurrences being far more frequent with herpes simplex type 2 than with herpes simplex type 1 first episodes (Barton et al. 1984; Kinghorn et al. 1986b; Mertz et al. 1984). In the latter study, involving 150 patients receiving acyclovir orally for 10 days, the median times to first recurrence were more than 360 days and 95 days in patients with type 1 and 2 genital infections, respectively. Recurrence rates were 0.11 and 0.44 per month, respectively, among acyclovir recipients infected with type 1 and type 2 virus. The authors suggest, as a possible explanation for the failure of therapy to influence subsequent recurrences, that acyclovir was initiated too late to prevent ganglionic establishment. However, whether administration of oral acyclovir during the incubation period will prevent the development of latent infection in the sacral ganglia is currently unknown.

Recurrent Episodes

The results of acyclovir treatment in acute recurrent genital herpes have not been as dramatic as those seen in the initial infection; this is accountable to the shorter, less severe natural course of recurrent genital herpes (True & Carter 1984) which tends to be a self-limiting condition in those with normal immune function (Sacks 1987). In several large double-blind multicentre studies, patient-initiated oral treatment (200mg 5 times daily for 5 days) has proven the most effective, with statistically significant reductions in duration of viral shedding and in formation of new lesions during treatment (Goldberg et al. 1986; Nilsen et al. 1982; Reichman et al. 1984; Ruhnek-Forsbeck et al. 1985; Salo et al. 1983). Placebo-controlled trials of topical acyclovir have generally shown some antiviral effect, but little or no clinical benefit (Kinghorn 1985; Luby et al. 1984), although acyclovir 5% cream compared favourably with systemic treatment when therapy was initiated by the patient early in the course of recurrent episodes (Fiddian et al. 1983a). Acyclovir treatment does not

alter the frequency or severity of future recurrent episodes.

As suggested by the results in the above studies utilising patient-initiated therapy, the short duration of viral replication during recurrences necessitates the early commencement of antiviral therapy, in order to maximise clinical benefit (Kinghorn 1985). The large study of Reichman et al. (1984) conducted in North America found significantly improved results *versus* placebo [shorter duration of viral shedding ($p \leqslant 0.05$) and time to crusting and healing ($p \leqslant 0.05$)] when oral acyclovir was initiated by patients at the onset of the prodrome or at the earliest signs or symptoms, rather than by a physician within 48 hours of recurrence outbreak. In contrast, further investigation has shown less of an effect of patient-initiated therapy *versus* clinic-initiated therapy (Goldberg et al. 1986), and no apparent difference between treatments was noted in a crossover study comparing patient-initiated therapy with that commenced within 24 hours of symptom onset (Ruhnek-Forsbeck et al. 1985).

Oral acyclovir markedly increases the incidence of so-called false prodromes (abortive episodes) compared to placebo; this effect appears to be accentuated when therapy is initiated as early as possible by patients themselves (Goldberg et al. 1986; Ruhnek-Forsbeck et al. 1985). Patient-initiated therapy at the prodromal stage appeared to abort the attack or stop the progression to lesion formation in 18% of acyclovir recipients *vs* 6% of placebo recipients in a double-blind study of 157 patients with recurrent disease (Goldberg et al. 1988). This latter study confirmed an earlier report in which a dosage of 800mg twice daily for 5 days was as effective as the standard regimen in treating recurrent episodes (Goldberg et al. 1986).

The limited efficacy of acyclovir 5% ointment in the treatment of recurrent genital herpes, as noted in the review of Richards et al. (1983), has been confirmed more recently by Luby et al. (1984) in a multicentre trial. Despite optimised timing of treatment (patient-initiated therapy as early as possible during a recurrence), acyclovir ointment produced a reduction in the duration of viral shedding

of borderline significance ($0.05 < p < 0.1$) in females only, and had no overall clinical benefit in either sex. In a smaller double-blind study, patient-initiated treatment with acyclovir ointment significantly ($p < 0.05$) shortened the time to healing of lesions, by at least 2 days, although only one-third of enrolled patients presented for observation of the treatment episode and the authors note the equivocal nature of the response to acyclovir between centres (Lacey et al. 1985). In contrast, as noted above, controlled trials with acyclovir 5% cream produced encouraging results when application was begun as early as possible by patients (Fiddian et al. 1983a). This discrepancy in results with topical therapy led to speculation that the polyethylene glycol vehicle was limiting percutaneous absorption of the drug from the ointment formulation (Kinghorn 1985; Luby et al. 1984). In the study of Fiddian et al. (1983a) viral shedding ($p < 0.01$), new lesion formation ($p = 0.001$), time to healing of all lesions ($p < 0.01$), and duration of all symptoms ($p < 0.001$), were significantly reduced (by 1 to 2 days compared with placebo) in 85 patients from several centres in England. This led the authors to conclude that the cream offered an effective alternative to oral administration for outpatient management of intermittent recurrences.

Thus, in recurrent genital herpes, early, especially self-initiated, treatment with oral acyclovir will reduce the episode duration, with the main benefit being the suppression of new lesion formation and virus shedding. Such treatment may increase the likelihood for attacks to abort without progression to the ulcerative or crusting stage. Trials involving the topical 5% cream show clinical efficacy, however the ointment has proved only marginally more effective than placebo. Neither oral nor topical acyclovir has produced a consistent alteration in the natural history of recurrent genital herpes. While more expensive than topical treatment, oral acyclovir remains the treatment of choice in more severe, frequently recurring infections, or if patient acceptance and/or lesion accessibility is problematic.

Prophylaxis

Several well-controlled clinical trials from England, North America and Scandinavia have shown that long term oral administration of acyclovir at dosages of 400 to 800mg daily for up to 1 year is extremely effective in suppressing recurrences of genital herpes lesions; subjects usually had a history of frequent ($\geq$ 6/year) recurrences. Generally, 60 to 90% of patients did not experience a full recurrence during prophylaxis (table IV) and in many cases of apparent treatment failure there was evidence of compliance problems (Blom et al. 1986; Kinghorn et al. 1985; Thin et al. 1985).

Mertz et al. (1988a) have recently reported suppressive oral acyclovir to be highly effective and well tolerated when administered continually for 2 years, the second year of which comprised open administration of acyclovir. 683 patients from a 1-year placebo-controlled study (Mertz et al. 1988b) completed 2 years of treatment. Of these 384 received continuous suppressive therapy, 276 acute acyclovir during episodes in the first year and suppressive treatment in the second, 24 suppressive treatment in the first year and acute treatment in the second, and 35 patients received acute therapy for 2 years. Those receiving intermittent acute acyclovir treatment experienced means of 7.0 to 12.6 recurrences per year, during treatment, compared with 1.4 to 1.9 recurrences per year among groups receiving continuous suppressive therapy. The proportion of patients remaining recurrence-free during each year of suppression was 39 to 50%, while this figure was 0 to 5% during each year of acute treatment. Thus, despite a high frequency of genital herpes recurrences prior to enrolment, a significant proportion of patients receiving acyclovir suppression remained free of outbreaks for prolonged periods (Mertz et al. 1988a).

The prophylactic benefits of acyclovir were confined to the periods when the drug was in continual use. Differences in time to first recurrence after the withdrawal of treatment were usually not statistically significant between acyclovir and placebo recipients, and in follow-up the recurrence rates in those treated with acyclovir returned to pretreatment frequencies. The lack of persistence of an an-

tiviral effect post-treatment was further illustrated in a comparison of intermittent (1.2g on Saturday and Sunday only) and continuous acyclovir treatment (600mg daily) [Straus et al. 1986]. Of 35 patients completing the study, significantly (p < 0.001) more failures occurred in the weekend group (13 of 17) than in the daily group (3 of 18). Recurrences with the weekend regimen became much more frequent towards the end of the week.

Extended treatment with acyclovir might be expected, by analogy with antibacterial therapy, to increase the likelihood of the emergence of resistant strains of herpes simplex, yet acyclovir-resistant strains have not been commonly or consistently recovered from patients receiving prophylaxis (Dorsky & Crumpacker 1987) [see section 1.4.3]. Straus et al. (1986) noted that the 3 patients in whom in vitro acyclovir resistance was associated with recurrence in a previous study (Straus et al. 1984b) did not shed resistant virus in the later investigation. Ambinder et al. (1984) suggested that long term suppressive therapy may reduce rather than enhance the development of resistance, by reducing the numbers of multiplying virions when latent sites are activated. Nevertheless, investigators uniformly agree on the wisdom of combining rational, selective use of long term acyclovir therapy with continued susceptibility testing of virus isolated from such patients.

Concern has been expressed that prolonged use of acyclovir may be associated with toxic effects and/or alter the generally favourable natural course of recurrent genital herpes (Raab 1985). However, there was no evidence of cumulative toxicity among patients receiving daily oral acyclovir for up to 2 years (Mertz et al. 1988a). In addition, the suppressive effects of acyclovir were maintained, as demonstrated by the fact that the frequency of recurrences and number of patients experiencing them did not increase as the study progressed.

The most appropriate indications and dosage for long term suppressive acyclovir treatment await confirmation. Although the efficacy and safety of 200mg oral doses administered 2 to 5 times daily has been demonstrated in prophylactic studies for up to 6 months (table IV), a dosage of 400mg twice

Table IV. Summary of double-blind, placebo (P)-controlled studies of prophylactic oral acyclovir (A) in recurrent genital herpes

Reference	No. of patients (% female)	Dosage	Duration of each treatment (weeks)	Results: A vs P[a]				
				patients with recurrence during treatment (%)	median time to first recurrence during treatment (days)	patients without full recurrence during treatment (%)	mean monthly recurrence rate	mean episode duration (days)
Blom et al. (1986)[b]	33 (33)	200mg qid	12	15*** vs 94	84 vs 20	85*** vs 6		
Douglas et al. (1984)	143 (55)	200mg bid	12	35*** vs 94	120*** vs 18	65 vs 6	0.14*** vs 0.86	6* vs 8
		200mg 5 times daily	12	29*** vs 94	120*** vs 18	71 vs 6	0.13*** vs 0.86	
Halsos et al. (1985)[b]	31 (0)	200mg qid	12		84*** vs 14	77*** vs 10	0.17*** vs 0.87	4.2* vs 6.6
Kinghorn et al. (1985)[b]	28 (43)	200mg qid	12 (or until recurrence)	11*** vs 93	>84*** vs 24			
Mertz et al. (1988b)[c,d]	950 (NR)	400mg bid	52	5*** vs 98	246**** vs 18	44*** vs 2		
Mindel et al. (1984)	56 (61)	200mg qid	12	14**** vs 96	100**** vs 14		0.05**** vs 1.4	
Sacks et al. (1985)[c]	47 (45)	200mg tid	26			29** vs 0		
Straus et al. (1984b)	32 (51)	200mg tid	18 (or until recurrence)	25*** vs 100	138*** vs 25			
Thin et al. (1985)[b]	88 (27)	200mg tid	12	13*** vs 88		87*** vs 13		

a * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.
b Crossover study.
c Recurrences were treated with acyclovir 200mg 5 times daily for 5 days.
d Multicentre study.
Abbreviations: bid = twice daily; tid = 3 times daily; qid = 4 times daily; NR = not reported.

daily is probably more convenient and may improve patient compliance. When 131 patients with frequently recurring genital herpes received reducing doses of oral acyclovir for 1 year, the time to first recurrence was significantly shorter ($p < 0.02$) in patients who began therapy with 400mg twice daily, compared with those on 200mg 4 times daily. At the end of 2 months' treatment with 200mg daily (the lowest daily dose), 56% of patients had experienced recurrences (Mindel et al. 1988).

Various authors have recommended that the use of prophylactic acyclovir should be restricted to reliable patients with severe or debilitating symptoms and, even so, used for a limited time (Salo 1985; Straus et al. 1984b; Thin et al. 1985). However, recommendations to discontinue suppressive treatment after 6 months now appear overly con-

servative (Mertz et al. 1988a). Although the relatively high cost of prolonged therapy represents a constraint, suppressive oral acyclovir effectively prevents the outbreak of lesions in the vast majority of frequently recurrent genital herpes sufferers, and thus provides relief, albeit temporary, from the disruption of sleep and sexual activity, and loss of self-esteem, which often accompany the recurrences. As the frequency of genital herpes recurrences varies over time, interruption of suppressive acyclovir treatment after 1 or 2 years is indicated in most patients, to reassess disease severity (Straus et al. 1988).

3.1.2 Orofacial

Recurrent perioral herpes simplex infection, due to the type 1 virus in 99% of cases, is a very common infection, with approximately 20 to 45% of the population of North America being afflicted. Outbreaks are usually mild and self-limiting, although frequent, painful and sometimes disfiguring lesions can prove extremely distressing. Recurrences of latent virus are also of concern, as is the risk of transferral to newborn infants, those with atopic eczema (see section 3.1.4) and immunocompromised patients, especially by health care workers (Shaw et al. 1985; Van Vloten et al. 1983; see also the review of Richards et al. 1983). As with recurrent genital herpes infection, the generally self-limiting, yet variable nature of recurrent orofacial herpes necessitates the use of large, controlled, double-blind studies in the appraisal of a therapeutic agent. As Shaw et al. (1985) point out, such trials are unfortunately difficult to conduct, because so many patients must be recruited, with whom regular contact must be maintained for some time thereafter. A further difficulty (Kingsley et al. 1985) is fulfilling the requirement that patients initiate therapy as early as possible after the first signs or symptoms appear. Nevertheless, a few double-blind, placebo-controlled studies have evaluated topical acyclovir treatment in patients with clinically and virologically confirmed recurrent episodes of orofacial herpes simplex (table V). While some symptomatic benefit has resulted from patient-initiated acyclovir therapy, in no case has treatment

of an acute recurrent episode produced an effect on future recurrences.

Unfortunately, perhaps as a result of the difficulty in recruiting patients with initial episodes of orofacial herpes simplex infection, the therapeutic effect of acyclovir on initial vs recurrent outbreaks has not been assessed. However, in a double-blind placebo-controlled trial involving 20 children (mean age, 2 years) with acute herpetic gingivostomatitis (a manifestation of primary orofacial herpes that typically involves children in the first 5 years of life and may cause symptoms severe enough to warrant hospitalisation) pain and hypersalivation ($p < 0.05$), but not the clinical course of lesions, resolved more quickly in the group treated with oral acyclovir 5 (presumably 200mg) tablets daily for 5 days than in the placebo group (Ducoulombier et al. 1988).

As prophylaxis in patients with frequently recurring disease, acyclovir has proven successful in markedly reducing the frequency of occurrence of outbreaks of lesions, when administered in topical (Gibson et al. 1986) and oral form (Thomas et al. 1985), However, studies to date have shown no statistically significant effect with regard to future recurrences.

Acute Recurrent Episodes

The relatively low patient numbers involved in many of the investigations discussed below (table V) places increased importance on adequate comparability of placebo and drug treatment groups. However, only in the studies of Shaw et al. (1985) and Spruance and Crumpacker (1982) were statistical comparisons between acyclovir and placebo groups reported for various variables: age, sex, race and the severity of prior herpetic episodes were not statistically different between groups in the studies. In the remaining trials, treatment groups appeared similar, based on the group comparability data reported.

