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The Future of Antiviral Chemotherapy

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The field of antiviral chemotherapy has expanded over the past two decades, resulting in a new therapeutic area of increasing interest to the clinician. Alongside the production of vaccines against such viruses as polio, measles, rubella, and hepatitis B, effective drugs have been developed for many other common viral infections, including influenza A (amantadine, rimantadine), respiratory syncytial virus (aerosolized ribavirin), herpes simplex and varicella–zoster (acyclovir), cytomegalovirus (ganciclovir), and the human immunodeficiency virus (zidovudine). Some of these agents are useful for both prophylaxis against illness and for therapy.

Initially, many antivirals were available only for topical application, as systemic administration was associated with unacceptable toxicity. Even those drugs that could be given systemically had limited clinical application, again largely because of toxicity. However, advances in our knowledge of viral replication and of the molecular and cellular mechanisms of antiviral action have identified virus-specific targets for chemotherapeutic intervention. For example, through selective inhibition of an essential viral enzyme such as reverse transcriptase or interference with a specific stage in viral replication such as attachment to a target cell, it has been possible to develop a range of antiviral agents associated with fewer side effects than were their less-specific predecessors.

This discussion outlines the features of viral replication that are important in understanding targeted viral chemotherapy. It provides an overview of the early history of antiviral agents and then focuses on currently available and investigational antiviral drugs.

PATHOGENETIC AND THERAPEUTIC CONSIDERATIONS

Viruses replicate intracellularly, invariably using some of the cellular apparatus of the host. Understanding the details of viral replication allows antiviral therapy to be targeted at critical steps that are unique to the virus, thereby minimizing damage to the host cell. This approach can be illustrated using the human immunodeficiency virus (HIV), which has been studied extensively since its recognition as the cause of the acquired immune deficiency syndrome (AIDS) in 1983[6, 106] (Fig. 1). Knowledge of the receptor for the human immunodeficiency virus, the mechanisms involved in viral entry into the host cell, and the unique enzymes involved in viral replication has allowed the development of a number of investigational and one licensed drug (zidovudine) that are active at various points in the replicative cycle of this virus (Table 1).

Blocking Virus Attachment

The initial step in the infection of a cell by HIV involves binding of the virus to a specific receptor on the surface of the target cell. Attachment occurs through an interaction between the viral envelope glycoprotein (gp120) and certain epitopes of the CD4 molecule.[84] The HIV selectively infects only cells that express CD4.[26, 70] The overall amino acid sequence of gp120 is highly variable among different strains of HIV,[145] but within this envelope glycoprotein are highly conserved regions, includ-

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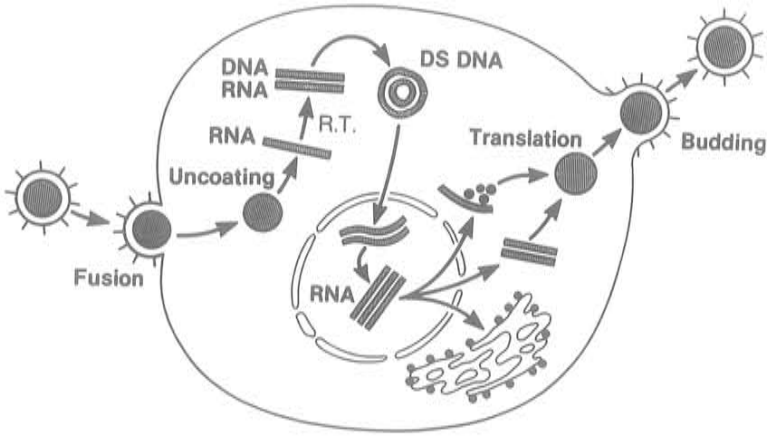

Figure 1. Schematic diagram of the replicative cycle of the human immunodeficiency virus.

ing that which binds to the CD4 molecule.[118] Infection has been inhibited in vitro by blockade of the receptor by a small synthetic peptide, peptide T, that mimics the binding portion of the viral envelope.[104, 136] Although monoclonal antibodies directed against both the CD4 molecule and the viral envelope glycoproteins have been considered as therapeutic agents, it is unlikely that they would be useful. First, blocking CD4 receptors throughout the host in itself produces immunodeficiency. Second, antibodies produced in vivo against gp120 do not prevent further lymphocyte depletion or progression of disease in HIV-infected individuals.[110, 135]

A related approach would be to alter the composition of the cell membrane, thus inhibiting viral attachment. Evaluation of the lipid compound AL721, which extracts cholesterol from cell membranes, is in progress.[79, 117]

Preventing Virus Entry or Replication

The mechanism of entry of HIV into the cell is incompletely defined but probably involves fusion of the viral-envelope glycoproteins with the host-cell membranes.[76] The glucosidase inhibitor castanospermine inhibits fusion and subsequent syncytium formation in vitro, but no animal or human data are yet available on its value in vivo.[54]

Table 1. *Target Sites for Antiretroviral Therapy*

TARGET	POTENTIAL THERAPY
Virus receptor	Monoclonal antibodies AL721
Viral entry	Castanospermine
Reverse transcriptase	Suramin HPA-23 Zidovudine Foscarnet
Regulation of gene expression	*TAT, trs/art* inhibitors
Translation of viral mRNA	Ribavirin
Assembly and release of viral proteins	Interferons Ampligen

Entry of the virus into the cytoplasm is followed by uncoating, thus exposing the single-stranded viral genomic RNA. By definition, retroviruses replicate through a DNA intermediate. A unique viral DNA polymerase, reverse transcriptase, uses the single-stranded RNA as a template for production of a plus strand of DNA, thus forming an RNA:DNA hybrid. Reverse transcriptase is a prime target for antiretroviral agents, as it can be inhibited selectively without interfering with host-cell DNA polymerase. Antivirals that act at this site include suramin, HPA-23, zidovudine and other dideoxynucleosides, and foscarnet. A complementary (minus) strand of DNA is synthesized through another action of the reverse transcriptase enzyme. The double-stranded DNA quickly circularizes within the cytoplasm of the cell and enters the nucleus. Viral DNA may then randomly insert into a host chromosome (this integrated form is known as proviral DNA) or remain unintegrated.

