THE YALE JOURNAL OF BIOLOGY AND MEDICINE 50 (1977), 507-532

Antiviral Therapy

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Received February 24, 1977

The current status of antiviral therapy is reviewed, including discussion of older approaches together with more recently developed chemotherapy. Following the introduction dealing with pathophysiological aspects of virus disease, the different approaches to antiviral therapy are presented. The reasons for the slow progress in antiviral therapy are discussed. These include: 1. the necessity of intracellular penetration of drugs acting on viral replication; 2. the severe toxicity of most antiviral drugs; 3. the narrow antiviral spectrum of most of these agents; 4. the difficulty of making a rapid etiological diagnosis in view of the necessity of starting (specific?) treatment early in the course of the disease; 5. the difficult evaluation of beneficial as compared with deleterious effects of antiviral therapy. After a detailed review of clinically tested substances, including immunoglobulins, synthetic antiviral drugs (amantadine, nucleoside analogs, thiosemicarbazones and photodynamic dyes) and interferon, a guide concerning indications and application of specific antiviral therapy is presented. Although at present there are few indications, clinicians should be aware of the (present and future) possibilities of antiviral therapy.

INTRODUCTION

Considering the remarkable progress made in antibacterial therapy in the past three decades, the advances made in specific treatment of viral disease have been disappointingly slow. So far there are only a small number of antiviral agents which are useful in a restricted number of clinical situations. Furthermore, most antiviral drugs do not selectively inhibit virus replication without simultaneously injuring the host cell, and are therefore accompanied by serious side effects. Thus, possible beneficial effects of antiviral drugs must be balanced against potential immunosuppressive and other undesirable side effects. Nevertheless, the physician, faced with a seriously ill patient or concerned about the individual and economic consequences of an incipient epidemic of viral disease, is under considerable pressure by the patient, by the public or by his colleagues, to apply antiviral therapy. Although the pharmacology and use of antiviral drugs has recently been reviewed [1–6] an overall reassessment of antiviral therapy, considering older approaches, such as postexposure immunization, along with the newer chemotherapy, is lacking. This review attempts to fill this gap: in the first section the pathophysiology of typical viral disease will be briefly described permitting a rational approach to antiviral therapy. The second part deals with the antiviral agents currently in use or under clinical investigation. The third part contains a guideline for antiviral therapy.

Pathophysiology of virus disease

Virus structure: Viruses contain a single type of nucleic acid, either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). The viral core, composed of the nucleic acid and nucleoproteins is protected by an outer protein coat (the capsid). In addition, some viruses are surrounded by a lipoprotein envelope (Fig. 1).

Virus cell interactions: Viruses are obligate intracellular parasites. They do not

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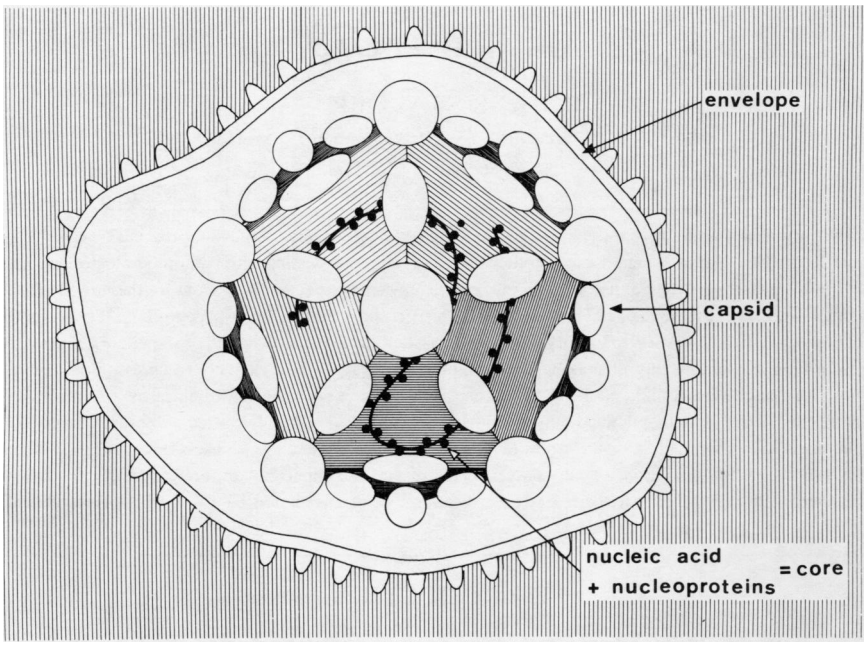

FIG. 1. Schematic illustration of an enveloped icosahedral virus.

contain the genetic information for all the enzymes involved in viral replication and they lack organelles required for energy generation and protein synthesis. The viral replication cycle may be depicted as follows (Fig. 2): before a virus penetrates a cell, it must come into close contact with, and attach itself to, the cell surface (step 1). This step is often determined by highly specific cell receptors and viral surface properties. Penetration into the cell (step 2) occurs through fusion of the viral lipid envelope with the cytoplasmic membrane (Fig. 2), or by engulfment of the virus by the cell. Inside the cell the viral protein mantle is removed (uncoated) (step 3), and the viral nucleic acid is transported to the site of replication (step 4), which may be either the nucleus, as shown in Fig. 2, or the cytoplasm, depending on the virus. Nucleic acid replication (step 5) and transcription into messenger RNA (step 6) as well as viral protein synthesis (step 7) are accomplished by cellular enzymes, and/or by specific enzymes induced by the virus. Viral proteins are synthesized on ribosomes, and, together with newly formed nucleic acid, are assembled into whole virus particles (step 8). These, in turn, are released from the cell (step 9). The viral envelope is acquired by budding through the nuclear or cytoplasmic cell membranes in which virus specific proteins may have been incorporated.