The results of topical administration of acyclovir for the treatment of recurrent orofacial herpes simplex infection have generally been disappointing. Although various investigations present conflicting conclusions, the drug has produced limited

Table V. Summary of randomised, double-blind studies comparing topical acyclovir (A) with placebo (P) in patients experiencing episodes of recurrent orofacial herpes simplex infection

Reference	No. of patients (no. of episodes analysed)	Annual frequency of episodes pretreatment	Formulation and no. of daily applications for 5 days	Duration of symptoms pretreatment (h)	Results: A vs P[b]				
					max. lesion virus titre (log$_{10}$ PFU)	pain duration (days)	abortive lesions (%)[c]	time to ulcer/ crust formation (days)	time to complete healing (days)
Acyclovir Ointment									
Fiddian & Ivanyi (1983)[a]	13 (31)	≥ 2; median = 10	5% × 5	Not reported			40 vs 14	3* vs 4	6** vs 8
Spruance & Crumpacker (1982)	208 (208)	Not reported	5% × 4	≤ 25 (all patients) ≤ 8 (n = 108)	3.2 vs 3.5 3.1 vs 4.1*	2.5 vs 2.6 2.2 vs 2.4		7.2 vs 7.3 7.0 vs 6.7	7.8 vs 7.3 7.8 vs 7.1
Spruance et al. (1984a)	69 (69)	≥ 3	10% × 8	≤ 7.0 (A); ≤ 16.7 (P)	4.8 vs 4.5	2.0 vs 2.3	9 vs 25		6.0 vs 5.2
Acyclovir cream									
Fiddian et al. (1983b)[a]	49 (74)	Median = 3	5% × 5	4 (A) 1 (P) (medians)			26 vs 10	1** vs 2	4** vs 6
Van Vloten et al. (1983)[a]	30 (60)	Mean = 6 to 7	5% × 5	≤ 12 (all patients)		1.7 vs 1.7		2.0 vs 2.1	5.4*d vs 6.6
Shaw et al. (1985)[a,e]	45 (72)	≥ 3; mean = 5	5% × 5	4.9 (A) 4.4 (P) (means)				2 vs 2	9 vs 10

a   Some patients were re-randomised to treatment after their first study episode.

b   * p < 0.05; ** p < 0.01; PFU = plaque-forming units.

c   Lesions not progressing beyond the papule stage.

d   Duration of vesiculation was also significantly lower in acyclovir-treated episodes (1.8 vs 2.7 days, p < 0.05).

e   Crossover study design.

clinical benefit and studies reporting statistically significant reductions in parameters such as time to healing show a shortening in symptom duration of just 1 to 2 days (table V).

In a large multicentre trial of acyclovir 5% ointment in recurrent labial herpes sufferers, Spruance and Crumpacker (1982) found a significant ($p < 0.05$) antiviral effect (as assessed by the reduction in maximum lesion viral shedding after 1 day of treatment) only in the subgroup of acyclovir-treated patients who were seen within 8 hours of lesion onset. However, no such differences from placebo occurred in the clinical measurements (table V). Similarly discouraging results were obtained by these investigators in a further double-blind investigation involving 69 patients who initiated treatment themselves with 10% acyclovir ointment during the prodromal or erythematous stage. The authors concluded inadequate penetration of drug from the polyethylene glycol vehicle to be the most likely reason for the lack of clinical effect. In contrast, a well-controlled but small study of patients with more frequent, severe episodes noted a significant reduction in time to crusting ($p < 0.05$) and in healing time ($p < 0.01$) when therapy was initiated during the prodromal phase (Fiddian & Ivanyi 1983).

Presumably as a result of increased drug delivery to mucocutaneous tissues, modification of the polyethylene glycol ointment vehicle to produce a modified aqueous cream formulation has improved the efficacy of topical acyclovir. Placebo-controlled, double-blind studies involving acyclovir 5% cream applied 5 times daily have generally found a trend towards a better clinical effect with the active formulation, although as noted in table V absolute reductions in symptom duration are small relative to the duration of a recurrent episode. The failure of patients to apply the cream early enough in the episode and a lack of patient numbers (such that studies have lacked the power to reveal treatment differences) have been suggested as possible reasons for the low efficacy to date (Gibson et al. 1986).

Shaw et al. (1985) proposed that the results of their own and an earlier study (Van Vloten et al.

1983) suggest a possible therapeutic effect attributable to the 40% polyethylene glycol base used in the cream formulation, which would have contributed to the difficulty of showing a statistically significant difference in antiviral efficacy between acyclovir and placebo treatments.

By analogy with genital herpes simplex infection, oral treatment of acute episodes of recurrent orofacial herpes simplex infection would be expected to be superior provided adequate tissue concentrations could be achieved within the first few hours after the appearance of signs or symptoms, but this has yet to be convincingly demonstrated in large patient populations (Raborn et al. 1987).

Prophylaxis

In contrast to acute topical treatment, prophylaxis against recurrent orofacial herpetic disease with 5% acyclovir cream and, to a greater extent, with oral acyclovir in small numbers of patients has ameliorated the severity of clinical disease during treatment.

Acyclovir 5% cream has been evaluated as a prophylaxis for recurrent herpes labialis in a small placebo-controlled crossover trial (Gibson et al. 1986). Over the 16 weeks of acyclovir prophylaxis, patients with a history of frequent attacks suffered from significantly fewer days with any symptom ($p < 0.001$) or cold sores ($p < 0.01$) than during 16 weeks of placebo administration (12.2 vs 17.4 and 9.5 vs 12.4, respectively). The reduction in mean number of physician-confirmed recurrences during active treatment was less marked, at 0.5 vs 1.1 ($p < 0.05$).

In a controlled crossover trial, oral acyclovir prophylaxis was effective in suppressing recurrent non-genital herpes simplex infection (Thomas et al. 1985). Only 2 of 11 patients experienced a recurrence while taking acyclovir 200mg 4 times daily for 12 weeks or until first recurrence; 9 of the patients suffered recurrent symptoms during placebo treatment ($p = 0.016$). Of those patients failing to develop lesions, abortive episodes (prodromal symptoms and occasionally erythema) were reported by 5 of 9 with acyclovir vs 1 of 2 with

placebo (not statistically significant), indicating that the dosage employed provided approximately minimal effective tissue concentrations for suppression of lesions.

Prophylactic treatment is likely to be most appropriate in sufferers of frequent and/or severe orofacial episodes, and during exposure to risk factors for precipitation of outbreaks. Oral therapy offers a simpler mode of treatment and a greater ceiling of activity against troublesome recurrences, however the exposure of patients to systemic drug when localised exposure would prove adequate is undesirable. The vexed issue of the emergence of viral resistance to acyclovir with long term use dictates caution in its use, although investigators appear to be well aware of the importance of measuring the *in vitro* susceptibility of clinical isolates from acyclovir recipients to monitor this hitherto unrealised possibility.

3.1.3 Herpetic Ocular Disease

Superficial Herpetic Keratitis

As reviewed by Richards et al. (1983), the efficacy of a 3% ophthalmic ointment of acyclovir applied 5 times daily for up to 14 days has been established in patients with superficial dendritic corneal ulcers due to herpes simplex virus, including some patients whose ulcers were clinically resistant to vidarabine or idoxuridine. In controlled comparisons, 95 to 100% of dendritic ulcers treated with acyclovir ointment healed in approximately 5 days. Acyclovir was at least as effective as idoxuridine 0.5 and 1% ointments, trifluridine formulated as a 2% ointment, and vidarabine 3% ointment, and healing was more rapid with acyclovir than with the comparative antivirals. Unfortunately, as with other antivirals, acyclovir does not protect patients from subsequent ulceration or stromal changes. The comparative efficacy of acyclovir and vidarabine ointments in the treatment of dendritic corneal ulcers has been confirmed more recently by Genée and Maith (1987) and Jackson et al. (1984).

A few of the controlled comparative studies reviewed by Richards et al. (1983) included patients with the larger, more difficult to treat, geographic ulcers. However, patient numbers were very small, making interpretation of comparative assessments difficult. More recently, Collum et al. (1985a) compared 3% ophthalmic ointments of acyclovir and vidarabine, applied 5 times daily until 3 days after completion of healing, in patients with geographic corneal ulceration. In this double-masked (double-blind) comparison, 25 patients were randomised to treatment with acyclovir and 26 to treatment with vidarabine; there were no statistically significant differences between the patient groups in age, duration or severity of symptoms (including involvement of the deeper structures of the eye), history of previous attacks or previous therapy of the present attack. However, the acyclovir group had a significantly ($p < 0.05$) higher proportion of patients with large ulcers. Two patients receiving vidarabine and 1 patient receiving acyclovir were withdrawn due to treatment failure. Lesions in all remaining patients healed in mean times of 12.2 days (acyclovir) and 11.0 days (vidarabine) [$p = 0.62$]. Neither ulcer size nor previous steroid therapy influenced healing times, and it was established by separate analysis that the inclusion of patients who had received antiviral treatment immediately prior to study entry did not prejudice the results.

The combination of acyclovir 3% ophthalmic ointment applied 5 times daily with a once-daily ophthalmic application of human α-interferon (leucocyte or recombinant) has been reported to be statistically superior to acyclovir ophthalmic ointment alone in randomised placebo-controlled double-masked studies in patients with superficial herpetic keratitis, including dendritic, large dendritic and geographic ulcers (table VI; fig. 7). Unfortunately the use of interferon treatment alone was not evaluated in these studies. De Koning et al. (1983) excluded patients with evidence of stromal keratitis and noted that the resulting patient groups were similar as to sex, age, duration of symptoms pretreatment and ulcer size. Similarly, Colin et al. (1983) excluded patients with stromal keratitis. However, some prognostic factors linked to a slower rate of healing of herpetic keratitis did not appear to be evenly distributed between the

Table VI. Double-masked randomised studies comparing the efficacy of acyclovir 3% ophthalmic ointment (A) applied 5 times daily in combination with placebo *versus* in combination with human interferon (IFN) in patients with superficial herpetic keratitis

Reference	Diagnosis	Drug regimen	No. of patients	Mean time to healing (days)	
Colin et al. (1983)	Dendritic keratitis	3% A plus human leucocyte IFN 30 × 10^6 IU/ml[a]	24	3.9	p < 0.01
		3% A plus placebo	21	7.0	
de Koning et al. (1983)	Superficial herpetic keratitis (dendritic or geographic)	3% A plus buffy coat human leucocyte IFNα 30 × 10^{6}IU/ml[a]	25	5.8	p < 0.01
		3% A plus placebo	26	9.3	
Meurs & van Bijsterveld (1985)	Acute, uncomplicated, superficial herpetic keratitis	3% A plus recombinant human 2 arg IFNα 1.5-3.0 IU/day	48	5.7	Statistically significant[b]
		3% A plus placebo	45	8.6	

a Daily dosage of interferon was 1 drop (Colin et al. 1983) and 2 drops (de Koning et al. 1983).
b Parameter not specified.

groups in this study; the acyclovir plus interferon group had less patients who had had symptoms for more than a week (21% *vs* 33%) and who were older than 50 years (41% *vs* 57%), and more patients with ulcers greater than 7mm^2 (50% *vs* 29%). Exclusion criteria and group comparability were not reported by Meurs and van Bijsterveld (1985). In these 3 studies, mean times to complete healing ranged from 7 to 9.3 days with acyclovir plus placebo, but were reduced to only 3.9 to 5.8 days with the combination of acyclovir plus interferon. Results for a small number of geographic ulcers were also analysed separately by de Koning et al. (1983); 2 of 11 ulcers (18%) showed no healing within 14 days, but the 5 remaining acyclovir plus interferon-treated ulcers healed in a mean time of 6.8 days, while the 4 remaining acyclovir plus placebo-treated ulcers healed in a mean time of 10.7 days. Thus, the combination of acyclovir ophthalmic ointment plus α-interferon appears to be a useful addition to the treatment of superficial herpetic keratitis.

Orally administered acyclovir has also been assessed in the treatment of superficial herpetic keratitis. A randomised placebo-controlled double-masked comparison of oral acyclovir 400mg and acyclovir ophthalmic ointment, each administered 5 times daily, resulted in identical mean rates of

healing of dendritic ulcers in the 2 treatment groups (5.6 days) [Collum et al. 1985b]. All 14 patients treated with acyclovir ointment and 14 of 15 treated with oral acyclovir healed, suggesting that oral acyclovir may be an effective alternative to topical
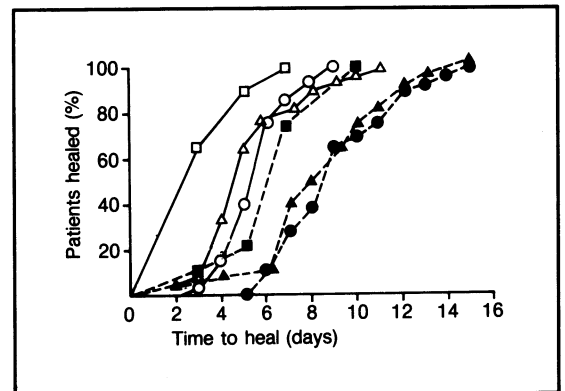
Fig. 7. Cumulative percentage of patients with superficial herpetic keratitis healed with acyclovir 3% ophthalmic ointment applied 5 times daily in combination with placebo in 26 (●, de Koning et al. 1983), 21 (■, Colin et al. 1983) and 45 patients (▲, Meurs & Bijsterveld 1985), in combination with recombinant human alpha 2 arg interferon in 48 patients (△, Meurs & Bijsterveld 1985), in combination with buffy coat human leucocyte alpha interferon in 26 patients (○, de Koning et al. 1983) and in combination with human leucocyte interferon in 21 patients (□, Colin et al. 1983).

therapy in the management of superficial herpetic dendritic corneal ulceration. In contrast, Hung et al. (1984a) reported that only 10 of 15 patients (67%) randomised to therapy with oral acyclovir 400mg 5 times daily for 7 days, preceded by mechanical debridement, experienced healing, versus 6 of 14 (43%) treated with mechanical debridement plus placebo, a difference which did not attain statistical significance. The disappointing efficacy rate associated with oral acyclovir in the latter study is difficult to explain, but tear drug levels were not measured. Using an identical dosage, Collum et al. (1985b) determined a mean tear fluid concentration of 0.64 μmol/L, which approaches the top of the range of herpes simplex type 1 50% inhibitory concentrations (section 1.1.1). The short duration of therapy (7 days) employed by Hung et al. (1984a) may better explain the lower efficacy rate observed.

Stromal Disease

Often, superficial herpetic keratitis progresses, to produce inflammation of the deeper corneal stroma as the epithelium heals (disciform keratitis); this complication may subsequently recur, without the ulcer formation, causing a painful red eye with a hazy cornea (Glasspool 1982). Disciform keratitis may be an immunologically mediated disease resulting from the presence of viral antigen, rather than due to viral proliferation within the stroma (Jackson et al. 1984). In contrast, necrotising stromal keratitis is a stromal complication that occurs in association with a corneal ulcer.

As reported by Richards et al. (1983), encouraging results were obtained in non-controlled studies in a few patients with herpetic stromal disease treated topically with acyclovir, usually administered in combination with concomitant corticosteroids. In contrast, neither acyclovir 3% ophthalmic ointment nor oral acyclovir 400mg, administered 5 times daily without concomitant corticosteroid therapy, proved effective in the treatment of stromal herpetic disease; no patients were healed and only 5 of 12 patients with disciform keratitis and 1 of 5 patients with necrotising stromal keratitis showed improvement (Sanitato et al.

1984). In a double-masked comparison, acyclovir 3% ointment applied 5 times daily was more successful in treating herpetic disciform keratitis when administered concomitantly with a local corticosteroid (betamethasone 0.1% drops) than when given on its own. Lesions healed in all 21 patients receiving the combined therapy and did so at a faster rate (p < 0.004) than in the 11 of 19 patients healed with acyclovir plus placebo (Collum & Logan 1982; Collum et al. 1983).