Upon cellular activation, host RNA polymerases transcribe proviral DNA into viral RNA, which is subsequently transported to the cytoplasm. This RNA comprises both messenger RNA, which is translated into viral proteins, and new viral genomic RNA. Following cleavage of polyproteins and post-translational modifications, the viral proteins are assembled and the new virions released by budding from the surface of the cell. These final stages provide further target sites for antiviral chemotherapy. The post-translational 5′ capping of viral mes-

Table 2. *Features of Ideal Antiviral Agent*

Inhibits viral replication in all infected cells
Nontoxic (no deleterious effect on host cells)
Orally absorbed
Penetrates CSF, brain, and other privileged sites of viral replication (*e.g.*, eye)

senger RNA can be inhibited in vitro with drugs such as ribavirin.[48] Interferons act in a nonspecific manner to prevent assembly and release of viral proteins.[105]

Regulation of viral gene expression in HIV is extremely complex and involves the combined action of a number of viral gene products. These regulatory proteins are still incompletely understood, although much is known about the *tat*-gene-encoded transactivator protein and the *trs/art*-gene-encoded antirepressor protein. The *tat* protein is thought to increase the rate of gene expression and replication of HIV by enhancing both transcription and translation of viral mRNA.[40] The *trs/art* gene product reduces the negative regulatory effects on translation of viral mRNA.[15] These regulator proteins may be a target for future antiretroviral therapy.

Other Considerations

In addition to the replicative cycle of the virus, other considerations in the treatment of viral infections include the cell type susceptible to infection and the access of the antiviral agent to these cells. Identification of the CD4 molecule as the receptor for HIV was followed by the realization that a variety of cells other than the helper–inducer ($CD4^+$) subset of lymphocytes can be infected.[97, 114] Perhaps the most important of these cells is the monocyte–macrophage,[22, 46] which provides a reservoir for HIV in vivo. One recent in vitro study has shown that zidovudine does not inhibit replication of HIV in macrophages yet is very active in lymphocytes.[108] This finding demonstrates the importance of testing for efficacy in different target cells. The virus has been cultured from blood, cerebrospinal fluid, genital secretions, tears, and saliva and is thus widely disseminated.[13, 62, 64] The ideal antiretroviral agent would therefore specifically inhibit viral replication in all infected cell types and in addition would traverse the blood–cerebrospinal fluid and blood–brain barriers. Moreover, it would be nontoxic and well absorbed when given by mouth and hence suitable for long-term administration (Table 2).

Although this discussion specifically relates to the HIV, the general principles described can be applied to the therapy of infections with most other human viruses. Viral attachment, uncoating, genome replication, synthesis of viral proteins, and assembly are in fact common to all viruses.

ANTIQUATED ANTIVIRALS

Antiviral chemotherapy is relatively new, having lagged the evolution of specific antibacterial agents by nearly a quarter of a century. Tissue culture technology was a significant early development, enabling evaluation of the efficacy of antiviral agents and facilitating classification of viruses. The first chemical shown to have clinically useful antiviral activity was methisazone, a thiosemicarbazone that was shown to inhibit poxvirus replication in mice and humans when given prophylactically.[7, 58] However, apart from kindling interest in antivirals, thiosemicarbazone had limited clinical utility. The next milestone was the recognition in 1957 that the naturally occurring proteins, interferons, can protect cells from the replication and cytopathic effects of a wide range of both DNA and RNA viruses.[52] Since then, three classes of interferons have been characterized. They have a semiselective inhibitory effect on viral replication, acting at a post-translational step.

Development of Nucleoside Analogues

The first generation of nucleoside analogues active against the herpesviruses was developed more than two decades ago but had only limited clinical application because of toxicity. Idoxuridine, which competes with thymidine for incorporation into viral and cellular DNA, was the first effective antiviral therapeutic agent.[69] The ocular preparation of this nucleoside analogue was successful in treating herpes simplex keratoconjunctivitis and received Food and Drug Administration (FDA) approval for the treatment of this condition in the mid 1960s. Because many of the early studies of parenteral idoxuridine were open trials, the efficacy and toxicity of the drug could not be adequately evaluated, although there were many enthusiastic anecdotal reports. Eventually, double-blind comparative studies of idoxuridine for the treatment of herpes simplex encephalitis showed that the drug had unacceptable toxicity when administered systemically, with no impact on the mortality rate.[3] Similarly, topical idoxuridine therapy proved ineffective for genital

herpes, and use of the drug was abandoned except for herpes simplex keratitis. Dimethylsulfoxide (DMSO) augments the cutaneous penetration of idoxuridine, but because this solvent is teratogenic and causes ocular damage in animals, it is not approved for cutaneous application within the United States.[4]

Since the discovery of idoxuridine, a variety of related nucleoside analogues have been synthesized and assessed in clinical trials. Cytosine arabinoside is active in vitro but was ineffective and toxic in vivo. Adenine arabinoside (araA; vidarabine) is a purine nucleoside analogue that is phosphorylated by cellular enzymes.[137] As the triphosphate, it competitively and selectively inhibits the DNA polymerase of some herpesviruses, poxviruses, and probably hepatitis B virus.[41, 137] At therapeutic concentrations, cellular toxicity is low, as the drug preferentially inhibits viral DNA polymerases rather than the cellular enzymes.[10] In 1977, Whitley and his colleagues showed that vidarabine treatment reduced the mortality rate from herpes simplex encephalitis.[138] This collaborative trial was criticized because of its premature closure and small numbers, which made it statistically impossible to assess the quality of life in survivors. In a larger, uncontrolled study that followed the initial trial, evidence that vidarabine improved the clinical outcome was unconvincing.

Recent Work with Vidarabine

The beneficial effects of systemic vidarabine for the treatment of varicella–zoster have been clearly demonstrated in immunocompromised individuals.[140] In a placebo-controlled crossover study, patients receiving vidarabine experienced less pain and more rapid healing of their lesions than those receiving a placebo.[144] Controlled trials have established the need for early intervention in varicella–zoster infections in immunocompromised individuals, as the frequency of cutaneous dissemination and visceral complications and the incidence of post-zoster neuralgia are reduced only if treatment is instituted within the first 72 hours after the onset of rash.[144]

Vidarabine was the first antiviral to receive FDA approval for the treatment of herpes simplex encephalitis, varicella–zoster virus infections of immunocompromised hosts, and neonatal herpes simplex infection.[142] Despite its undisputed efficacy, the drug has several limitations, including relatively common gastrointestinal side effects, poor intramuscular absorption, and the requirement that it be given intravenously in a large volume of fluid.[146] Concern regarding possible mutagenicity or carcinogenicity in humans has mandated its use only in life-threatening infections. Today, vidarabine is recommended only for disseminated herpes simplex infection in the neonate. Although acyclovir is not licensed for this indication, it appears to be equally effective, easier to administer, and probably less toxic. Vidarabine can be considered only a second-line agent for the treatment of herpes simplex encephalitis and varicella–zoster infections.