Conflicting results have been reported in comparisons with other antiviral medications. In a double-masked study in patients with herpetic keratitis, results were also analysed for the small subgroup of patients having undefined stromal involvement; healing was reported in 7 of 8 patients treated with acyclovir 3% ophthalmic ointment 5 times daily, without concomitant corticosteroids, but only 4 of 10 patients treated with idoxuridine 0.5% ophthalmic ointment were cured and the healing rate was significantly (p < 0.025) less rapid than with acyclovir (Klauber & Ottovay 1982). In contrast, in a second randomised double-masked study, neither acyclovir nor trifluridine ophthalmic ointments, administered without concomitant corticosteroids, were effective in the treatment of stromal (disciform or necrotising) keratitis, only 1 of a total of 8 patients experiencing resolution (Behrens-Baumann et al. 1986). However, when betamethasone 0.01% ophthalmic drops were administered 5 times daily, concomitantly with ophthalmic acyclovir or ophthalmic vidarabine in a double-masked randomised comparison in disciform keratitis, efficacy was noted in both treatment groups (Collum & Grant 1987). In the latter study, patients who had had corneal ulceration within the previous 6 weeks were excluded, as were those who had utilised local corticosteroids during the previous 6 months; the resulting groups showed no statistical or clinical differences in age, sex, duration of symptoms, history of previous attacks or the presence of cutaneous herpes on entry. 13 of 15 (86.7%) patients administered acyclovir healed *versus* 10 of 13 (76.9%) administered vidarabine (p = 0.64), with no statistically significant difference between the groups in time to healing (22.5 and

26.7 days, respectively) or time to resolution of signs and symptoms. Six vidarabine recipients developed superficial punctate keratopathy, a side effect not present in the acyclovir treatment group (p = 0.02).

Keratouveitis

Acyclovir 3% ophthalmic ointment applied 5 times daily has been compared with trifluridine 1% ophthalmic solution instilled 6 times daily in a non-randomised unmasked study in 37 patients with herpetic keratouveitis (Hoang-Xuan et al. 1984). The 2 treatment groups were statistically comparable as to sex, age, history of ocular herpes, presence of corneal ulceration, duration of symptoms prior to treatment, treatment of previous episodes, and previous treatment of the present episode. Corticosteroid therapy (usually local injection of dexamethasone) was withheld as long as the degree of inflammation permitted. 19 of 21 patients (90.5%) administered acyclovir alone (5 patients) or in combination with corticosteroid therapy were healed, as were 10 of 16 (62.5%) administered trifluridine alone (1 patient) or in combination, a difference which did not attain statistical significance. While there was also no significant difference (p > 0.05) between the treatment groups in the number of corneal ulcers healed (17 of 18 acyclovir-treated vs 10 of 11 trifluridine-treated), the mean time to healing was significantly (p < 0.05) shorter in the trifluridine group (4 days) than the acyclovir group (7.6 days). Prognostic indicators included the duration of symptoms prior to inclusion in the study and the use of corticosteroids during this period; the mean duration of symptoms was significantly (p < 0.05) shorter (38 days) and the percentage of patients utilising corticosteroids during this period was significantly (p < 0.05) smaller (17%) among the 29 patients who were healed than among the 8 treatment failures (98 days and 62.5%, respectively). A similarly significant relationship (p < 0.05) was evident between the 21 patients in whom the disease did not recur within a year (27 days and 5%, respectively) and in the 8 in whom the disease did recur (65 days and 50%, respectively).

Recent evidence indicates systemic acyclovir to be a promising adjunct to the management of herpetic uveal or stromal disease. Oral acyclovir (200mg 5 times daily) for 2 to 3 weeks consistently produced both subjective and objective improvement of disease in a retrospective trial of 20 patients with active herpetic keratouveitis or stromal keratitis, usually accompanied by herpetic epithelial disease (Schwab 1988). 16 of these patients were receiving topical corticosteroid therapy when acyclovir was started, and in most the antiviral facilitated a substantial tapering of steroid dosage. When acyclovir dosage was gradually lowered, immediate recurrence of disease was seen in only 1 patient (keratouveitis). Of 12 study subjects who were adequately followed during maintenance therapy with a lower, prophylactic acyclovir dose, there were recurrences in 3 after stopping the drug, while 9 patients remained recurrence free for treatment periods of 3 to 17 months. Several of these had had multiple recurrences before acyclovir therapy. Nevertheless, as noted by Cobo (1988), the implications of these data are modified by the fact that 19 of 20 subjects had concomitant epithelial ocular herpetic disease, which is not typical of keratouveitis. Since acyclovir is known to be effective in herpetic epithelial keratitis (see above), the improvement in deeper ocular symptoms reported may have been partly the result of resolution of steroid-enhanced epithelial infection. In the absence of larger studies, though, this anecdotal evidence strongly suggests a reduction in the recurrence rate of ocular infections attributable to oral acyclovir, in patients with recalcitrant herpetic ocular disease.

Acute Retinal Necrosis

Acute retinal necrosis is characterised by the acute onset of uveitis, vitritis, and retinal vasculitis and necrosis, leading frequently to retinal detachment and visual loss (Urayama et al. 1971). Previously attributed to herpes zoster (Culbertson et al. 1986), the disorder now appears to be caused by herpes simplex (D. Pavan-Langston, personal communication). There is a paucity of firm evidence nevertheless, and no consensus about the aetiology, which has also been attributed to vasculitis

of unknown aetiology (Hirst et al. 1987). Case reports in 4 patients (6 eyes) record the successful use of intravenous acyclovir (Hirst et al. 1987) or intravenous acyclovir plus vitrectomy, intravitreal infusion of acyclovir and prophylactic scleral buckling procedures (Peyman et al. 1984) along with traditional medical management of this condition.

3.1.4 Encephalitis and Disseminated Infection

Occasionally herpes simplex infection can manifest systemically in patients normally considered to be immunologically competent. Systemic disease can be characterised by encephalitis, or by widespread (disseminated) mucocutaneous involvement and/or spread to visceral organs (e.g. hepatitis, pneumonitis). The presence of atopic eczema predisposes to dissemination, as does pregnancy (particularly the third trimester). In addition, neonates are highly susceptible to the development of systemic infection.

Encephalitis

Herpes simplex encephalitis is a devastating infection, the natural history of which reveals a mortality of approximately 70% and disabilities in most survivors (Whitley 1988) as a result of progressive cerebral necrosis and consequent oedema produced by viral replication. Large collaborative studies from Sweden (Sköldenberg et al. 1984) and North America (Whitley et al. 1986a) have established intravenous acyclovir 10 mg/kg 8-hourly administered for at least 10 days to be the treatment of choice for biopsy-proven herpes simplex encephalitis.

In a randomised, controlled comparison of 51 evaluable patients with herpes simplex encephalitis, mortality was 19% after 12 months in 27 acyclovir-treated patients but 50% in 24 patients who received vidarabine 15 mg/kg/day for 10 days (p = 0.04); 56% of acyclovir recipients had no, or mild, sequelae compared with 13% in the vidarabine group (p = 0.002) [Sköldenberg et al. 1984]. Improvement in outcome was especially striking in patients who were semicomatose or comatose at entry: 40% of the acyclovir group but none of the
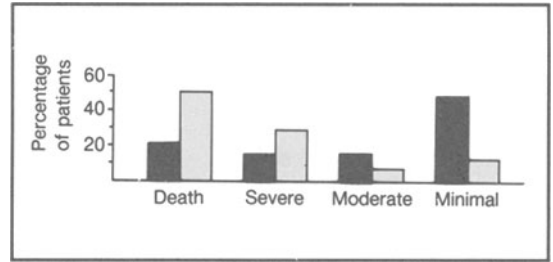
Fig. 8. Frequency of mortality and severe, moderate and minimal sequelae after 12 months in 51 patients with confirmed herpes simplex virus encephalitis treated with acyclovir 10 mg/kg 8-hourly (■) or vidarabine 15 mg/kg/day (▢) for 10 days (after Sköldenberg et al. 1984).

vidarabine recipients in this category survived with minimal sequelae (figs 8 and 9).

Very similar findings to those of Sköldenberg et al. (1984) were later reported by Whitley et al. (1986a) who studied 68 patients with biopsy-proven disease. Overall survival rates for acyclovir and vidarabine recipients were 69% and 46%, respectively (p = 0.008). Fewer than 15% of vidarabine-treated patients recovered to near normality as against 38% of the acyclovir group. However, the prognosis for useful survival among elderly or comatose patients was bleak whatever the drug administered.

It has been established that early diagnosis and treatment are necessary to obtain the best outcome in herpes simplex infections of the CNS (Whitley et al. 1986a), but there remains debate regarding the most appropriate methods to be used in establishing a diagnosis (Whitley et al. 1985b). The optimal dosage or duration of acyclovir therapy also awaits definition. Recent reports of patient deterioration due to rapid reappearance of acyclovir-susceptible virus following treatment with the drug suggest a longer duration of acyclovir therapy (e.g. 14 to 21 days) should be considered in this condition (Gulliford et al. 1987; VanLandingham et al. 1988).

Disseminated Infection

A single case study reported the successful treatment, with parenteral acyclovir 5 mg/kg 8-hourly, of disseminated herpes simplex infection accom-

**Fig. 9.** Influence of level of consciousness (■ = lethargy, □ = semicoma or coma) at the start of treatment on the frequency of mortality and severe, moderate and minimal sequelae after 12 months in 51 patients with confirmed herpes simplex virus encaphalitis treated with acyclovir 10 mg/kg 8-hourly (A) or vidarabine 15 mg/kg/day (V) for 10 days (after Sköldenberg et al. 1984).
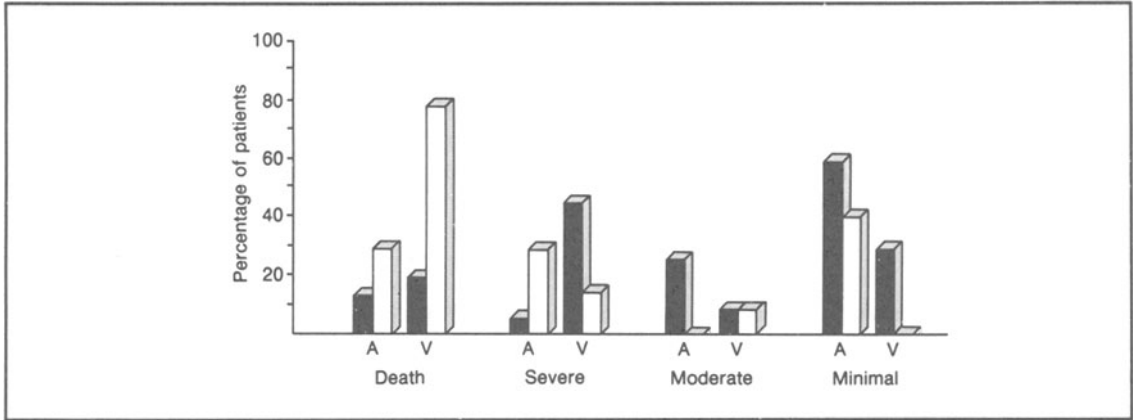
panied by hepatitis in a previously healthy 19-year-old non-pregnant woman (Baxter et al. 1986). Several case studies have reported the successful treatment with intravenous or oral acyclovir of severe mucocutaneously disseminated primary eczema herpeticum in infants (Jawitz et al. 1985; Taieb et al. 1985), young children (David & Longson 1985) and adults (Robinson et al. 1984) having a pre-existing diagnosis of atopic eczema. Similarly, a patient with severe mucocutaneously disseminated primary eczema herpeticum complicating Darier's disease, another skin disorder associated with eczema herpeticum, responded within 24 hours of the initiation of oral acyclovir 200mg 5 times daily (Parham et al. 1985). More recently a multicentre, double-blind investigation in 60 patients with eczema herpeticum found acyclovir 200mg 5 times daily to be superior to placebo in efficacy rate (81.3 vs 42.9%; p < 0.01) [Niimura & Nishikawa 1988].

Encephalitis and Disseminated Infection of Pregnancy

Several case studies in otherwise normal third-trimester gravidas have reported the use of intravenous acyclovir 5 to 10 mg/kg 8-hourly in disseminated herpes simplex infections manifested as widespread mucocutaneous infection alone (Cox et al. 1986; Grover et al. 1985) or complicated by hepatitis (Lagrew et al. 1984), or in herpes simplex encephalitis (Berger et al. 1986). A rapid resolution of the 3 disseminated infections followed the initiation of acyclovir therapy; in all instances healthy infants were delivered by caesarean section, the infants demonstrating neither complications attributable to acyclovir nor evidence of herpesvirus infection during follow-ups ranging from 6 to 12 months. In contrast, the woman with herpesvirus (type 2) encephalitis delivered by caesarean section an infant with herpes neonatum in whose serum (measured 10 hours after birth) acyclovir was not measurable despite delivery occurring immediately following 5 days' therapy with acyclovir; the mother, who was described as having been in good health prior to the encephalitis, but is stated nonetheless to have been receiving prolonged administration of a corticosteroid (for an unreported diagnosis), died 2 days after delivery, having also received an unsuccessful 8-day course of vidarabine 2g daily. The infant recovered following 5 days' administration of intravenous acyclovir 5 mg/kg 8-hourly for 10 days.

An additional case study reported the successful treatment, with intravenous acyclovir 400mg 6-

hourly, of third-trimester disseminated herpes simplex infection with hepatitis in an immunocompromised gravida (7 years' history of systemic lupus erythematosus, maintained with prednisone 35mg daily). A normal infant who manifested no evidence of herpes infection was delivered vaginally (Chazotte et al. 1987).

The survival, without complications, of all mothers and infants in these 4 reported cases of disseminated herpes simplex infection (2 of which manifested as hepatitis) is in sharp contrast to the results reviewed by Cox et al. (1986) in which vidarabine (1 of 3 mothers and all 3 infants died) or no treatment, supportive measures or antibiotics (5 of 8 mothers and 4 of 8 infants died) were utilised in the treatment of disseminated herpes simplex infection manifested as hepatitis.

It remains difficult to draw conclusions concerning the use of acyclovir in herpes simplex encephalitis of pregnancy, given the sole unsuccessful case reported to date in a patient whose situation may have been complicated by an underlying immunosuppression due to corticosteroid therapy. There is also a paucity of data on comparative antiviral treatments in herpes simplex encephalitis of pregnancy, the sole gravida reported to have been treated with idoxuridine also dying (the infant survived) while both a mother and infant survived following vidarabine treatment (Cox et al. 1986).

Encephalitis and Disseminated Infection in Neonates

Herpes simplex infections in neonates can be manifested as localised skin, eye and mouth involvement only, or severe disease characterised by encephalitis or disseminated disease with visceral organ involvement (e.g. hepatitis). Since the early 1970s the National Institute of Allergy and Infectious Diseases in the United States has conducted a series of studies in babies with neonatal herpes simplex virus infection: comparing vidarabine with placebo; assessing high-dose vidarabine therapy in a non-comparative analysis; and comparing vidarabine with acyclovir (Whitley et al. 1985a). Infants with localised involvement do well regardless of the therapeutic modality, although if untreated, 75%

of these infections will disseminate internally. However, in those with severe disease vidarabine 15 or 30 mg/kg daily for 10 days reduced mortality (to approximately 40% from a value of 74% with placebo) and morbidity was similarly reduced. The preliminary analysis of the data in the vidarabine versus acyclovir comparative study indicates that these 2 antivirals are comparable in efficacy in the treatment of neonatal herpes (Whitley et al. 1985a, 1986b).

The question of antiviral prophylaxis of neonates delivered through a herpesvirus-infected birth canal has not been answered by controlled study. However, it has been suggested that, given the low (approximately 4%) risk of infection in infants of mothers with active recurrent infection, empiric antiviral chemotherapy is not indicated unless additional risk factors are present; cultures of the exposed mucous membranes of all potentially infected infants at 24 to 36 hours after birth may differentiate the presence of actively replicating virus from the situation where contamination was transient. In addition, these neonates should be observed carefully for evidence of the disease (Overall et al. 1984). If the mother has primary genital herpes and if the infant has a significant risk factor, such as prematurity or invasive instrumentation or lacerations, the above authors concluded that it would be appropriate to start antiviral chemotherapy, including ophthalmic prophylaxis, on the second day of life, after obtaining cultures.