New Drugs and Their Testing

As a result of the AIDS epidemic, the therapeutics industry has been pressured to develop effective antiretroviral agents urgently. This epidemic also has re-emphasized the necessity for randomized, double-blind prospective trials to expedite the evaluation of any potential agent: in circumstances where these trials have not been performed, doubts remain regarding safety and efficacy. An example is HPA-23, an antimoniotungstate compound shown in vitro to have antiviral activity.[11] No controlled trials were performed to assess the clinical benefit of this drug compared with placebo, and the literature contains isolated reports of beneficial effects intermixed with communications describing toxicity. As a result, the value of the drug remains obscure.[112, 134]

Another illustration is the history of suramin, a reverse transcriptase inhibitor that also has in vitro activity against HIV.[30, 95] More than half a decade of clinical experience with this drug in the treatment of trypanosomiasis[33] and onchocerciasis allowed investigators a degree of comfort in proffering this drug for use in patients with AIDS or AIDS-related complex. On the basis of published safety and efficacy in a preliminary clinical study involving 10 patients with AIDS,[9] a multicenter phase I trial was organized. The results of this trial showed that despite modest antiviral activity in vivo, there was no favorable clinical or immunologic effect, yet there was unacceptable serious toxicity (severe neutropenia, fatal hepatic failure, renal dysfunction, and adrenal insufficiency).[16, 68] Without a well-controlled trial in this patient population, both the lack of efficacy and the toxicity of suramin might not have been so quickly realized.

LICENSED AND INVESTIGATIONAL ANTIVIRALS

Amantadine and Rimantadine

In 1964, amantadine, a primary amine with an unusually structured tricyclic carbon ring, was reported to inhibit the replication of influenza A virus in vitro[27] (Fig. 2*A*). (The drug has little or no activity against influenza B virus at concentrations achievable in vivo.[100]) Over the next few years, clinical trials demonstrated the prophylactic and therapeutic efficacy of amantadine, and in 1966, it was licensed for prophylaxis of influenza A and subsequently released under the brand name Symmetrel. A structurally similar derivative, rimantadine, has greater in vitro antiviral activity than amantadine[119, 129] and was recently licensed for use in the U.S. (Fig. 2*B*).

Controlled studies of amantadine and rimantadine demonstrate 70 to 91 per cent efficacy in preventing disease from influenza A when the drug is given in an oral dose of 200 mg per day.[32] Most of these studies have been performed in healthy young adults, although trials of both drugs have also been conducted in households, schools, and nursing homes and in each setting have demonstrated prophylactic efficacy when compared with placebo.[17, 101, 103] Few studies have compared amantadine and rimantadine for protection against influenza A. In one such study, 450 volunteers participated in a placebo-controlled, double-blind trial during an outbreak of A/H1N1 and A/H3N2 in Vermont; each subject received an antiviral dose of 100 mg twice daily for 7 days.[32] Both drugs had efficacy rates of 85 per cent or higher in preventing disease. However, the incidence of withdrawal from the study because of central nervous system side effects (insomnia, jitteriness, difficulty in concentrating) was 13 per cent in the amantadine-treated group compared with 6 per cent and 4 per cent in the rimantadine and placebo groups, respectively. These dose-related side effects of amantadine are thought to be secondary to its dopamine-enhancing properties, which are the basis for its benefit in Parkinson's disease. Adverse central nervous system reactions are more common in elderly individuals, and the incidence is increased by concomitant antihistamine therapy.[91] Although rimantadine may also cause central nervous system toxicity, the different pharmacokinetics of the two drugs result in a much lower frequency of adverse reactions with rimantadine.[32] The plasma concentration of rimantadine is much lower than that of amantadine with identical oral doses, especially in the elderly.[102]

Apart from their prophylactic value, amantadine and rimantadine have also been shown to be useful in the treatment of adults with mild self-limited influenza.[133] Efficacy requires beginning treatment within 48 hours of the onset of symptoms.[128] Although the studies have had mixed results, the majority demonstrate a modest but statistically significant effect when compared with aspirin or placebo. In general, there is a reduction in fever and systemic complaints by 50 per cent and a shortening of illness by at least 1 day.[128, 133] The dose is usually 200 mg per day orally for 5 days; however, intermittent aerosol administration has also been effective.[61] (Aerosolized amantadine remains investigational.) There have not yet been controlled studies examining the effect of these agents in the treatment of patients with complications of influenza such as pneumonia.

Current recommendations by the Immunization Practices Advisory Committee in the U.S. are that amantadine be combined with vaccination for seasonal prophylaxis in individuals considered to be at high risk for complications and death from influenza.[67] Such persons would include adults and children with cardiopulmonary disease, elderly institutionalized individuals, adults over 65 years of age, and children on long-term aspirin therapy. Amantadine is also considered useful for patients exposed to influenza during a nosocomial outbreak and for household contacts after recogni-

Figure 2. Structure of amantadine hydrochloride (*A*) and rimantadine hydrochloride (*B*).

Table 3. *Clinical Antiviral Spectrum of Ribavirin*

VIRAL INFECTION	MODE OF ADMINISTRATION
Respiratory syncytial virus*	Aerosol
Influenza A, B	Aerosol
Measles†	Oral
Human immunodeficiency virus	Oral
Lassa fever‡	Oral, intravenous

*Only licensed indication in the USA.
†Studies in Mexico, Brazil, Philippines.
‡Studies in Sierra Leone.

tion of influenza in a family member. However, despite accumulated evidence for the prophylactic efficacy of amantadine, the drug is little used for this purpose, and immunization, which affords similar incomplete protection, remains the mainstay of prevention. A recent cost–benefit analysis of the efficacy of seasonal chemoprophylaxis compared with vaccination in 100 nursing home residents showed that amantadine therapy resulted in fewer cases of influenza, hospitalizations, and deaths but was 6.5 times as expensive as vaccination alone.[101] With either strategy, influenza control programs in nursing homes were both beneficial and cost-effective.[101]

Ribavirin

Ribavirin is a synthetic triazole nucleoside with in vitro activity in its triphosphate form against a broad range of viruses, including respiratory syncytial virus, influenza A and B, parainfluenza 1 and 2, measles, HIV, and the agent of Lassa fever[57, 71, 82, 83] (Table 3). The mechanism of its action is via both inhibition of viral polymerases and prevention of 5′ capping of mRNA, a step essential for translation of the mRNA into viral proteins.[127] In the U.S. clinical use is limited to aerosol administration; elsewhere, the drug is also available for oral and parenteral therapy.