3.1.5 Other Conditions

In addition to the above studies in initial genital herpes, a double-blind trial specifically assessed the efficacy of acyclovir in initial rectal herpes simplex (Rompalo et al. 1988). 29 homosexually active men with first episode rectal herpes simplex virus infection were randomised to treatment with oral acyclovir 400mg 5 times daily for 10 days or placebo. Patient groups were comparable as to age and race, and all patients were in general good health, none being diagnosed as having the acquired immunodeficiency syndrome, its related complex, or generalised lymphadenopathy. There was a trend (not statistically significant) to a shorter duration

of symptoms in the acyclovir-treated patients, and the median duration of both viral shedding (p < 0.01) and rectal lesions (p < 0.05) was significantly shorter in the acyclovir recipients than in the placebo recipients. However, the mean number of days from onset of symptoms to enrolment was 6.1 days in the acyclovir group *versus* 4.9 days in the placebo group (p = 0.18), a difference for which the test of duration of symptoms, but not duration of viral shedding or rectal lesions, was stated to be adjusted.

Individual case studies have reported the successful treatment of herpes simplex whitlow with intravenous (Schwandt et al. 1987) and oral (Tschen & Baack 1987) acyclovir, the latter in a third-trimester gravida. Prophylaxis of frequently recurring herpetic whitlow in a 30-year-old woman with administration of acyclovir 200mg 3 times daily prevented recurrence for the 6-month duration of prophylaxis; recurrence occurred 3 to 4 days after the end of prophylaxis (Laskin 1985).

Several case studies have reported the prevention of frequently recurring herpes simplex (genitalis, labialis or whitlow)-associated erythema multiforme with oral acyclovir 400 to 1000mg daily administered prophylactically for up to 12 months (Goldberg & Sperber 1986; Green et al. 1985; Lemak et al. 1986; Molin 1987). Results of prophylaxis with the topical formulations (ointment or cream) have been more variable, with both success (Huff 1988; Kennedy et al. 1981) and failure (Fawcett et al. 1983; Molin 1987) being reported.

In an uncontrolled study, 17 couples suffering from longstanding (average 45 months) infertility, totally unexplained except for persistent subacute inflammation of the endometria, were given oral acyclovir 200mg 3 times daily (both husband and wife) for 6 cycles (Kundsin et al. 1987). Five of the original 17 couples dropped out after approximately a month: 2 of these adopted, 2 gave up and 1 couple separated. Of the 12 couples who completed the treatment protocol, 5 women became pregnant, and had successful pregnancies; this in contrast to the past history of spontaneous abortion in 2 of them. No abnormalities of the pregnancy or the offspring have been evident.

3.2 Varicella Zoster Virus Infections

3.2.1 Varicella (Chickenpox)

Little work has been performed to evaluate acyclovir as a treatment for chickenpox, the primary infection caused by varicella zoster virus; in otherwise normal children the disease is not severe enough to warrant therapy (Fiddian et al. 1984). Nevertheless, in poorly nourished children in developing countries and in adults not exposed to infection during childhood, the disease may have serious complications, sometimes with systemic involvement (Fiddian et al. 1984). Al-Nakib et al. (1983) found a 5-day course of intravenous acyclovir (10 mg/kg 8-hourly) to be effective in reducing the duration of vesicle eruption and fever (p < 0.05), but not pain, in a double-blind placebo-controlled study in young adults. Additionally, intravenous acyclovir in dosages of 5 to 10 mg/kg/day for 3 to 5 days led to prompt clinical improvement and the disappearance of skin lesions in 3 neonates who developed congenital varicella 6 hours, 5 days and 8 days, respectively, after delivery (Wirth et al. 1987).

3.2.2 Herpes Zoster

Recrudescence of previous varicella zoster virus infection results in cutaneous expression as zoster, predominantly among the elderly. This disorder is usually dermatomal in distribution and may be associated with severe pain in the acute phase. A number of neurological disorders are associated with zoster, most commonly post-herpetic neuralgia. Central nervous system complications of the cutaneous disorder are relatively rare, but notable among these is herpes zoster-associated encephalitis (Johns & Gress 1987). The aims of treatment are to alleviate the pain during the acute phase, heal the cutaneous manifestations, and prevent the development of post-herpetic neuralgia (McKendrick 1985).

The efficacy of any treatment for acute herpes zoster will be restricted by the self-limiting nature of the disease. Thus, when administration of oral acyclovir occurred within 48 to 72 hours of the onset of rash, modification of the disease course and

pain relief produced by the drug was maximised (Cobo et al. 1985, 1986; Finn & Smith 1984; McKendrick et al. 1986; Wood et al. 1988).

As described below, variability of the bioavailability of the oral formulation of acyclovir may limit the achievement of therapeutically effective tissue concentrations for the treatment of zoster. According to Whiteman et al. (1982) acyclovir 800mg 4-hourly by mouth produces mean steady-state peak and trough drug concentrations of 1.7 and 1.0 mg/L, respectively, and thus appears to be more rational than lower-dose oral regimens, based on the median effective acyclovir dose (ED_{50}) for most strains of varicella zoster virus.

Intravenous Acyclovir

Intravenous acyclovir administered 3 times daily for 5 days has been shown to attenuate the development of rash and acute pain in zoster in several double-blind placebo-controlled studies, and appears to afford some protection against ocular involvement in patients with trigeminal zoster (table VII). Patient groups were statistically similar with regard to sex, age, affected dermatomes, presence of fever, and duration of rash and pain prior to admission. However, Bean et al. (1982) reported a higher percentage of women (13 vs 3) and a lower proportion of patients with virologically proven zoster at the study outset (74 vs 90%) among those treated with the drug. In the study of van den Broek et al. (1984) 10 acyclovir recipients but only 5 placebo patients had zoster localised in the trigeminal nerve. This latter disparity may have influenced the study outcome since, compared with other subjects, those with trigeminal zoster experienced less pain on study day 4 (p = 0.04), earlier disappearance of papules (p = 0.002) and faster healing and crusting (p = 0.02). Nonetheless, compared with earlier investigations, van den Broek et al. (1984) found limited clinical efficacy with acyclovir, as evidenced by a lack of statistically significant effects on healing of pretreatment lesions and new lesion formation; patients with severe pain or those with trigeminal involvement appeared to benefit the most from acyclovir therapy.

Unfortunately, in the above studies the incidence of post-herpetic neuralgia was similar in patients receiving intravenous acyclovir or placebo. Significant reductions in pain severity associated with acyclovir treatment were generally limited to the period of drug administration, such that recurrence or worsening of pain frequently occurred at the conclusion of treatment.

Oral Acyclovir

In recent years the oral formulation of acyclovir has become more widely available and has undergone clinical trials in outpatients suffering from acute zoster infections (Finn & Smith 1984; Peterslund et al. 1984; see also table VII).

In a Danish double-blind study involving 40 elderly patients with a maximum prodromal history of 96 hours, similar results were obtained with intravenous (5 mg/kg 8-hourly) and oral (400mg 5 times daily) acyclovir, with respect to pain duration and rate of healing; mean vesicular acyclovir concentration sampled after oral administration was deemed to be satisfactory, at 1.2 mg/L (Peterslund et al. 1984). However, the same oral acyclovir regimen (400mg 5 times daily) produced only modest clinical benefit when compared with placebo, when prodromal history exceeded 96 hours in 48% of placebo recipients and 67% of acyclovir recipients (McKendrick et al. 1984) [table VII]. In addition, Peterslund et al. (1984) studied patients of greater mean age than McKendrick et al. (1984) [75 vs 69 years], which may have improved the efficacy of acyclovir treatment.

It was suggested that, in view of the wide individual variation in the bioavailability of orally administered acyclovir, a regimen of 400mg 5 times daily was not consistently achieving adequate plasma drug concentrations (McKendrick et al. 1984). Thus, this group conducted a multicentre controlled investigation of acyclovir administered at a dosage of 800mg 5 times daily for 7 days, among 205 elderly patients in the United Kingdom. As seen in table VII, statistically significant reductions in the times to arrest of new lesion formation, loss of vesicles and full crusting occurred in those patients who received acyclovir within 2 days of the onset of rash. Additionally, a significant

Table VII. Summary of randomised, double-blind studies comparing systemically administered acyclovir (A) with placebo (P) in immunocompetent patients with acute herpes zoster infection

Reference	No. of patients		Daily dosage (duration)	Max. pre-treatment rash duration (days)	Results: A vs P[a]						complications
	A	P			crusting time (d)	time to loss of vesicles (d)	duration of new lesion formation (d)	healing time (d)	pain severity during treatment	incidence of post-herpetic neuralgia (%) [follow-up]	
Intravenous acyclovir therapy											
Bean et al. (1982)	19	10	500 mg/m² × 3 (5d)	3	2 vs 2	NR	2* vs 4	7**,b,c vs 14	A < P	37 vs 60 [1 month] 32 vs 50 [2 months]	Post-treatment worsening or recurrence of pain: 6 of 17 vs 2 of 5 pts
Juel-Jensen et al. (1983)	20	20	10 mg/kg × 3 (5d)	3	A = P	NR	A = P	A = P	A ≤ P	A = P [5 months]	Ocular complications in pts with trigeminal zoster: 0 of 6 vs 3 of 4
McGill et al. (1983a)	17	20	5 mg/kg × 3 (5d)	4	3** vs 5	3.0*** vs 4.5	0**** vs 2	NR	A ≤ P	13 vs 26 [3 months]	Ocular involvement requiring topical steroid therapy in pts with trigeminal zoster: 6 of 8 vs 10 of 10
Peterslund et al. (1981)	27	29	5 mg/kg × 3 (5d)	2.0 (A); 2.3 (P) [means]	A^d < P	A^d < P	NR	A ≪ P	A^d,e < P (duration)	A = P [1 and 2 months]	
van den Broek et al. (1984)	26	24	10 mg/kg × 3 (5d)	3	A = P	NR	2.8 vs 3.4	A = P	A < P	NR	Keratitis in pts with trigeminal zoster: 0 of 10 vs 2 of 5

Oral acyclovir therapy										
Huff et al. (1988)[f]	38	19	400mg × 5 (10d)	} 3	A = P[g]	A = P	9 vs 10[b]	A = P	A = P [6 months]	
	91	91	800mg × 5 (10d)		3.3**** vs 4.8[g]	A ≪ P	7.1**** vs 9.6[b]	A < P	A < P [6 months]	
McKendrick et al. (1984)	18	23	400mg × 5 (5d)	3	5.2 vs 7.4	6.9 vs 6.8	1.2* vs 2.0	A = P	A P	17 vs 22 [6 months]
McKendrick et al. (1986)[h]	100	103	800mg × 5 (7d)	2	7.8* vs 10.0	6.4**** vs 8.2	1.7*** vs 2.2	NR	A ≪ P (all pts)	NR
				2 to 3	5.2 vs 5.5	0.9 vs 1.3				
Wood et al. (1988)[f,h]	181	183	800mg × 5 (7d)	3	8.4* vs 10.1	6.2** vs 7.4	1.4** vs 1.9	A < P	A < P	A = P [6 months]

a   = indicates similar results for both groups; ≤ indicates a non-statistically significant tendency; < indicates $p < 0.05$ or an undefined statistically significant difference from placebo; * indicates $p < 0.05$; ≪ and ** indicate $p \leq 0.01$; *** indicates $p \leq 0.005$; ≪≪ and **** indicate $p \leq 0.001$; NR = not reported.

b   50% healing time.

c   Acyclovir recipients experienced significantly faster cutaneous ($p = 0.03$) and clinical ($p = 0.004$) improvement.

d   p value not reported.

e   Especially responsive to acyclovir therapy were patients with fever of at least 2 days' duration, patients older than 67 years, and those with pain duration of less than 4 days pretreatment.

f   Multicentre study.

g   50% scabbing time.

h   Patients were 60 years and older.

reduction in pain during treatment was found with acyclovir (*vs* placebo); of the 25 patients with severe pain on entry who received acyclovir, 10 (40%) had no or only mild pain at the completion of treatment, whereas all placebo recipients remained in moderate or severe pain (p < 0.001). These findings have been confirmed more recently in large, well controlled investigations employing this higher oral dose (Huff et al. 1988; Wood et al. 1988). Using a treatment period of 10 days and more sensitive methods for measuring pain than previously employed, Huff et al. (1988) demonstrated a reduction in the overall frequency of post-herpetic neuralgia in acyclovir recipients, who achieved even more statistically significant benefits when the frequency of chronic pain over the 6-month study period was assessed. Studies to date indicate that acyclovir 800mg 5 times daily is superior to a regimen of 400mg 5 times daily in the acute therapy of herpes zoster, the higher dosage producing more rapid improvement in the virological, cutaneous and pain parameters of the disease.

The benefits of early initiation of oral acyclovir treatment in acute herpes zoster are further evidenced by a small report of 10 individuals aged 42 to 85 years who received a 5-day course of acyclovir 200mg 5 times daily in non-blind fashion and 6 untreated controls who appeared comparable with regard to demographic and clinical parameters (Finn & Smith 1984). Only in the 5 acyclovir recipients who received treatment within 24 hours of the onset of rash was the rash arrested at the papule stage, to later resolve within 10 days. The stage of the infectious process at which acyclovir therapy is begun thus appears to be an important determinant of its benefit in acute herpes zoster, with early intervention (preferably at the occurrence of prelesion pain) being highly desirable.

A 10-day course of acyclovir 600mg 5 times daily was assessed in a well-reported double-blind, placebo-controlled multicentre investigation involving 71 patients with ophthalmic zoster who presented within 1 week of skin eruption (Cobo et al. 1985, 1986). Study subjects were well matched statistically, although there were more females in the acyclovir-treated group (23 of 36) than in the placebo-treated group (14 of 35). Acyclovir treatment led to a more prompt resolution of signs and symptoms, notably in patients treated within 72 hours of the appearance of skin rash (p < 0.05), and reduced the duration of viral shedding from a median of 4.8 days in the placebo-treated group to 0.7 days (p = 0.02). However, some of the findings pointed to only a marginal antiviral effect from this dosage; in some acyclovir-treated patients viral shedding persisted for as long as 14 days, while new skin lesions occurred in 28% and viral dissemination in 5.6% of acyclovir recipients. Long term follow-up indicated no clear effect of the drug on the incidence of post-herpetic neuralgia.

3.2.3 Zoster Ophthalmicus

Herpes zoster ophthalmicus is a manifestation of varicella zoster infection of the first division of the trigeminal nerve, and accounts for 10 to 25% of initial episodes of the dermatomal disease. An estimated 50 to 72% of patients with herpes zoster ophthalmicus will suffer ocular morbidity, which is frequently chronic and can lead to serious visual impairment (Cobo et al. 1985). In non-comparative studies in the immunocompetent host with ocular involvement, intravenous and 3% ophthalmic ointment formulations of acyclovir appeared to control the ocular signs (McGill & Chapman 1983; see also the review of Richards et al. 1983). In contrast, another uncontrolled study indicated that intravenous administration of 5 mg/kg 3 times daily suppressed the cutaneous rash but was without effect on ocular lesions (McGill et al. 1983a).

A double-masked comparison between acyclovir 3% ophthalmic ointment and topical steroids in 40 patients with keratouveitis caused by herpes zoster indicated acyclovir to be superior to topical steroids alone (McGill & Chapman 1983). The average duration of treatment was significantly longer in the steroid-treated group (280 days *vs* 72 days; p < 0.001), and there was a 63% recurrence rate among steroid recipients (*vs* no recurrences after acyclovir treatment). Corneal epithelial lesions (superficial punctate keratitis or ulceration) resolved significantly more quickly with acyclovir (p

< 0.001), but there was no difference in the stromal, uveal or scleral response between the treatment groups. Steroid treatment was associated with recurrences of keratouveitis which involved parts of the eye not initially infected and were more difficult to resolve than the initial attack. However, a further report from these workers contradicts the above results with respect to the ultimate effect of acyclovir 3% ophthalmic ointment on stromal keratitis and keratouveitis (McGill et al. 1983b).

In contrast to the results with topical use (McGill 1985), Cobo et al. (1985, 1986) found high-dose oral administration of acyclovir to reduce and ameliorate the frequent ocular sequelae of herpes zoster ophthalmicus. As noted above (section 3.2.2), administration of a dose of 600mg 5 times daily for 10 days during an acute attack of zoster led to a more prompt resolution of signs, symptoms and viral shedding *versus* placebo. Further, over 12 months of follow-up, a marked reduction occurred in the incidence of dendritiform keratopathy, stromal keratitis and keratouveitis compared with placebo treatment, leading the authors to recommend systemic acyclovir as a routine treatment in this form of varicella zoster infection.

3.2.4 Other

Several case reports detail successful treatment with intravenous acyclovir 5 to 10 mg/kg 8-hourly of patients with herpes zoster-associated encephalitis (Bowman et al. 1985; Cheesbrough et al. 1985; Ehrensaft & Safani 1985; Nickols et al. 1988; Whyte & Ind 1986), varicella pneumonia (Bryer et al. 1984; Chitkara et al. 1985; Eder et al. 1988) and herpes zoster oticus (Hall & Kerr 1985; Ivarsson et al. 1987). The striking feature among the few patients reported with these conditions was the rapid response to acyclovir therapy.

Clinical resolution of the encephalopathic state usually occurred within 72 hours, whereas the mean duration is approximately 14 days in immunocompetent individuals not receiving acyclovir (Jemsek et al. 1983). The clinical rarity and serious nature of these infections, together with the difficulty of unequivocal diagnosis, seem likely to preclude large, randomised clinical studies of the efficacy of acy-

clovir. However, the results, albeit tentative, are thus far impressive.

3.3 Other Viral Infections

In addition to the herpes simplex and varicella zoster viruses, acyclovir has been assessed in several other infections attributed to viruses. The results of a double-blind comparative study suggest a potential therapeutic benefit with intravenous acyclovir in patients suffering from severe infectious mononucleosis (section 3.3.1); confirmation of these results in a larger well-controlled study will be awaited with interest. As discussed in section 3.3.2, acyclovir alone or administered sequentially with interferon appears to offer little if any clinical benefit in chronic active hepatitis B infection, although a transient reduction in viral replication may occur; the concurrent administration of interferon plus acyclovir may be of benefit and deserves further study.

Several case studies have attributed clinical benefit to systemic acyclovir therapy in cutaneous lymphoproliferative disorders (e.g. mycosis fungoides, lymphomatoid papulosis) which have been theoretically ascribed to known or unknown viruses (Baumgartner et al. 1986; Burg et al. 1986; Scheman et al. 1986).

3.3.1 Epstein-Barr Virus

31 patients with clinical and laboratory diagnosis of infectious mononucleosis, and symptoms severe enough to warrant hospitalisation, were included in a randomised double-blind comparative trial of intravenous acyclovir 10 mg/kg 8-hourly (15 patients) and placebo (16 patients) [Andersson et al. 1985]. Only patients with symptoms not exceeding 7 days were included, and medication (or placebo) was administered for a duration of 7 days. There were no apparent differences between the groups in age, sex, clinical or laboratory parameters, or pretreatment, although a statistical analysis of this data was not provided. The median durations of fever, weight loss, tonsillar swelling and sore throat were shorter in the acyclovir-treated group; while statistical significance was not de-

monstrable for any of these single symptoms, a combination of all these parameters with patient self-assessment of general health gave a significantly (p ≤ 0.01) positive effect for acyclovir. There were no statistically significant differences between the groups concerning effect on lymphadenopathy, or liver or spleen enlargement.

3.3.2 Hepatitis B Virus

Two randomised controlled studies have assessed the efficacy of intravenous acyclovir 45 mg/kg daily for 28 days administered as a continuous infusion (Alexander et al. 1984, 1987) and both a continuous infusion and intermittently at 8-hourly intervals (Guarascio et al. 1986a) in chronic hepatitis patients who were positive for both HBeAg and HBsAg for at least 6 months. Placebo (Guarascio et al. 1986a) and no-treatment (Alexander et al. 1984, 1987) control groups were included; in both studies groups were stratified for sex, liver histology and homosexuality, and appeared comparable for age and clinical and serological evidence of disease. Neither study demonstrated a statistically significant effect on the rate of seroconversion with acyclovir treatment. This lack of efficacy may be partially explained by the results of a series of small non-controlled studies in which Trépo et al. (1986) ascertained that acyclovir efficacy (defined as reduced viral replication or seroconversion) in chronic active hepatitis appeared to be limited to patients with low levels of hepatitis B virus replication pretreatment (DNA-polymerase levels ≤ 80 cpm) administered high dosages of acyclovir (4g daily) for extended periods (4 months).

Combination or sequential therapy with interferon plus acyclovir has also been assessed in chronic hepatitis B. In an uncontrolled study, 10 patients positive for HBeAg and HBsAg for at least 12 months received 5 MU/m² human lymphoblastoid interferon intramuscularly daily for 3 days, followed by 7.5 MU/m² daily for 7 days, then oral acyclovir 800mg 4 times daily for 6 weeks (Guarascio et al. 1986b). There was a significant (p < 0.01) fall in serum DNA polymerase concentration (a measure of viral replication) after 1 week's treatment, which then slowly increased to pretreatment

values over 8 weeks; at 6 months 2 patients had become HBeAg-negative and 1 had developed anti-HBe (seroconversion), but the authors concluded that the effect of oral acyclovir was minimal and that a more effective drug is needed to combine with interferon. In contrast, a small comparative study involving 12 chronic hepatitis B patients (HBeAg-positive for at least 6 months and actively replicating virus) determined a significantly (statistical values not reported) lesser fall in DNA polymerase and HBeAg concentrations during sequential antiviral therapy (1 × month of α-interferon 2.5 MU/m² intramuscularly daily or intravenous acyclovir 15 mg/kg twice daily, with crossover to the alternative medication following a month's washout period) than during subsequent concurrent therapy (same dosages) in 5 of the 12 patients who had experienced persistently active viral replication (Schalm et al. 1985). In the latter study, seroconversion was not reported, although viral replication remained suppressed in 5 of 12 sequentially treated patients (at 6 months after treatment) and in 3 of 5 patients administered the combination (at 1 to 12 months after treatment).

4. Therapeutic Trials in Immunologically Compromised Patients

The potential for severe complication, serious sequelae and the occasional mortality associated with herpesvirus infections in the immunocompromised dictates an extreme need for effective antiviral therapy for this subgroup of patients. As expected in patients with a reduced ability to eradicate viral infection, the effect of systemic acyclovir treatment on virological and clinical parameters is highly significant, compared with placebo, in mucocutaneous herpes simplex infection. Relatively few controlled trials assessing the use of acyclovir in herpes zoster are available; in these studies improvements in clinical and virological parameters of infection were generally of borderline statistical significance at best, however a most encouraging feature of treatment with acyclovir was the reduction in progression or dissemination of zoster.

Prophylactic use of acyclovir in immunocompromised patients at high risk of reactivation of herpesviral infection has been well investigated and found to be extremely successful, such that it is the standard prophylaxis in such patients undergoing events such as bone marrow or renal transplantation, or induction chemotherapy. As with acute therapeutic administration, prophylactic acyclovir was limited in its antiviral effects on herpesviruses other than herpes simplex and varicella zoster.

In addition to the use of acyclovir in the treatment and prophylaxis of herpesvirus infections in immunocompromised patients, the contention that the combination of acyclovir plus zidovudine synergistically inhibited replication of HIV virus in ATH8 cells *in vitro* (Mitsuya et al. 1987) has prompted 2 small clinical studies assessing this combination of antivirals in patients with various manifestations of HIV infection [symptomless antigenaemia (de Wolf et al. 1988) and the acquired immune deficiency syndrome (AIDS) or AIDS-related complex (Surbone et al. 1988)]. Complete suppression of herpesviral infection was achieved, but the contribution of acyclovir to amelioration of manifestations of HIV infection was questionable. Nonetheless, further investigation of this combination therapy may be warranted.

4.1 Treatment of Established Infections

4.1.1 Herpes Simplex

Oropharyngeal or genital mucocutaneous infection is the most common manifestation of herpes simplex infection in the immunocompromised host and is primarily due to reactivation of latent virus (Meyers 1985); such infections are a major cause of morbidity (Whitley et al. 1984). Seropositive recipients of bone marrow and organ transplants, patients with haematological malignancies undergoing induction chemotherapy, patients with AIDS, malnourished subjects, and individuals with primary immunodeficiency syndromes tend to develop severe and frequent outbreaks of herpes simplex virus infection (Richards et al. 1983; Whitley et al. 1984). Approximately 50 to 80% of seropositive bone marrow or renal transplant recipients

or acute leukaemics undergoing induction chemotherapy experience reactivation, usually within the first 30 days (Saral et al. 1983; Seale et al. 1985). Although some of these patients are asymptomatic, infectious episodes usually cause prolonged pain and may occasionally disseminate to involve the oesophagus and stomach or bladder. As noted by Meyers (1985), the factors associated with severity of herpes simplex infection are poorly defined, and the value of antiviral chemotherapy will generally depend on the severity of infection in the individual patient circumstances.

Double-blind, placebo-controlled studies have shown intravenous acyclovir (250 mg/m^2 8-hourly for 5 to 7 days) to be virologically and clinically effective in the treatment of mucocutaneous herpes simplex virus infection in the immunologically compromised host (Richards et al. 1983). The period of virus shedding is dramatically reduced, to 2 to 3 days, with parallel improvements seen in healing parameters. Being the established treatment in this situation, acyclovir has not been compared with alternative antiviral agents since none appear to be sufficiently efficacious. Topical acyclovir 5% in polyethylene glycol has also been shown to be effective, shortening the period of virus shedding and producing non-significant reductions in time to healing of lesions (for a review see Richards et al. 1983). The efficacy of topical acyclovir appeared to be almost equivalent to that of the intravenous formulation when only external infection was considered in patients having renal allografts or steroid therapy, or in patients with leukaemia (Whitley et al. 1984). However, the usefulness of the topically applied drug is limited to patients with solely external mucocutaneous lesions, and cannot benefit those with intraoral or intravaginal infection or patients with viscerally disseminated disease (see the review of Meyers 1985).

More recently, orally administered acyclovir has been used successfully in the treatment of culture-proven recurrent mucocutaneous herpes simplex infection at a dosage of 400mg 5 times daily for 10 days in bone marrow transplant recipients (Shepp et al. 1985). Compared with placebo, acyclovir sig-
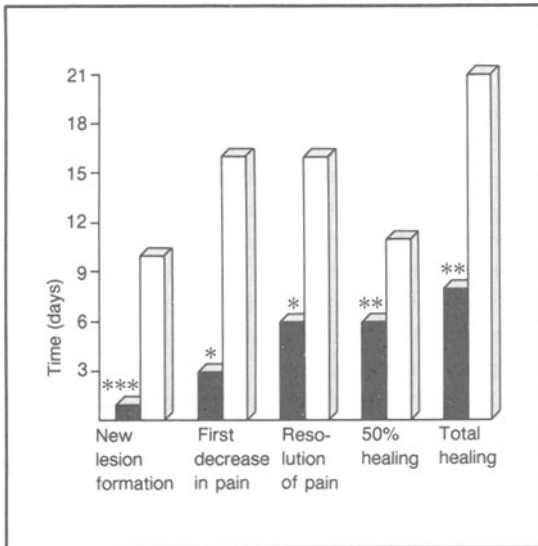
Fig. 10. Clinical results with oral acyclovir 400mg 5 times daily (■; n = 12) and placebo (□; n = 9) administered for 10 days in a randomised, double-blind trial involving bone marrow transplant recipients with culture-proven mucocutaneous herpes simplex infection. *Significant difference from placebo:* ✱ = p ≤ 0.05; ✱✱ = p ≤ 0.01; ✱✱✱ = p < 0.005 (after Shepp et al. 1985).

nificantly shortened the median duration of viral shedding (2 *vs* > 9 days; p = 0.0008), new lesion formation (1 *vs* 10 days; p = 0.003), time to first decrease in pain (3 *vs* 16 days; p = 0.04), resolution of pain (6 *vs* 16 days; p = 0.05), 50% healing (6 *vs* 11 days; p = 0.01), and total healing (8 *vs* 21 days; p = 0.01) [fig. 10]. Although interstudy comparisons are difficult to support, these results appear similar to or better than those seen in marrow transplant recipients treated with intravenous acyclovir in earlier placebo-controlled comparisons reviewed by Richards et al. (1983). However, the improved result with oral acyclovir was likely to have been influenced by the relatively late treatment of patients (median 28 days after transplantation), who were consequently less likely than patients in the earlier intravenous studies to have concomitant chemoradiation-induced mucositis and more likely to have had some reconstitution of immune function (Shepp et al. 1985). Oral acyclovir also compared favourably with topical application for the treatment of cutaneous herpes simplex infection in immunocompromised subjects, in regard to median durations of virus positivity, pain and time to healing (Whitley et al. 1984), and the former has the advantage of effectiveness against lesions inaccessible to topical application and the potential to treat disseminated infection.

Although most of the patients in the above controlled trials have been immunosuppressed secondary to bone marrow, renal or heart transplantation, or underlying haematological malignancies, anecdotal reports indicate that acyclovir is also effective in treating recurrences of herpes simplex infection in patients with AIDS, common variable immunodeficiency, and heart-lung transplants (Brooks et al. 1985; Straus et al. 1984a). In addition, intravenous acyclovir was believed to be of benefit in several case reports involving immunocompromised patients with complications such as diffuse herpes simplex colitis (Adler et al. 1987), herpes simplex oesophagitis (Kadakia et al. 1987) and pneumonitis or encephalitis (Rothman et al. 1988; also see the review by Richards et al. 1983).

4.1.2 Varicella Zoster

Varicella zoster virus infections are common and occasionally severe in immunocompromised patients. Disseminated disease, which results from primary (varicella) or recurrent (herpes zoster) infection, has been associated with a 6 to 17% mortality rate (Shepp et al. 1986). However, the most common complications are painful skin lesions of several weeks' duration, post-herpetic neuralgia, bacterial superinfection, and postponement of scheduled chemotherapy. The potential morbidity and mortality of varicella zoster virus infection in such patients is greater than those associated with herpes simplex infection. Primary infection alone in susceptible immunocompromised children (e.g. with acute lymphocytic leukaemia) has a reported mortality as high as 7%, due to the occurrence of visceral dissemination and varicella pneumonia (Meyers 1985). Incidences of herpes zoster as high as 30 to 50% have been described in profoundly immunosuppressed patients, such as those with Hodgkin's disease or receiving marrow transplants;

cutaneous dissemination rates of 20 to 50% have also been reported (Balfour et al. 1983).

Intravenous Administration

Although varicella vaccine and early postexposure zoster immune plasma or globulin may prevent or ameliorate the course of varicella infection, effective antiviral therapy remains highly desirable. Richards et al. (1983), in the previous review in this journal, were able to cautiously ascribe benefit to intravenous acyclovir treatment of varicella zoster infection in immunocompromised patients, although only non-comparative and a couple of placebo-controlled studies were available. More recently, a couple of additional non-comparative trials have supported the earlier optimism (McMonigal et al. 1987; Meyers et al. 1984), but controlled trials evaluating the clinical and virological efficacy of intravenous acyclovir in the treatment of immunocompromised patients remain few, and patient numbers are low overall in these studies. Thus, there remains a relative lack of adequately controlled or comparative trials of acyclovir in this type of infection, although objections have been raised regarding the ethics of conducting such studies, when established therapeutic agents exist (Glaser & Seligman 1983; Vildé et al. 1986).