Whereas antibiotics play no role in the treatment of uncomplicated respiratory syncytial virus infections in developed countries, recent work has shown that aerosolized ribavirin results in demonstrable clinical improvement in infants with severe respiratory syncytial virus pneumonia, bronchiolitis, and croup.[56, 126] Placebo-controlled clinical studies of continuous aerosolized ribavirin therapy (delivered in a tent or oxy-hood) have shown a reduction in retraction, lower respiratory tract signs, lethargy, and cough, as well as an improvement in arterial oxygen saturation, within 48 hours of initiating therapy.[56, 126] Despite these benefits, there have been no studies showing reduced mortality rates. Viral shedding is decreased in treated infants compared with controls who receive aerosolized water.[56] No toxicity or side effects have been reported. As with amantadine and rimantadine therapy, ribavirin is most effective when administered within the first few days of the illness.[111]

A number of specialized pediatric intensive care units have gained experience administering aerosolized ribavirin to intubated and mechanically ventilated babies.[111] Problems relating to drug precipitation within tubing, thus potentially blocking air flow, have led to the current FDA recommendation that ribavirin aerosol not be used for infants requiring assisted ventilation.

Who should receive aerosolized ribavirin? Any infant hospitalized with severe respiratory syncytial virus infection who is not responding to conventional therapy (supplemental oxygen) should be considered for aerosolized ribavirin in an attempt to avoid intubation. Infants in high-risk categories (those less than 2 years of age with underlying cardiorespiratory disease or immunosuppression) who have a higher chance of requiring intervention should also be given aerosolized ribavirin as soon as the diagnosis of respiratory syncytial virus infection is suspected.

Although the principal (and only FDA-approved) clinical use of aerosol ribavirin is for treatment of respiratory syncytial virus infection, several investigators have demonstrated the efficacy of this therapy for the treatment of uncomplicated influenza A and B in college students.[49] Symptoms were reduced and viral shedding from the respiratory tract was decreased with 3 days of therapy. Also, oral and intravenous ribavirin have been used successfully in the treatment of Lassa fever in trials conducted by the Centers for Disease Control in collaboration with workers in Sierra Leone.[83] Oral therapy has also been used in Mexico, Brazil, and the Philippines in the treatment of measles, resulting in a reduction in the severity and duration of illness as well as the frequency of complications.[131]

Most recently, the efficacy of oral ribavirin has been examined in the treatment of HIV infection. In three small uncontrolled phase I trials of increasing duration (2 weeks, 8 weeks, and 1 year) in patients with AIDS and symptomatic advanced AIDS-related complex, there was a virologic response and immunologic improvement. Because of the study design, clini-

cal efficacy could not be addressed.[24] At a dose of 600 mg per day, the therapy was well tolerated, and anemia necessitating blood transfusion was uncommon. In a randomized, blinded, multicenter trial, more than 160 homosexual men with symptomatic AIDS-related complex were treated with placebo or 600 mg or 800 mg per day of ribavirin for 24 weeks. With the highest dose, no patient went on to have AIDS during the trial, whereas AIDS appeared in 6 of 55 and 10 of 56 who were treated with 600 mg per day or placebo, respectively.[80] Because of the possibility that the observed beneficial effects attributed to ribavirin may actually have been attributable to an excess of highly immunosuppressed patients in the placebo group, the results of this study were not accepted by the FDA. Further controlled studies are needed to assess the efficacy of ribavirin in the therapy of HIV-related disease.

Acyclovir

The development of acyclovir by the Burroughs Wellcome Co. in 1978 may mark the most important achievement in the field of antiviral therapy to date. This drug has radically changed the approach to treatment as well as the outcome of herpesvirus infections.

The antiviral activity of acyclovir depends on its conversion to the triphosphate[89] (Fig. 3). The initial activation step, resulting in acyclovir monophosphate, is mediated by the herpesvirus-specified enzyme, thymidine kinase, which is present only in infected cells.[34] Cellular kinases are responsible for subsequent conversion to acyclovir triphosphate, the active form of the drug. Acyclovir triphosphate inhibits viral DNA polymerases, and its incorporation into newly synthesized viral DNA results in chain termination.[34] Host cells are spared from toxicity, as activation occurs virtually exclusively in virus-infected cells; also, binding of acyclovir to viral thymidine kinase is about 100-fold greater than binding to the cellular kinases.[34] Herpes simplex virus 1 and 2 and varicella–zoster virus are all susceptible to acyclovir; because Epstein-Barr virus (EBV) and cytomegalovirus lack thymidine kinase, they are less susceptible (host-cell kinases enable limited phosphorylation). However, EBV DNA polymerase is highly sensitive to acyclovir triphosphate; levels achieved in normal cells appear to inhibit EBV in vitro and in vivo.

Acyclovir has numerous advantages over vidarabine, including less toxicity, higher solubility (and thus less fluid for intravenous administration), and a higher therapeutic index. Unlike vidarabine, the drug is not rapidly degraded in plasma; hence the 20 per cent absorption following oral administration is sufficient to provide therapeutic serum levels.[31] Good corneal penetration has given acyclovir further clinical value in the topical therapy of herpes simplex keratitis. A combination of oral and topical acyclovir is the treatment of choice for this condition.

Prior to the advent of antivirals effective against herpes simplex, the outcome of this type of viral encephalitis was grim, with a mortality rate of 70 per cent and severe residual neurologic disability in many survivors.[143] Use of vidarabine for the treatment of herpes simplex encephalitis reduced the mortality rate to between 39 and 54 per cent, depending on patient age and level of consciousness at the initiation of therapy.[139] The mortality rate in published studies is now around 28 per cent, with two thirds of the survivors having normal neurologic function.[139]

The treatment of genital herpes has changed

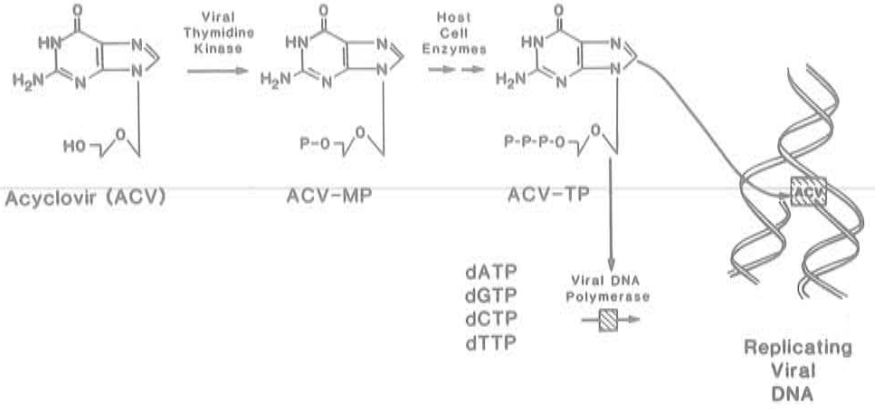

Figure 3. Pathway of phosphorylation of acyclovir to the monophosphate and triphosphate derivatives.

dramatically since the advent of acyclovir. Topical, oral, and intravenous administration have all proved efficacious, although oral therapy has provided the most benefit (Table 4). In placebo-controlled trials of patients with first-episode genital herpes, systemic (oral or intravenous) acyclovir reduced the duration of virus shedding by 75 per cent, virtually completely suppressed the formation of new lesions, and shortened the time to healing by 50 per cent.[20] Oral therapy (200 mg five times daily for 10 days) and intravenous therapy (5 mg per kg infused over 1 hour every 8 hours) appear to be about equally effective, but oral acyclovir is the drug of choice in terms of cost and convenience.

For episodic therapy of recurrences, acyclovir treatment resulted in slightly shortened viral shedding and a 10 to 20 per cent reduction in time to healing when compared with placebo.[51] Patient-initiated therapy (at the onset of the first symptom) was somewhat more effective than physician-initiated therapy (commenced within 48 hours of onset).[107] Thus, self-initiated treatment is recommended, and patients with frequent and severe outbreaks should have medication available at home. Untreated episodes are, however, often mild, and intervention with acyclovir may be of limited value. Topical acyclovir therapy for mucocutaneous lesions in immunocompromised hosts achieves results similar to those of oral therapy, but the latter has the additional benefit of treating intraoral lesions, which cannot be treated effectively with topical therapy, as well as the potential advantage of preventing virus dissemination.[122, 141] Topical therapy is not effective for recurrences of herpes simplex in patients with normal immune function.[77]

Whereas episodic therapy of genital herpes simplex infection offers only modest clinical benefit, long-term suppressive therapy for individuals who have frequent recurrences has produced more striking results. Trials have generally involved individuals with 12 or more recurrences per year and have proved acyclovir to be both safe and effective. In a recent study, oral therapy (400 mg twice daily) in 348 subjects over a 2-year period prevented or reduced the annual frequency of recurrences in more than 90 per cent of individuals. However, fewer than 30 per cent of those treated remained recurrence free for the 2-year period.[90]

Who should receive suppressive therapy? Continuous daily therapy should be considered for any individual with frequent or severe recurrences of genital herpes. In immunosuppressed patients, particularly those with AIDS, suppressive therapy is beneficial for those with increasing severity and frequency of recurrences. For individuals who experience recurrences of oral herpes associated with sun or wind exposure, prophylaxis with acyclovir is

Table 4. *Recommended Acyclovir Therapy for Herpes Simplex and Varicella–Zoster Virus Infections*

	DOSE (mg)	REGIMEN	ROUTE	DURATION
Immunologically normal host				
Initial genital herpes	400	3 × daily	Oral	Until lesions heal
	200	5 × daily	Oral	
Recurrent genital herpes				
Mild	nil			
Severe	200	5 × daily	Oral	Until lesions heal (patient initiated)
Frequent	400	2 × daily	Oral	Chemoprophylaxis indefinitely?
Recurrent oropharyngeal				
Sun/wind induced	400	2 × daily	Oral	1 day before, during, and 2–3 days after exposure
Varicella				
No complications	nil			
Pneumonia	10/kg	q8 hours	IV	Until lesions heal (unproved)
Zoster				
No complications	nil			
Ophthalmic	800	q4 hours	Oral	Until lesions heal
Compromised host				
Recurrent mucocutaneous herpes	400	5 × daily	Oral	Until lesions heal
	400	2 or 3 × daily	Oral	Duration of immunosuppression (suppressive therapy)
Varicella	10/kg	q6 hours	IV	Until healed or oral therapy feasible
Zoster	10/kg	q8 hours	IV	Until healed or oral therapy feasible

useful (400 mg twice daily starting the day prior to expected exposure and continuing until several days after exposure).[125] Acyclovir is definitely superior to sunscreen, even with SPF-15 protection, in preventing recurrent orofacial herpes in skiers.[92] Suppressive acyclovir has also been reported to control recurrences of herpetic whitlow and other nongenital herpetic diseases.[73]

There is some concern regarding the potential for development of mutant strains of herpesvirus resistant to acyclovir with long-term therapy. Indeed, mutant strains of the virus have been isolated, usually lacking thymidine kinase and thus termed "TK^-" mutants.[5] The majority of these strains are not associated with a poor clinical outcome; however, there have been reports of disease in immunocompromised patients, from whom TK^- strains have been isolated, characterized by progressive mucocutaneous ulceration and resistance to acyclovir.[25] Whether these failures are due in part to noncompliant use of acyclovir or to an inadequate dose of the drug has not been fully evaluated. Management in these rare instances involves a trial of intravenous acyclovir with repeated viral cultures to prove resistance, cessation of immunosuppressive therapy if possible, intensive local skin care, and consideration of other therapy such as vidarabine or foscarnet.

Intravenous acyclovir has proved beneficial for the treatment of varicella–zoster in previously healthy as well as immunocompromised individuals. In two small prospective randomized trials against varicella–zoster infection in patients with hematologic malignancies and in bone-marrow transplant recipients, intravenous acyclovir was superior to vidarabine.[120] Acyclovir therapy decreased the duration and severity of infection and reduced the rate of cutaneous and visceral dissemination. However, the drug had variable effects on acute pain and no effect on postzoster neuralgia.[85] Corticosteroids were also ineffective for preventing postzoster neuralgia, even when combined with acyclovir.[37]

Serum acyclovir concentrations of 3 to 7 μg per ml, fifteen times that necessary to inhibit herpes simplex, are required in order to inhibit varicella–zoster virus.[8] Thus, the dose of oral acyclovir for varicella–zoster infection is much higher than that for herpes simplex, and even then, optimal serum concentrations are achieved only erratically. In a recent British study of 205 healthy elderly individuals with herpes zoster who were given oral acyclovir (800 mg five times daily) or placebo within 72 hours of the onset of the rash, acyclovir accelerated healing of vesicles and reduced acute pain.[85] Stratification of these patients within the study illustrated the importance of early therapy. Early oral acyclovir is also beneficial in herpes zoster ophthalmicus, expediting resolution of signs and symptoms and shortening the duration of viral shedding.[18] In patients with AIDS or AIDS-related complex, dissemination of infection from dermatomal zoster is unusual, and it is arguable whether those individuals require any therapy. A placebo-controlled study is planned. If dissemination or progressive local infection is apparent, however, it would be prudent to use intravenous acyclovir rather than to rely on oral therapy.