Generally, a higher intravenous acyclovir dosage (10 mg/kg or 500 mg/m^2 8-hourly) has been administered in the treatment of varicella zoster virus infections than that used in infections due to herpes simplex virus, broadly paralleling the in vitro susceptibilities of these viruses to the drug.

In the controlled comparative studies (table VIII), patients evaluated were suffering from underlying haematological or other malignancies, primary immune deficiency, or were bone marrow or renal transplant recipients. Patient groups in each investigation were generally comparable on the basis of pretreatment characteristics such as age, sex, preceding or concomitant immunosuppressive chemotherapy, status of malignancy, severity of varicella zoster virus infection and duration of infection prior to enrolment. However, Prober et al. (1982) noted that 6 (50%) of their placebo-treated patients had received prophylactic zoster immune globulin (1 patient) or zoster immune plasma (5 patients), in contrast to only 2 acyclovir-treated patients (25%) who received zoster immune globulin; this difference would appear to have introduced bias in favour of the placebo recipients. In addition, 1 of 6 (17%) placebo patients receiving prophylaxis before enrolment in the latter study was removed to receive open-label acyclovir, vs 4 of 6 (67%) who had not received immunoprophylaxis (p = 0.12), supporting an effect of immunoprophylaxis on the severity of illness in the study. Because of transferral of these 5 placebo patients to open acyclovir treatment, a meaningful comparison of healing between study groups was precluded.

The most important benefit ascribable to acyclovir in the controlled studies has been protection against progression and dissemination of varicella zoster virus infection (table VIII). In the multicentre investigation of Balfour et al. (1983), 1 week's therapy with acyclovir 500 mg/m^2 3 times daily reduced the development or progression of cutaneous dissemination, the development of visceral zoster, and the incidence of treatment failures, to a statistically significant extent versus placebo in patients with localised or cutaneously disseminated zoster pretreatment. In this study, significantly fewer acyclovir recipients treated within 3 days of the onset of signs or symptoms developed complications of zoster (p = 0.02). Nonetheless, even among patients with a rash duration of more than 3 days pretreatment, none of 29 acyclovir patients vs 3 of 17 placebo patients developed cutaneous or visceral dissemination (p = 0.05). Although Balfour et al. (1983) could show no statistically significant differences from placebo overall in the various clinical parameters, the duration of viral shedding (p = 0.05) and time to scabbing (p = 0.04) were significantly reduced by acyclovir therapy in the subgroup of patients with cutaneous disseminated zoster at entry (Breslow test on Kaplan-Meier plots). A statistically significant overall efficacy advantage with acyclovir was achieved, however, in children with varicella (p = 0.004). This study also demonstrated a preventative effect of

Table VIII. Summary of randomised clinical trials comparing intravenous acyclovir (A) with placebo (P) and vidarabine (V) in immunocompromised patients with varicella zoster infections

Reference	Max. pretreatment duration of infection	Daily treatments (duration)	Type of infection (no. of patients)	Results (A vs P or V)[a]				
				scabbing time (days)	duration of new lesion formation (d)	duration of viral shedding (d)	time to healing (d)	complications
Double-blind comparisons with placebo								
Balfour et al. (1983)[b]	3d, or if new lesions still forming	A 500 mg/m² q8h (7d)	Localised zoster (24A/18P)	A = P (9.2 vs 9.9)	A = P (1.8 vs 2.7)	A = P^c (2.6 vs 3.3)	A = P (20.6 vs 26.5)	Progression of zoster overall: A ≪ P (9/28 vs 17/24) [localised], A < P (0/24 vs 4/18) [disseminated] Treatment failures: A ≪ P (0/52 vs 8/42)
			Zoster with cutaneous dissemination (28A/24P)	A < P (5.2 vs 9.6)	A = P (1.8 vs 2.2)	A < P^c (1.4 vs 2.6)	A = P (22.4 vs 21.3)	Development of visceral zoster: A < P (0/52 vs 8/42) Progressive cutaneous dissemination: A ≪ P (1/52 vs 8/42) Post-herpetic neuralgia: 28d (1/15 vs 4/13); 49d (1/13 vs 4/14)
Nyerges et al. (1988)	3d (90%)	A 500 mg/m² q8h (5d)	Varicella in children (25A/25P) [mean age: 5.6 years]	A ≪ P (5.7 vs 7.1)	A = P (2.8 vs 2.7)			Deterioration of condition leading to withdrawal: A ≪ P (1/25 vs 12/25)
Prober et al. (1982)[b,d]	NR (mean ≈ 2d)	A 500 mg/m² q8h (8d)	Varicella in children (8A/12P) [mean age: 6.4 years]	A = P (8.6 vs 5.4)	NR	A = P (2.2 vs 4.4)	A = P (12.4 vs 13.0)	Development of viral pneumonitis: A < P (0/7 vs 5/11)
Non-blind comparisons with vidarabine								
Shepp et al. (1986)	3d	A 500 mg/m² q8h (7d) V 10 mg/kg/ day (7d)	Varicella zoster (11A/11V)	A ≪ V^e (7 vs 17)	A < V (3 vs 6)	A ≪ V (4 vs 7)	A ≪ V (17 vs 28)	Cutaneous dissemination: A < V (0/10 vs 5/10) Treatment failures: A < V (0/11 vs 4/11) Recurrence of zoster: 5 wks (1/11 vs 0/11)

Reference		Dosage	Infection					
Vildé et al. (1986)	3d, or if new lesions still forming	A 10 mg/kg q8h (5d)[g]; V 30 mg/kg/day (5d)[g]	Varicella (10A/8V)	NR	A = V (3.9 vs 4.7)	A ≪ V[h]	NR	Recurrence of varicella: 3d (2/10 vs 0/8)
			Disseminated zoster (10A/10V)	NR	A = V (2.6 vs 2.9)	A ≪ V[h]	NR	

a = indicates similar results for both groups; < indicates a non-statistically significant tendency; ≤ indicates $p \leq 0.05$; ≪ indicates $p \leq 0.01$; ≪≪ indicates $p \leq 0.001$.
b Multicentre study.
c Virus was isolated from 35 acyclovir and 24 placebo recipients.
d Withdrawals from the study because of continuation (1A recipient) or development (5P recipients) of viral pneumonitis were not included in the results analysis.
e Crusting time.
f Patients entering with localised dermatomal disease.
g Two vidarabine-treated patients and 3 acyclovir-treated patients received therapy for 7 days due to the severity of illness.
h Virus was isolated from 9 acyclovir and 10 vidarabine recipients.
Abbreviations: q8h = 8-hourly; d = days; NR = not reported.

acyclovir on dissemination and rash progression (Nyerges et al. 1988).

In comparison with vidarabine, acyclovir proved superior for protection against dissemination of zoster infection, and for the promotion of cutaneous healing and pain relief in 22 severely immunocompromised recipients of bone marrow transplant or intensive induction chemotherapy who presented within 3 days of infection onset; visceral dissemination of varicella zoster infection did not occur in any of the study subjects (Shepp et al. 1986). In addition to the results reported in table VIII, acyclovir also proved significantly superior to vidarabine with regard to time of first decrease in pain (4 vs 7 days; p = 0.005) and pustulation of all lesions (4 vs 7 days; p = 0.0004); acyclovir treatment tended to alter the pattern of zoster rash evolution such that new lesions were less likely to pustulate and a late increase in perilesional erythema was usually absent.

In contrast, Vildé et al. (1986) found no statistically significant differences between the effects of acyclovir and vidarabine on the formation of new lesions, disappearance of fever, time to healing of lesions and duration of viral shedding. The shorter (5-day) duration of drug treatment in the latter study may have contributed to the occurrence of rapid relapses of varicella infection in 2 acyclovir-treated patients, and the more pronounced comparative efficacy of acyclovir in the study of Shepp et al. (1986) may have resulted from the substantially lower vidarabine dosage employed. Additionally, Shepp et al. (1986) excluded patients with infections of longer than 3 days' duration, which may have increased the probability of demonstrating a treatment difference with acyclovir. However, as noted by Balfour et al. (1983), admission of patients having a wider variety in duration of infection may provide a study population which better reflects those likely to seek medical attention in this therapeutic area. Importantly, acyclovir may be preferable to vidarabine for patients at high risk of cardiorespiratory failure (e.g. those with previous pulmonary lesions or renal insufficiency) since vidarabine requires a relatively large amount of solute for its administration (Vildé et al. 1986).

As expected, recurrence of symptoms has frequently been reported after the cessation of acyclovir treatment, since the drug does not eliminate the latent virus. However, the prompt response of recurrent infection to repeated administration of acyclovir is usually noted in immunocompromised individuals, which mitigates against the emergence of acyclovir-resistant strains of varicella zoster virus (Meyers et al. 1984; Oblon et al. 1986; Shepp et al. 1986; Vildé et al. 1986). Meyers et al. (1984) noted recurrence within 4 days of the completion of therapy in several patients included in a noncomparative study, and suggested that the specific immune response to varicella zoster virus may be delayed by acyclovir treatment in some severely immunocompromised individuals.

Primary varicella infection in immunocompromised children is frequently associated with visceral dissemination and high attendant mortality (Schulman 1985). Parenteral acyclovir treatment has generally been effective in children with underlying malignancies and appears to be at least as effective as vidarabine (table VIII). Further, due to a lack of response to therapy, vidarabine 15 mg/kg/day was replaced after 3 days with acyclovir 500 mg/m^2 8-hourly in 8 children with malignant neoplasms and chickenpox with visceral involvement; progressive visceral involvement (pneumonitis, encephalitis or coagulopathy) was halted and complete recovery ensued in 7 of the 8 (Schulman 1985). In a retrospective comparison with cytarabine, intravenous acyclovir in dosages of 1000 to 1500 mg/m^2/day for 5 to 10 days was more effective with respect to median times to cessation of new lesion formation, lesion crusting and lesion healing (Boguslawska-Jaworska et al. 1984). Anticancer treatment was able to be continued without modification in most patients receiving acyclovir.

Oral and Topical Administration

In addition to intravenously administered acyclovir, encouraging preliminary results have also been reported with the use of the oral and topical formulations of the drug in immunocompromised patients suffering from varicella zoster virus infection.

In a double-blind placebo-controlled investigation, topical acyclovir in polyethylene glycol ointment base favourably influenced the healing of localised herpes zoster in immunocompromised patients when applied within 72 hours of the onset of cutaneous lesions (Levin et al. 1985). The mean time to pustulation was decreased from 12.4 to 6.7 days (p = 0.038), and the mean time to crusting from 16.0 to 11.4 days (p = 0.086) in those treated with acyclovir ointment 4-hourly for 10 days. The mean time to 50% healing was shortened from 24.5 to 15.2 days (p = 0.023) and the mean time to 100% healing from 34.9 to 25.8 days (p = 0.033). Clinical success, however, did not correlate with reductions in viral shedding, and pain resolution was similar in drug and placebo recipients (p = 0.195). The role of topical acyclovir, while undoubtedly limited in this situation, requires definition in further controlled investigations.

Orally administered acyclovir is currently being tested for the treatment of the immunosuppressed host and early results have been encouraging (Novelli et al. 1984). If effective, the oral route should broaden the indications and usefulness of acyclovir therapy in varicella zoster virus infection, since hospitalisation would not be mandatory with use of the oral route (Meyers 1985).

4.1.3 Cytomegalovirus

Cytomegalovirus has a variety of manifestations in the immunocompromised host, being a considerable cause of morbidity and mortality in these patients. Infections due to cytomegalovirus constitute a major hazard in the period immediately after organ transplantation, having been associated with up to 20% of graft failures, 25% of deaths, 30% of fever cases and 35% of all episodes of leucopenia in the first 6 months following renal transplantation (Barnett et al. 1984). In marrow transplant recipients, disseminated infection and pneumonia have been particularly common (Meyers 1985).

Acyclovir has modest activity against cytomegalovirus *in vitro*, and most published trials and reports of use of the drug for symptomatic cytomegalovirus infection in renal or bone marrow

allograft recipients or neonates have shown no clear efficacy. For example, Shepp et al. (1984) administered high-dose acyclovir (usually 1 g/m^2 8-hourly) in combination with high-dose purified lymphoblast (α) interferon to 8 marrow transplant recipients with leukaemia who had biopsy-proven cytomegalovirus pneumonia. No clear benefit resulted from varying treatment durations with this regimen; 7 patients died from respiratory failure due to their pneumonias, although some reduction in viral titre was found in 2 of 4 patients with quantitative viral cultures of biopsy and autopsy lung specimens. Thus, in general, despite transient effects on viraemia and possibly viral titre in the target organ, survival of acyclovir-treated patients in this disease state has been unaffected. Efforts have more recently been directed towards investigating the efficacy of prophylactic acyclovir regimens against cytomegalovirus in immunosuppressed individuals, where the results have been more promising (see section 4.2.1).

4.1.4 Epstein-Barr Virus

There are few published data and some apparently conflicting uncontrolled reports as to the efficacy of acyclovir treatment of the various manifestations of Epstein-Barr virus infection (Richards et al. 1983). In contrast to the antiviral effect of the drug, success in terms of the clinical response has been limited. Recurrence of symptoms due to reactivation of latent infection has frequently been observed following discontinuation of acyclovir administration in a range of these conditions, especially in highly immune-deficient patients (Andersson et al. 1986; Pagano et al. 1983).

More recently, encouraging results have been reported with the use of acyclovir in 6 men seropositive for human immunodeficiency virus and with histologically confirmed oral hairy leucoplakia (Resnick et al. 1988). Oral hairy leucoplakia is an early manifestation of immunodeficiency secondary to infection with human immunodeficiency virus; actively replicating Epstein-Barr virus, in addition to human papillomavirus, has been detected in lesions (Greenspan et al. 1984). Resnick et al. (1988) administered oral acyclovir 800mg

6-hourly for 20 days to the patients mentioned above. In confirmation of an earlier case report (Friedman-Kien 1986), 5 of the 6 patients exhibited clinical regression, with responses observed after 2 to 4 weeks from the initiation of treatment. Biopsy specimens from 2 patients with complete responses revealed a normalisation of histological abnormalities and an inability to detect Epstein-Barr virus in previously involved mucosa by immunofluorescence or in situ DNA hybridisation assay. Unfortunately, after stopping acyclovir, recurrences occurred in all responders.

Acyclovir also had a beneficial effect on the accelerated phase of Chediak-Higashi syndrome, which has been associated with seroconversion and abnormal antibody response to Epstein-Barr virus (Conley & Henle 1987).

4.2 Prevention of Viral Infections

Prophylaxis is likely to be most successful where there exists a high incidence of a specific disease, a predictable time of occurrence, and the availability of an effective chemoprophylactic regimen (Seale et al. 1985). Although acyclovir speeds healing in acute episodes of herpes simplex infection in the immunocompromised, these patients still require on average 2 weeks of treatment before lesions resolve. Moreover, prompt recurrence has been observed not infrequently upon cessation of acyclovir therapy for mucocutaneous herpes simplex infection in these patients. Thus, acyclovir has been administered prophylactically, in a variety of oral and intravenous regimens, to bone marrow allograft and organ transplant recipients and to patients receiving timed sequential chemotherapy who were identified as being at high risk of infection by pretreatment herpes simplex serology.