An acyclovir prodrug, BW515 (6-deoxyacyclovir), which is converted to acyclovir by xanthine oxidase,[21] is being considered for clinical evaluation. As a result of its high oral bioavailability (close to 100 per cent), it may be possible to give BW515 in lower doses or at less-frequent intervals for oral treatment of herpesvirus infections. Another acyclovir prodrug, A134U, is a diamino analogue of acyclovir.[72] After rapid in vivo deamination to acyclovir by adenosine deaminase, the oral absorption of A134U approaches 80 per cent. Human studies with these drugs have not yet begun.

Ganciclovir

A recently developed experimental drug, ganciclovir (dihydroxy-propoxy-methyl-guanine; DHPG) is an acyclic guanine analogue structurally similar to acyclovir, which was shown to be beneficial for treatment of cytomegalovirus infection (Fig. 4). Ganciclovir triphosphate inhibits the DNA polymerase of all herpesviruses, including cytomegalovirus.[14] As cytomegalovirus does not encode a thymidine kinase, the mechanism by which ganciclovir is phosphorylated in cytomegalovirus-infected cells is unknown. This drug has shown promising results in predominantly uncontrolled studies for life-threatening and sight-threatening cytomegalovirus disease in AIDS patients and other immunocompromised individuals.[19, 35] In patients with AIDS, the drug has demonstrated virologic efficacy and clinical benefit against cytomegalovirus retinitis and, to a lesser extent, colitis.[19] In patients with retinitis, ganciclovir delays the progression of retinopathy and decreases retinal opacification, hemorrhage, and vasculitis, allowing stabilization or even improvement in visual acuity.[63, 74] The drug is administered initially in a dose of 5 mg per kg

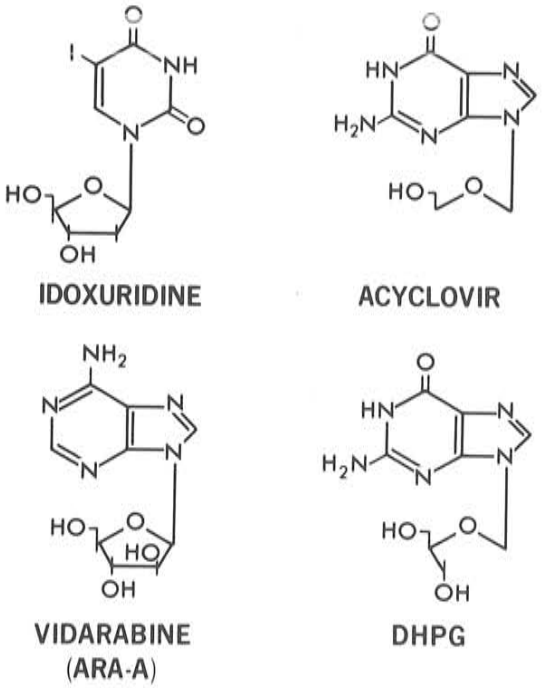

Figure 4. Structure of some nucleoside analogues with activity against herpesviruses.

in a 1-hour infusion every 12 hours for 10 to 14 days. In both AIDS patients and other immunocompromised individuals, maintenance therapy then is required in an attempt to prevent reactivation (4 to 7 mg per kg infused once daily for 5 to 7 days per week). However, disease may worsen despite continuous maintenance therapy.[63]

Although there is no clear-cut answer as to which patients with cytomegalovirus retinitis should receive ganciclovir, we believe the drug should be reserved for those individuals with visual symptoms or those with progressive disease threatening the macula. Controversy exists among the small number of physicians who have clinical experience with the drug whether it should be used for patients with only peripheral disease evident on funduscopic examination, for those who have already suffered complete loss of vision, or both.

There appears to be no improvement in AIDS patients treated with ganciclovir for cytomegalovirus pneumonitis. The isolation of cytomegalovirus from bronchoalveolar lavage is of doubtful clinical significance in this population.

The most common side effect of ganciclovir is neutropenia, which develops in 20 to 50 per cent of patients and may necessitate dosage modification or cessation of therapy.[63, 121] Less commonly, thrombocytopenia,[74] retinal detachment,[63] hallucinations,[19] and rash[19] have been reported. A significant limitation of ganciclovir is the lack of an oral preparation. Despite these restrictions, ganciclovir offers important clinical and virologic advantages over early therapies for cytomegalovirus disease. The drug is currently available only on a compassionate-plea basis. Although there is a wealth of data indicating its efficacy, prospective placebo-controlled studies appear to be necessary in order for ganciclovir to obtain FDA approval.

Foscarnet

Foscarnet (phosphonoformate), a pyrophosphate analogue, has been known for at least a decade to inhibit replication of all herpesviruses in vitro through selective inhibition of viral DNA polymerases.[99] Poor oral absorption necessitates intravenous administration.[86] Although there have been only a handful of studies, it would seem that herpes simplex types 1 and 2 are less susceptible to phosphonoformate than to agents such as acyclovir. Studies examining topical therapy for recurrent genital herpes have shown reduced viral shedding but have failed to demonstrate clear clinical benefit.[113]

The principal side effect of phosphonoformate is renal toxicity with reversible tubular dysfunction.[47] Anemia and muscle twitching may also occur. The drug is deposited in bones, but no adverse effects related to this have been recognized.

Clinical studies are ongoing to evaluate the efficacy of phosphonoformate in the treatment of cytomegalovirus disease in AIDS. The drug has been given to patients with severe cytomegalovirus infections as a constant intravenous infusion over 1 to 4 weeks with clear evidence of benefit.[47] Of interest, the drug inhibits reverse transcriptase activity, and therapy results in a decrease in serum HIV p24 (core) antigen.[116] A pilot study involving 11 patients with AIDS and AIDS-related complex who received a 3-week constant infusion of phosphonoformate showed that the drug suppresses HIV replication.[39] Thus, the drug may serve a dual virologic purpose in this population by inhibiting replication of both cytomegalovirus and HIV.

Zidovudine

Zidovudine (3′-azido-3′-deoxythymidine, azidothymidine, Retrovir) was first synthesized in 1964 by Horwitz and colleagues as an anticancer

drug[66] (Fig. 5). In 1974, Ostertag and colleagues demonstrated that this thymidine analogue could inhibit the replication of type-C murine retroviruses. However, there was no clinical application for the compound until early 1985, when it was shown to have in vitro activity against HIV.[96] Within 6 months of this observation, the first clinical trials commenced to evaluate zidovudine in the treatment of AIDS. The phase I study demonstrated good oral bioavailability (approximately 60 per cent) with cerebrospinal fluid levels about half the plasma levels.[148] This feature is particularly important because HIV replicates within the central nervous system.[75] The drug was reasonably well tolerated over the 6-week trial, and clinical and immunologic improvement was noted.[148]

On the basis of these promising preliminary data, a multicenter prospective, randomized, placebo-controlled study was initiated in the U.S. in February 1986. About 160 patients with AIDS who had recovered from one episode of *Pneumocystis carinii* pneumonia and about 120 patients with symptomatic advanced AIDS-related complex were enrolled. Approximately half of the individuals received zidovudine (250 mg every 4 hours); these individuals were well matched in terms of sex, age, and immunologic variables with those receiving the placebo. The trial was designed to run 12 months. However, interim analysis by an independent data monitoring board in September 1986 showed a significant decrease in the mortality rate in patients receiving zidovudine (19 deaths in the placebo group compared with one death among those receiving zidovudine).[42] On ethical grounds, the placebo arm of the study was thus abandoned, and those individuals were offered zidovudine. Thus altered, the trial has continued in order to assess long-term toxicity and efficacy.

At the time of the interruption of the trial, the zidovudine-treated patients showed other evidence of clinical and immunologic improvement. Within this group, there were fewer opportunistic infections, an improvement in weight and Karnofsky performance scores, and a statistically significant increase in the number of CD4-bearing (T-helper) lymphocytes.[42] However, serious adverse reactions, particularly bone-marrow suppression, were observed. The majority of zidovudine-treated patients developed a macrocytosis within several weeks of the start of therapy.[109] Anemia, often necessitating blood transfusion, or neutropenia (less than 750 polymorphonuclear leukocytes per μl) occurred in 45 per cent of zidovudine recipients. Stratified data showed that patients with AIDS (rather than AIDS-related complex) and those with low CD4 counts at entry to the study were the most likely to suffer hematologic toxicity.[109] Zidovudine therapy is also associated with relatively frequent occurrences of headaches, nausea, insomnia, and myalgias[109] (Table 5). Other, less commonly reported, neurologic toxicities include the development of seizures[55] and acute onset of Wernicke's encephalopathy.[29] Pancytopenia with irreversible bone-marrow suppression has been documented.[50] Progressive nail pigmentation has been reported, with transverse bluish discoloration at the base of fingernails and toenails.[43] Fever and a maculopapular skin rash, usually involving the trunk, develops in a few patients after several weeks to months of zidovudine therapy (Ed Kirk, Burroughs Wellcome Company, unpublished data; Mark Jacobson and coworkers, submitted for publication). Because zidovudine undergoes hepatic

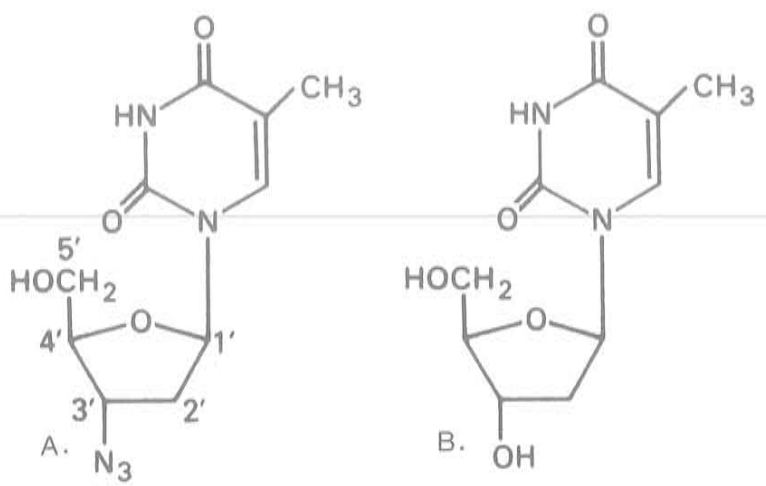

Figure 5. Comparative structures of zidovudine (*A*) and thymidine (*B*).

Table 5. *Adverse Effects Associated with Zidovudine*

Anemia*	Myalgia
Leukopenia (particularly neutropenia)*	Insomnia
Macrocytosis	Fever and rash (rare)
Headaches	Seizures (rare)
Nausea	Nail pigmentation (rare)

*More common in patients with CD4 <100 per mm^3.

glucuronidation, toxicity may be potentiated by concomitant administration of acetaminophen or other compounds that have similar metabolism.[109]

There was a reduction in serum HIV p24 (core) antigen in the zidovudine group but not the placebo group, demonstrating that the drug has in vivo antiviral activity.[42] However, on cessation of therapy, antigenemia returns to baseline levels, suggesting that life-long therapy with zidovudine will be necessary.

At the termination of the trial in September 1986, all patients receiving the placebo were offered zidovudine. Analysis in April 1987 showed that the mortality rates in the original zidovudine and original placebo-treated groups after 36 weeks of therapy were 6.2 and 39.3 per cent, respectively, indicating longer survival in patients treated with zidovudine.[42] Although this phase II study was prematurely terminated, it emphasizes the importance of controlled trials.

Zidovudine received FDA approval for the treatment of HIV infection in March 1987 and has been marketed by Burroughs Wellcome under the brand name Retrovir at a current approximate cost of $5000 to $8000 per patient per year. It is anticipated that the cost to an individual will soon be reduced. Controlled studies are under way to evaluate the usefulness of this drug in asymptomatic HIV-infected individuals, those with Kaposi's sarcoma, and children with AIDS and to assess further interactions with other drugs such as acyclovir. A small uncontrolled study of patients with HIV-related dementia has demonstrated clinical, neurophysiologic, and radiologic improvement with zidovudine therapy,[147] but more extensive and controlled evaluations are necessary in this subgroup of patients.

Spurred on by encouraging data with zidovudine therapy, investigators have quickly examined other 2′-3′-dideoxynucleoside derivatives in the hopes of finding an analogue with similar efficacy but less toxicity. One of these compounds, 2′-3′-dideoxycytidine, has proved more potent on a molar basis than zidovudine in inhibiting the HIV reverse transcriptase and in terminating viral DNA synthesis.[94] However, early clinical studies have revealed severe toxicity, particularly the development of peripheral neuropathy (T. Merigan, unpublished data).