Several placebo-controlled trials report a dramatic reduction in the number and duration of herpes simplex infection recurrences during the time of drug administration, with up to 50% of breakthrough recurrences in acyclovir-treated subjects consisting solely of asymptomatic viral shedding. Some investigators have extended the period of prophylaxis to 6 months in an attempt to protect

Table IX. Randomised, double-blind, placebo-controlled studies of acyclovir (A) prophylaxis in immunocompromised patients undergoing bone marrow transplant (BMT) or induction chemotherapy (IC), for haematological malignancy

Reference	Acyclovir regimen (follow-up)	No. of patients A	No. of patients P	Procedure	Results: %A vs %P[a] — infection rate[b] during prophylaxis	infection rate post-prophylaxis	viral shedding during prophylaxis	viral shedding post-prophylaxis
Intravenous administration								
Hann et al. (1983)	5 mg/kg bid IV during period of neutropenia[c] (10 to 24 months)	10	10	BMT	0* vs 50 (HSV)	70 vs 30 (HSV); 20 vs 0 (VZV); 40[d] vs 20 (CMV)		
		19	20	IC	10 vs 0 (CMV); 11* vs 50 (HSV)	10 vs 30 (HSV); 0 vs 0 (VZV); 10 vs 0 (CMV)		
Ljungman et al. (1986)	250 mg/m² bid IV for 6 weeks, beginning 5 days before BMT, followed by 400mg tid PO to 6 months post-BMT[e] (6 months)	20	22	BMT	5*[f] vs 32 (HSV); 0* vs 23 (VZV); 50 vs 59 (CMV)	5 vs 0 (HSV); 20 vs 5 (VZV); 0 vs 0 (CMV)	0 vs 14 (HSV); 5 vs 9 (VZV)	5 vs 5 (HSV)
Saral et al. (1981)	250 mg/m² tid IV for 3 weeks beginning 3 days before BMT (12 weeks)	10	10	BMT	0** vs 70 (HSV)	50 vs 0 (HSV); 0 vs 10 (CMV)	0 vs 10 (HSV); 10 vs 0 (CMV)	20 vs 0 (HSV); 40 vs 10 (CMV)
Saral et al. (1983)	250 mg/m² tid IV for 21 to 32 days beginning 4 days after initial IC (1 to 6 months)	14	15	IC	0*** vs 73 (HSV)	43 vs NR (HSV)	0 vs 7 (HSV); 14 vs 0 (CMV)	
Shepp et al. (1985)	250 mg/m² od IV for 4 weeks beginning 6 days before BMT (day 100)	14	13	BMT	29 vs 69 (HSV)	21 vs 0 (HSV)	14 vs 0 (HSV)	7 vs 0 (HSV)
Shepp et al. (1987)	250 mg/m² bid or 500 mg/m² tid IV[g] for 5 weeks (max.) beginning 5 days before BMT followed by 800mg bid PO to day 75 (day 100)[h]	25	26	BMT	0 vs 50 (HSV)	28 vs 0 (HSV)		
Oral administration								
Anderson et al. (1984)	200mg qid PO for 6 weeks, beginning day 1 of IC	20	20	IC	5*** vs 60 (HSV)		5 vs 10 (HSV)	
Gluckman et al. (1983)	200mg qid PO for 4 weeks, beginning day 8 after BMT (day 100)	20	19	BMT	0**** vs 68 (HSV)	28 vs 37 (HSV); 0 vs 16 (CMV)	0** vs 36 (CMV)	39 vs 58 (CMV)

| Wade et al. (1984) | 400mg 5 times daily po for 5 weeks beginning 1 week before BMT (15 weeks) | 24 | 25 | BMT | 21** vs 70 (HSV) 25 vs 36 (CMV) | 21 vs 4 (HSV) 0 vs 4 (VZV) 17 vs 16 (CMV) | 17 vs 4 (HSV) |

a * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001.
b Infection refers to virologically confirmed mucocutaneous herpes lesions or a clinical picture accompanied by viral shedding.
c Neutrophil count < 1 × 10⁹/L.
d Includes 2 cases of pneumonia with hepatitis, 1 fatal.
e Children less than 6 years of age received 200mg tid PO.
f This single episode occurred in a patient whose serum contained no detectable acyclovir.
g Dosage of IV acyclovir was based on pretreatment CMV antibody titre (< 1 : 8 – low dose; ⩾ 1 : 8 – high dose).
h Seven acyclovir recipients and 9 placebo recipients withdrew from the oral phase due to noncompliance, open administration of acyclovir or worsening medical condition.
i Of these 5 patients, 3 had voluntarily stopped acyclovir for at least 6 days, the remaining 2 remained asymptomatic, with only single positive throat cultures.
Abbreviations: od = once daily; bid = twice daily; tid = 3 times daily; qid = 4 times daily; PO = orally; IV = intravenously; HSV-1 = herpes simplex virus type 1; HSV = herpes simplex virus; VZV = varicella zoster virus; CMV = cytomegalovirus; NR = not reported.

against herpesvirus reactivations until a period of relative immunocompetence, with varying success in terms of a reduction in the rate of post-treatment recurrence. Direct comparisons of the efficacy of oral *versus* intravenous prophylactic acyclovir regimens or of intermittent therapeutic *versus* long term prophylactic acyclovir administration have not been reported.

Some reduction in the incidence of varicella zoster virus and cytomegalovirus reactivations has been noted during acyclovir prophylaxis, although the longer time courses of reactivations of varicella zoster virus and cytomegalovirus (*vs* herpes simplex virus) regarding the extent of the granulocytopenic period makes evaluation of the true protective effect of acyclovir against these viruses difficult.

Acyclovir prophylaxis has had no consistent effect on the incidence, severity or time of occurrence of graft-*versus*-host disease in bone marrow transplant patients.

4.2.1 Patients with Haematological Disorders

Several well-designed placebo-controlled studies, in patients with bone marrow failure as a result of underlying leukaemias, lymphomas or primary anaemias, and/or immunosuppression as a result of intensive radiotherapy or cytotoxic chemotherapy, have evaluated the efficacy of prophylactic acyclovir administered for 3 to 11 weeks during the period of most profound immunosuppression associated with these procedures (table IX). Patients were usually required to have serological evidence of previous herpes simplex virus infection, since most infectious episodes due to herpes simplex in this situation are the result of reactivation of latent virus. However, the herpes simplex antibody titre in over 50% of subjects in the trial of Gluckman et al. (1983) was < 1 : 8 at entry and several bone marrow transplant recipients evaluated by Ljungman et al. (1986) were seronegative for herpes simplex antibody pretreatment; hence these patients were at lower theoretical risk of suffering recurrence during the follow-up period. Similarly, Anderson et al. (1984) included 10 subjects with a pretreatment complement-fixation herpes simplex

antibody titre of < 1 : 10, although the authors state that the statistical significance of the results remained if these patients were excluded from analysis. Since investigations were chiefly concerned with the effect of acyclovir administration on recurrence of herpes simplex infection, patients had varying varicella zoster virus and cytomegalovirus pretreatment serologies, if indeed these were reported at all.

Overall, acyclovir and placebo treatment groups were statistically similar with regard to pretreatment characteristics such as age, sex, diagnosis, herpesvirus serological status, therapeutic regimen and degree of leucopenia. Therapeutic courses of acyclovir were administered to several placebo patients during the study periods, to control severe outbreaks of herpes simplex virus.

Prophylaxis Against Herpes Simplex Virus

Intravenous acyclovir at dosages of 250 mg/m^2 or 5 mg/kg 2 to 3 times daily, initiated around the time of bone marrow transplantation or initial chemotherapy and continued for periods of up to 6 weeks, has produced virtually complete clinical and virological suppression of herpes simplex virus reactivation. Infection rates during the period of prophylaxis thus proved highly statistically significant when acyclovir was compared with placebo treatment (table IX). A simpler once-daily regimen of intravenous acyclovir 250 mg/m^2 proved less effective in terms of infection rate, although the median time to first culture-positive herpes simplex lesion was significantly delayed by acyclovir, compared with placebo (33 vs 10 days after transplant; p = 0.05) [Shepp et al. 1985]. As with other clinical settings, the protection conferred by the drug was confined to the period of treatment, with infectious episodes generally occurring at least as frequently in acyclovir patients as in placebo-administered subjects during extended follow-up.

Orally administered acyclovir was used successfully to extend the initial period of intravenous prophylaxis for up to a total of 6 months in 2 studies (Ljungman et al. 1986; Shepp et al. 1987). Several other studies which utilised the oral formulation alone for prophylaxis reported results which

appeared to be similarly positive to those achieved in studies of intravenous administration (table IX). Although circumventing the need for venous access and inpatient care associated with intravenous administration, the use of prophylactic oral acyclovir in bone marrow transplant recipients has been associated with compliance problems, such that only 11 of 24 patients assigned to acyclovir took 75% or more of their prescribed 5-week treatment course (Wade et al. 1984). The tolerance of oral medications in this patient group may be impaired due to mucosal damage resulting from radiation and intensive cytotoxic chemotherapy. Reanalysis of the results of Wade et al. (1984), excluding patients who failed to take at least 40% of their prescribed acyclovir dose during any of the 5 treatment weeks (patients were not excluded if herpes simplex infection preceded their low compliance level), showed a substantial increase in the efficacy of acyclovir. Prophylaxis proved 96% virologically and 100% clinically effective with censoring at the 40% level, and increased the median time to first reactivation to 84 days after transplantation (p = 0.0002 vs placebo).

It is possible that an increased duration of prophylaxis has an ameliorative effect on the severity and incidence of post-treatment herpes simplex recurrences, by preventing virus reactivation until a period of relative immune competence. Thus, when acyclovir prophylaxis was administered for 3 weeks after transplant, recurrences were recorded in 7 of 10 patients at a mean of 22.5 days after drug discontinuation (Saral et al. 1981), whereas prophylaxis for 5 weeks led to recurrences in 9 of 19 acyclovir recipients followed up, who did not become culture-positive for herpes simplex virus until a median of 8 weeks after stopping acyclovir (Wade et al. 1984). Contrasting results with regard to this theory are presented in studies employing extended acyclovir prophylaxis, for 6 months after marrow transplant (table IX); Ljungman et al. (1986) reported a low incidence of herpes simplex reactivations during post-treatment follow-up in both acyclovir and placebo patient groups, while Shepp et al. (1987) noted recurrences in acyclovir recipients only, and suggest this finding may be due

to the delay in reconstitution of herpes simplex virus-specific immune responses associated with acyclovir treatment (see below).

Prophylaxis Against Other Herpesviruses

In addition to demonstrating efficacy against herpes simplex infection, sequential intravenous and oral acyclovir prophylaxis for a total of 6 months led to complete suppression of varicella zoster virus reactivation in a predominantly seropositive patient population (Ljungman et al. 1986; table IX). However, a high recurrence rate with respect to this virus was seen after the cessation of acyclovir in this and a more recent study (Perren et al. 1988); after 6 months of follow-up the total number of varicella zoster virus reactivations was similar in the acyclovir and placebo treatment groups.

Despite a promising trend observed by Gluckman et al. (1983; table IX) towards protection against cytomegalovirus infection, the lower acyclovir susceptibility of cytomegalovirus is reflected in the lack of prophylactic effect seen overall. Cytomegalovirus infections of varying severity occurred in several patients receiving prophylactic acyclovir in the placebo-controlled studies (table IX). More positive results were obtained in a nonrandomised controlled study which utilised a relatively high intravenous dosage of acyclovir (500 mg/m² 8-hourly), administered for 6 weeks beginning 5 days prior to allogeneic bone marrow transplantation, in 86 patients with haematological malignancy who were seropositive for cytomegalovirus (Meyers et al. 1988). The results of acyclovir prophylaxis were compared to those in the 65 seropositive controls, who were comparable with the exception of being significantly younger than the acyclovir recipients (p < 0.01). Compared with control subjects, acyclovir-treated patients suffered from a significantly lower incidence of invasive cytomegalovirus disease (pneumonia or gastrointestinal infection) [22 vs 38%; p = 0.008] and mortality (29 vs 54%; p < 0.01) at 100 days post-transplant. Herpes simplex virus infection was also suppressed, the infection rates being 51% in control patients and 5% in acyclovir recipients (p < 0.001).

As expected, the protective effect of acyclovir did not extend to established cytomegalovirus infection at the commencement of treatment. Rather, the drug reduced the risk of reactivation.

Although not randomised in design, the study of Meyers et al. (1988) provided some evidence that acyclovir prophylaxis is able to reduce the morbidity and mortality associated with cytomegalovirus in high-risk immunocompromised patients, presumably by protecting against such infection until a period of relatively improved immune function. Nonetheless, as noted by Hann et al. (1983), the later occurrence of cytomegalovirus and varicella zoster virus reactivation (usually 3 to 6 months and up to several years after transplantation, respectively) compared to herpes simplex virus reactivation, probably precludes completely successful acyclovir prophylaxis against these viruses if drug administration is confined to the period of granulocytopenia. Thus, most of the studies presented in table IX were of too short a duration to adequately assess the effects of prophylaxis with acyclovir on clinical reactivation of these viruses.

Effects on the Immune System

Acyclovir prophylaxis in bone marrow transplant recipients has been associated with a slower reconstitution of the herpes simplex virus-specific in vitro lymphocyte proliferation response, where this has been evaluated in placebo-controlled studies. Wade et al. (1984) reported a significant (p = 0.001) lowering of the lymphocyte transformation response to herpes simplex virus antigen in patients receiving oral acyclovir 400mg 5 times daily for 5 weeks compared with that seen in placebo recipients when tested during the period of prophylaxis, while a similar though non-significant trend remained, but was diminishing, 13 weeks post-treatment. The authors suggested that these findings were a result of the delay in virus reactivation associated with extended administration of acyclovir, which produced a delay in the exposure of the immune system to viral antigen. Similarly, significant (p < 0.05) differences between placebo and acyclovir recipients in lymphocyte proliferation response to herpes simplex virus and varicella zoster

virus antigens were later noted in patients receiving acyclovir prophylaxis for 6 months, who were followed for a further 6 months (Ljungman et al. 1986); the response to herpes simplex virus antigen was significantly lower at 3, 6 and 12 months following marrow transplantation in acyclovir-treated patients, while the rsponse to varicella zoster antigen was significantly lower at 6 but not at 12 months (p = 0.08). The clinical significance of these findings awaits further clarification.

4.2.2 Renal Transplant Recipients

Continuous low-dose oral administration of acyclovir beginning at the time of transplantation has been found in placebo-controlled studies in renal transplant recipients to offer protection from herpes simplex virus infection similar to that provided by higher prophylactic doses in the more highly immunocompromised patients discussed in section 4.2.1. Complete suppression of clinical herpes simplex and varicella zoster infections occured during several weeks of treatment, although acyclovir was less effective in preventing virological breakthrough (table X). Among patients followed up for 2 months, Seale et al. (1985) reported active herpes simplex infection in 7 of 16 acyclovir-treated patients and 3 of 5 placebo-administered patients who had been free of infection during the 30-day treatment phase of the study. At 90 days after renal transplantation, 9 of 17 recipients of acyclovir prophylaxis and 2 of 19 placebo recipients remained free of an infectious episode (p < 0.01).

5. Adverse Effects

The relative safety of all formulations of acyclovir has been well established, although 2 important serious adverse effects (neurological and/ or psychiatric effects, and renal precipitation resulting in renal insufficiency) have been reported in a few patients administered intravenous acyclovir. High peak plasma concentrations have been implicated in both of these adverse effects, and the potential for renal complications may be minimised with slow infusion of doses, adequate hydration, and lower dosages in patients with renal dysfunction.

Table X. Randomised, double-blind, placebo (P)-controlled studies of oral acyclovir (A) prophylaxis in renal transplant recipients

Reference	No. of patients		Initial serological status			Acyclovir regimen (duration)	Results: % A vs % P[a]	
	A	P	antibody titre	A	P		infection rate[b]	viral shedding
Pettersson et al. (1985)	19	21	HSV ≥ 1:16		(all)	400mg stat pre-surgery, then 200mg tid[c] (30 days)	0 vs 52 (HSV)[d]	5 vs 14 (HSV)
Seale et al. (1985)	18	17	HSV	19 (mean values)	23	200mg qid (4 weeks)	0** vs 35 (HSV) 0 vs 12 (VZV)	0** vs 18 (HSV) 12 vs 12 (CMV)
Stoffel et al. (1987)	48	50	HSV < 1:8 VZV < 1:4	8 13	10 16	200mg qid (6 weeks)	0* vs 12 (HSV) 0 vs 4 (VZV)	12.5 vs 24 (HSV)

a   * p < 0.025; ** p < 0.001.
b   Viral shedding accompanied by lesions.
c   Patients with a creatinine clearance below 30 ml/min received 200mg bid
d   When patients with a positive herpes simplex virus culture (not necessarily accompanied by lesions) were compared statistically, acyclovir treatment was associated with a significantly lower infection rate (5% vs 67%, p < 0.001).
Abbreviations: bid = twice daily; tid = 3 times daily; qid = 4 times daily; HSV = herpes simplex virus; VZV = varicella zoster virus; CMV = cytomegalovirus.

5.1 Ophthalmic Administration

As noted in the previous review in the Journal (Richards et al. 1983) and in the more recent review of Grant (1987), tolerance to acyclovir ophthalmic ointment has been extremely good, and compares favourably with alternative antiviral therapies for herpes simplex virus ophthalmic disease. The most commonly reported adverse reactions in the published clinical trials assessed in the above reviews were superficial punctate keratopathy and burning and stinging on application. A wide-ranging incidence (0 to 70%) of superficial punctate keratopathy was reported, the frequency being associated most closely with the frequency and nature of ophthalmic examinations. Postmarketing surveys of adverse reactions reveal an incidence of spontaneously reported reactions of only 1 : 25,000 treatment courses (0.004%); reactions were generally allergic or inflammatory in nature, no cases of superficial punctate keratopathy were reported, and a number of these reactions (such as corneal ulcer, conjunctivitis, eye pain, eye disorder and keratitis) might be attributable to the disease itself (Grant 1987).

5.2 Topical Administration

Topically administered acyclovir has been associated with no adverse local, systemic or laboratory effects that are not seen with placebo (see the reviews of Arndt 1988; Richards et al. 1983). The manufacturer reports that transient burning or stinging may follow application of acyclovir cream, and erythema or mild drying and flaking of skin have been reported in a small proportion of patients.

5.3 Systemic Administration

5.3.1 Intravenous Acyclovir

The adverse reactions most frequently reported with intravenously administered acyclovir during controlled clinical trials were inflammation and phlebitis at the injection site, in some instances following infiltration of tissues with intravenous fluids (see the reviews of Arndt 1988; Richards et al. 1983). In addition to these relatively common local reactions, a single case study has reported a localised vesicular eruption that appeared proximally to each of 3 infiltrated venipuncture sites in a patient who had received high-dose (500 mg/m^2), high-concentration (12 mg/ml) intravenous acyclovir for a varicella zoster infection (Sylvester et al. 1986).

Abnormalities of renal function due to precipitation of acyclovir in renal tubules may occur when the solubility of the drug in intratubular fluid is exceeded. Such reactions are encountered more frequently following rapid bolus injection, in patients with renal disease, in dehydrated patients, and when other nephrotoxic drugs are administered concurrently (Richards et al. 1983). Thus, the potential for this complication may be minimised with slow infusion of doses, adequate hydration and lower dosages in patients with renal dysfunction.

In a randomised, placebo-controlled assessment of high-dose (500 mg/m^2) intravenous acyclovir in ambulatory patients with acute herpes zoster, both serum creatinine concentrations and symptomatic reactions (which consisted mostly of nausea, vomiting, other gastrointestinal symptoms and lightheadedness) were related to high peak concentrations of the drug in plasma (> 25 mg/L) [Bean & Aeppli 1985]. The unusually high frequency of adverse effects reported in this study (74%) was attributed by the authors to suspected poor hydration in the outpatient population, and may have been contributed to by concomitant administration of narcotic analgesics, which had been administered to 10 of 16 acyclovir recipients and 2 of 3 placebo recipients who experienced nausea and vomiting. Other researchers have also reported nausea and vomiting rarely in association with high-dose intravenous acyclovir therapy in adults (Balfour et al. 1983; Juel-Jensen et al. 1983) and children (Lisby et al. 1986) with varicella zoster infection.

As reported by the manufacturer, reversible neurological reactions, usually consisting of tremor and sometimes associated with confusion and electroencephalographic change, have been associated with intravenous acyclovir therapy. In addition,

psychiatric symptoms, including confusion, hallucinations and delusions, have been reported. Neurological and/or psychiatric symptoms are more likely in immunocompromised patients (Auwerx et al. 1983; Meyers et al. 1982; Saral et al. 1981; Sirota et al. 1988; Straus et al. 1982; Vartian & Shlaes 1983; Wade & Meyers 1983) and in patients with renal insufficiency receiving higher than recommended dosages (Bataille et al. 1985; Rubin 1987; Tomson et al. 1985) and have been linked to high plasma concentrations of the drug (Bataille et al. 1985).

In addition to the above, several other clinical and laboratory abnormalities have been reported rarely in patients being administered intravenous acyclovir (see the review of Richards et al. 1983) but their association with acyclovir therapy remains to be confirmed.

5.3.2 Oral Acyclovir

The most frequently reported adverse reactions associated with short term use of oral acyclovir are nausea and vomiting (see the reviews of Arndt 1988; Richards et al. 1983). The long term safety of low-dose prophylactic oral acyclovir has also been demonstrated (see below). However, high-dose treatment with oral acyclovir for herpes zoster results in the observation of more side effects (nausea, vomiting, abdominal pain, lightheadedness).

Among 950 subjects with a history of at least 6 recurrences yearly of genital herpes, who completed a 12-month, multicentre, placebo-controlled assessment of prophylactic oral acyclovir (400mg twice daily), adverse effects such as nausea and vomiting, diarrhoea, stomach pain, rash and headache were reported at an incidence of less than 5%, and in similar percentages of placebo- and acyclovir-administered patients (Mertz et al. 1988b). No significant differences in laboratory parameters were observed over time or between the study groups, although statistical details were not provided.

Case reports on individual patients have described the rash associated with oral acyclovir as a lichenoid eruption (Robinson et al. 1985) and a maculopapular eruption (Grattan & Boyle 1984).

In addition to the above reactions, single re-

ports have been published of thrombocytopenia (Salo et al. 1983) and reversible neurotoxicity (Krigel 1986) associated with oral acyclovir therapy. However, interestingly, acute renal insufficiency, associated in 4 patients with high-dose intravenous acyclovir administration, did not emerge during rechallenge with oral acyclovir (Sawyer et al. 1988).

6. Dosage and Administration

The manufacturer's recommended dosages of the various formulations of acyclovir are presented in table XI.

Therapy with acyclovir should be initiated as early as possible following onset of signs and symptoms. For recurrent episodes of mucocutaneous herpes simplex infection this should preferably be during the prodromal period or when lesions first appear.

Rapid or bolus intravenous, and intramuscular or subcutaneous injection of parenteral acyclovir must be avoided. The recommended intravenous dosage of acyclovir should be administered slowly over 1 hour, and adequate hydration must be maintained to establish sufficient urine flow, to prevent precipitation in renal tubules. Infusion concentrations lower than 7 mg/ml are recommended, as higher concentrations may produce phlebitis or inflammation at the injection site upon inadvertent extravasation.

Recommended systemic dosages of acyclovir for adults with acute or chronic renal function impairment are given in table XII. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance, and children with impaired renal function also require an appropriately modified dosage of systemic acyclovir, according to the degree of impairment.

While animal studies have revealed no mutagenic embryotoxic or teratogenic effects, experience in humans is limited. Thus, acyclovir should be considered for use in pregnancy only when the potential benefits outweigh the possibility of unknown risks.

Probenecid increases the acyclovir mean half-life and area under the plasma concentration-time

Table XI. The manufacturer's recommended dosage of acyclovir in patients with normal renal function

Formulation	Indication	Patient group	Dose	Dosage interval	Duration
Intravenous	HSV or VZV inf.	Adults	5 mg/kg	8-hourly	5 days
		Children (3 mo. to 12 yrs)	250 mg/m^2	8-hourly	5 days
	VZV inf.	IC adults	10 mg/kg	8-hourly	7 days
		IC children (3 mo. to 12 yrs)	500 mg/m^2	8-hourly	7 days
Oral[a]	Mucocutaneous HSV inf.	Adults and children (> 2 yrs)	200mg	5 times daily	5 days[b]
		Children (≤ 2 yrs)	100mg	5 times daily	5 days[b]
	Chronic suppression of recurrent HSV genitalis	Adults	200mg	3-5 times daily	Up to 6 months[c]
	Herpes zoster	Adults	800mg	5 times daily	7 days
	Prophylaxis of HSV inf.[d]	IC adults and children (> 2 yrs)	200mg	4 times daily	...[e]
		IC children (≤ 2 yrs)	100mg	4 times daily	...[e]
Topical cream	Mucocutaneous HSV inf.	Adults and children	As needed	5 times daily	5-10 days
Topical ointment	Mucocutaneous HSV inf.	Adults and children	As needed	6 times daily	7 days
Ophthalmic ointment	HSV keratitis	Adults and children	As needed	5 times daily	≥ 3 days after healing

a   Available as 200mg capsules, 200mg and 400mg tablets, and as a suspension containing 200 mg/5ml.
b   In severe initial infections the duration of therapy may require extension.
c   Restriction applies in the US only.
d   Duration of prophylactic administration is determined by the period at risk.
e   In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg or, alternatively, intravenous administration may be considered.
Abbreviations: HSV = herpes simplex virus; VZV = varicella zoster virus; IC = immunocompromised.

curve, presumably by competitive inhibition of organic acid secretion, an interaction of probable limited clinical significance (Laskin 1983).

Use of a finger cot or rubber glove for application of topical acyclovir is recommended to prevent autoinoculation of other body sites and transmission of infection to other persons.

7. *Place of Acyclovir in Therapy*

Intravenous and oral acyclovir have been confirmed in numerous placebo-controlled investigations to produce significant reductions in the duration of viral shedding and overall duration of symptoms in immunocompetent patients with genital or orofacial herpes simplex infections, the therapeutic effects being greater in the more severe primary episodes. Prophylactically, oral acyclovir has often produced complete suppression of recur-

rences of genital and non-genital herpes. However, acyclovir is unable to eradicate latent virus and hence no consistent effect of the drug is seen on the natural history of recurrent herpes simplex infection, even after prolonged prophylaxis.

Compared with systemic administration, topical 5% acyclovir has generally proved less efficacious clinically and virologically, in the treatment of initial and recurrent episodes of genital and orofacial herpes simplex in immunocompetent patients, even when therapy was initiated as early as practicable. Nevertheless, statistically significant amelioration of the course of primary initial genital and recurrent orofacial herpes infection was demonstrable in some studies with topical therapy, although symptoms of pain and dysuria in the former were less susceptible to treatment. Topical acyclovir does not eradicate the latent and thus recurring aspect of herpes simplex infections.

Table XII. The manufacturer's recommended dosages of intravenous and oral acyclovir in adults with acute or chronic renal impairment

Creatinine clearance (ml/min)	Dose	Dosage interval
25-50	IV: see table XI	IV: 12-hourly
	Oral: see table XI	Oral: see table XI
10-25	IV: see table XI	IV: 24-hourly
	Oral: see table XI	Oral: see table XI
0-10	IV: 2.5-5 mg/kg[a]	IV: 24-hourly and after dialysis
	Oral: 200mg	Oral: 12-hourly

a One-half of dose recommended for patients with normal renal function (see table XI).

Acyclovir 3% ophthalmic ointment is highly effective when applied 5 times daily to herpetic dendritic corneal ulcers, and is at least as effective for this condition as ointments containing 0.5 or 1% idoxuridine, 2% trifluridine, or 3% vidarabine. Ophthalmic application of acyclovir in combination with human α-interferon significantly improves upon the effect of acyclovir alone in superficial herpetic keratitis (dendritic or geographic ulcers). As expected, in herpetic disciform keratitis the response to ophthalmic administration of acyclovir is improved with the addition of topical corticosteroids to the treatment regimen, but acyclovir was no more effective than vidarabine for this indication, when both were administered topically in combination with ocular betamethasone.

Intravenous acyclovir is now a standard antiviral agent for the treatment of a range of serious manifestations of herpes simplex virus infection in immunocompetent patients. Notably, it is the treatment of choice in herpes simplex encephalitis, in which acyclovir has been shown to give a superior outcome when compared to vidarabine. However, preliminary evidence suggests that acyclovir and vidarabine are of similar efficacy in the treatment of neonatal herpes simplex infection. Acyclovir administered systemically also attenuates the development of rash and acute pain in herpes zoster in immunocompetent patients, although higher oral doses than used against herpes simplex infection and early initiation of therapy are required for maximal benefit. Importantly, with respect to acute herpes zoster, acyclovir protects against cutaneous dissemination or visceral involvement in susceptible patients, and against the long term occurrence of ocular sequelae of ophthalmic zoster. Unfortunately, post-herpetic neuralgia has usually been unaffected by acyclovir, however a recent multicentre study suggests acyclovir does confer protection against chronic pain, provided the drug is administered in adequate dosage as early as possible after acute symptom onset.

Immunocompromised patients with a variety of underlying illnesses and suffering from herpes simplex infection have also derived marked clinical and virological benefit from intravenous or oral acyclovir administration, in placebo-controlled clinical trials. More modest effects of acyclovir on time to healing in varicella zoster infections are seen among immunocompromised patients; the principal benefit ascribable to intravenous therapy is the protective effect of the drug against progression and disseminated infection. Although difficult to conduct, further comparative studies are required to assess the relative benefits of acyclovir and vidarabine treatment of varicella zoster virus infection in this patient group. Reactivation of cytomegalovirus can be delayed or prevented by high-dose intravenous acyclovir, however cytomegaloviral pneumonia and most conditions attributed to Epstein-Barr virus have not responded well to intensive systemic acyclovir therapy.

As prophylaxis against herpes simplex reactivations in leukaemic patients undergoing cytotoxic chemotherapy, and in bone marrow and renal transplant recipients, intravenous and oral acyclovir regimens have led to complete protection from recurrences during the period of drug administration (up to 6 months). Similar results were achieved with regard to varicella zoster virus reactivations, but not cytomegalovirus reactivations. Acyclovir prophylaxis during the period of most profound immunosuppression would appear justified in

patients identified by pretreatment serology and previous history of herpes simplex infection as being at high risk of potentially life-threatening recurrences.

Thus, in recent years the place of acyclovir in antiviral therapy has become more firmly established. Acyclovir has a unique position as the agent of choice in various manifestations of herpes simplex virus, whatever the immune status of the patient. In line with the *in vitro* antiviral activity of acyclovir, higher doses of the drug are required for maximal benefit in other herpesvirus infections. However, acyclovir appears to be at least as effective as alternative antiviral therapy (which at present is limited) for the treatment of varicella zoster virus infections. Despite an often life-saving benefit ascribed to acyclovir in acute herpetic disease, viral latency is unfortunately not eradicated, and recurrences of infection may follow the completion of therapy or prophylaxis. Comparisons with newer antiviral drugs are awaited to further define the place in therapy of acyclovir.

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Authors' address: *J.J. O'Brien*, ADIS Press Limited, 41 Centorian Drive, Private Bag, Mairangi Bay, Auckland 10 (New Zealand).

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For further information, please contact:
Dr E. Lopes Soares
R. Cidade de Cádiz, 14-3°, Dt° A
1500 Lisbon
PORTUGAL