Investigational Antiretroviral Agents

There are currently in excess of 70 antivirals undergoing assessment for antiretroviral activity, some of which have reached the stage of clinical evaluation.

AL721 is a lipid mixture containing neutral glycerides, phosphatidylcholine, and phosphatidylethanolamine in the ratio 7:2:1.[79] AL721 alters the lipid content of cell membranes and possibly the HIV envelope by extracting cholesterol and thereby preventing viral attachment and infection.[117] In vitro studies have demonstrated antiretroviral activity; however, there have been no controlled clinical studies.

Ampligen, a mismatched double-stranded RNA polymer, has in vitro antiretroviral and immunomodulatory activity through induction of interferons.[98] Ten patients with AIDS and AIDS-related complex were given 200 to 250 mg of ampligen twice a week for as long as 18 weeks. The drug was well tolerated, and in 9 of 10 patients, HIV replication was suppressed during therapy.[12] In vitro studies have shown synergy between ampligen and zidovudine in inhibiting the replication of HIV.[93] This could allow a reduction in the dose of zidovudine and thus decrease toxicity. Clinical studies of this combination have not yet been initiated.

One of the newest antiretrovirals is castanospermine, an alkaloid isolated from the seeds of an Australian chestnut tree. By inhibiting glucosidase and thus preventing normal processing of glycoproteins, castanospermine interferes with fusion of the viral envelope glycoproteins with the CD4 receptor.[54] Whether this compound offers a realistic prospect for a new treatment is uncertain at this early stage.

Interferons

A decade ago, condylomata acuminata (anogenital warts) were considered a trivial illness; more recently, the recognition of the relation between human papillomavirus infections (especially with HPV-16 and HPV-18) and the development of genital malignancy has emphasized the importance of diagnosis and therapy.[23] Local treatment options are numerous and include podophyllin, trichloroacetic acid, 5-fluorouracil cream, cryotherapy, and laser therapy.[36] For patients with small condylomata

limited to the external genitalia, the topical application of podophyllin has traditionally been considered the first line of treatment and has met with variable success.[78, 123] For more extensive disease, and particularly for intravaginal, urethral, or anal lesions, laser therapy is the best method for direct destruction. Recurrence rates are generally low.

Recent clinical trials of alpha-interferon have shown it to have a beneficial effect on anogenital warts. Intralesional administration, consisting of an injection of 10^6 units of recombinant alpha-interferon directly into warts three times weekly for 3 weeks produced a marked reduction in the size of the warts compared with placebo-treated individuals (in whom the warts grew).[37] In one third of treated patients, all warts cleared. However, as many as 70 per cent of individuals experienced mild to moderate local pain during and shortly after the injection, making this form of administration unfeasible for those with extensive disease. Intramuscular injection of interferon has also proved efficacious for the treatment of anogenital warts.[44] The primary limitation on parenteral administration is the marked systemic adverse reactions (fever, chills, malaise, myalgia, headache, and leukopenia) that appear in about one third of individuals. This reaction can be minimized by proper selection of dose and interval of administration (Mills and associates, submitted for publication). As yet, interferon has not received FDA approval for the treatment of condylomata acuminata. (See also articles by Galbraith and Landow in this issue.)

Interferons are also beneficial for other papillomavirus infections, including respiratory papillomatosis[81] and epidermodysplasia verruciformis.[2] The latter condition is notoriously difficult to treat. In a recent small study, both intralesional and parenteral administration of human leukocyte interferon resulted in a regression of lesions compared with placebo controls. However, lesions recurred after discontinuation of therapy. For reasons that are not clear, neither intralesional nor parenteral administration of alpha-interferon is effective treatment for verruca vulgaris lesions.[132]

The prophylactic efficacy of intranasal alpha-interferon against acute respiratory virus infections has been studied in healthy adult volunteers.[59, 115, 130] To summarize these trials, the intranasal administration of interferon before and after challenge with either rhinoviruses or coronaviruses reduced the frequency of respiratory symptoms, with a variable effect on viral shedding. The doses of interferon required for prophylaxis are high (10 to 35 million units per day) and cause dose- and duration-dependent local reactions, including nasal stuffiness, mucosal erosions, and epistaxis.[59]

Trials of interferon for treatment of chronic hepatitis virus infection have met with mixed, but mostly disappointing, results.[53] The inhibitory effect of alpha-interferon on the replication of hepatitis B virus was first reported more than a decade ago. However, lack of a readily available commercial supply precluded extensive clinical testing until the last few years. Unfortunately, the efficacy of alpha-interferon has generally been discouraging, with disappearance of HBeAg (and less commonly HBsAg) in only 25 to 40 per cent of individuals.[1, 28, 65] The second generation of therapy for chronic hepatitis B includes combinations of specific antivirals with interferon. In a recent double-blind placebo-controlled study of more than 60 patients, vidarabine alone and in combination with human leukocyte interferon resulted in unacceptable toxicity without any statistical benefit in treated versus placebo groups.[45] Thus, there is no safe and effective drug currently available to eradicate hepatitis B or to treat its diseases.

Disoxaril (WIN51711)

This compound, synthesized by Sterling Winthrop Research Institute in the early 1980s, belongs to a new class of antivirals with broad-spectrum activity against the picornaviruses.[88] This family of viruses includes the rhinoviruses and the enteroviruses, of which polio virus, Coxsackie A and B, ECHO virus, and hepatitis A are the principal subgroups. Disoxaril has a novel mode of action: through binding to specific amino acids within the viral coat proteins (particularly viral protein 1, which is the major structural protein of the viral capsid), this drug stabilizes the coat and thereby inhibits viral uncoating without affecting cellular attachment and penetration.[124] Disoxaril inhibits the replication of human enteroviruses in a mouse model without causing serious adverse reactions.[87] Disoxaril or related drugs will doubtless be subjected to clinical trials in the near future.

SUMMARY

This article has reviewed the principal antiviral agents and their application in the therapy and prevention of viral diseases. Only acyclovir, amantadine, ribavirin, zidovudine, and vidarabine have received FDA approval for therapy of systemic viral infections. Although ganciclovir, phosphonoformate, the acyclovir prodrugs,

disoxaril, and the interferons are now being used only on an investigational basis, it is likely that at least some of these agents will soon be licensed. The search for more effective and safer antivirals continues, and with increasing academic and industrial interest, the prospects for this branch of chemotherapy appear promising.

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