During replication most viruses induce cytopathic effects, often leading to cell death. Some viruses induce syncytia formation by altering the surface properties of the cell. In addition, aggregation of viral components or alterations of cell organelles may result in characteristic inclusion bodies. The mechanism by which viruses induce cytopathic effects [7] is often poorly understood. However, inhibition of essential cellular metabolic reactions such as protein or nucleic acid synthesis may occur. Cytopathic effects may be induced by viral parts or intermediate viral products without involving a complete viral cycle.

Virus-host interactions: Virus infection occurs only if the virus is able to breach barriers, such as skin or mucous membranes. Virus replication may be limited to the

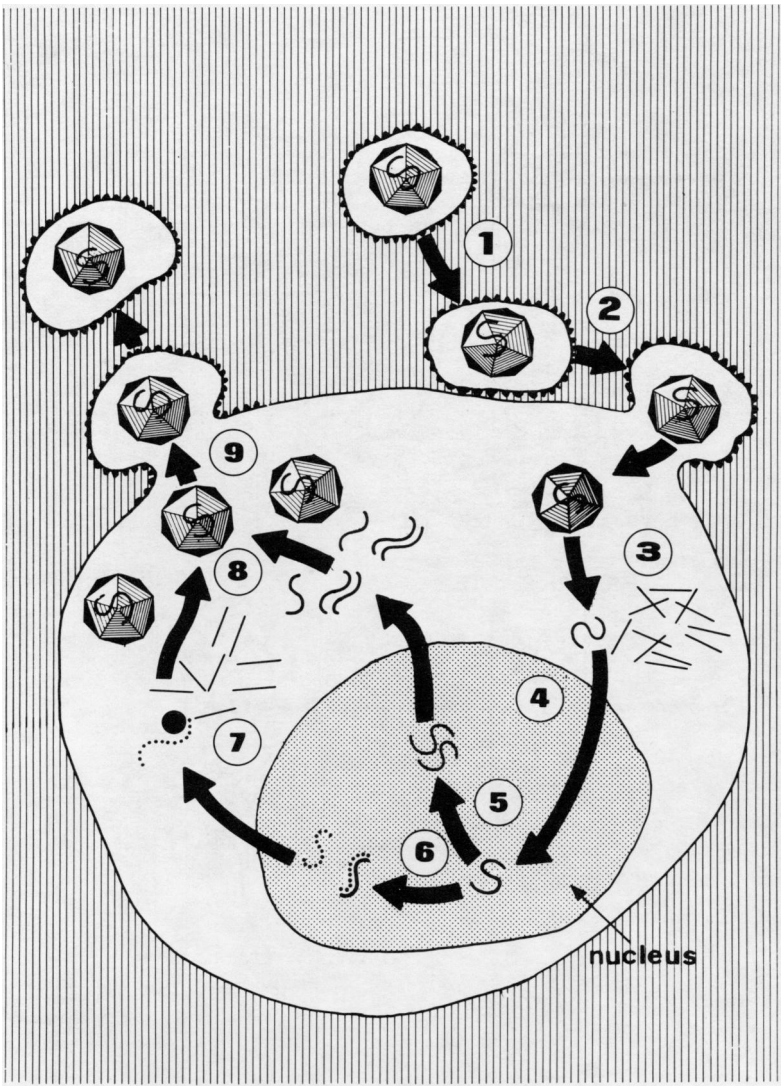

FIG. 2. Schematic illustration of the steps involved in the replication of an enveloped virus (see text).

barrier site, as, for example, in most viral respiratory infections (Fig. 3A). In virus diseases with this pattern the interval between exposure to the virus and the clinical appearance of viral damage (clinical symptoms)—the incubation period—will be short. Symptoms will prevail at the site of viral replication, although host reactions (see below) and viral and cellular toxic products can produce systemic symptoms. Certain viruses (e.g., measles, rabies, etc.) not only replicate at the barrier site, but spread to a secondary replication site by the blood stream, lymphatic, bronchial, or neural routes (Fig. 3B). Viral replication at the barrier site in these diseases may be asymptomatic and symptoms appear only when a secondary target organ is affected: the incubation period of these diseases is longer.

The symptomatology of viral disease is not only due to virus-induced cell injury [8] but is also influenced by the host response [9] (Fig. 4). Host reactions may be non-specific, such as inflammation, phagocytosis, interferon production and fever, or specific, such as humoral and cellular immune responses. Often they restrict viral

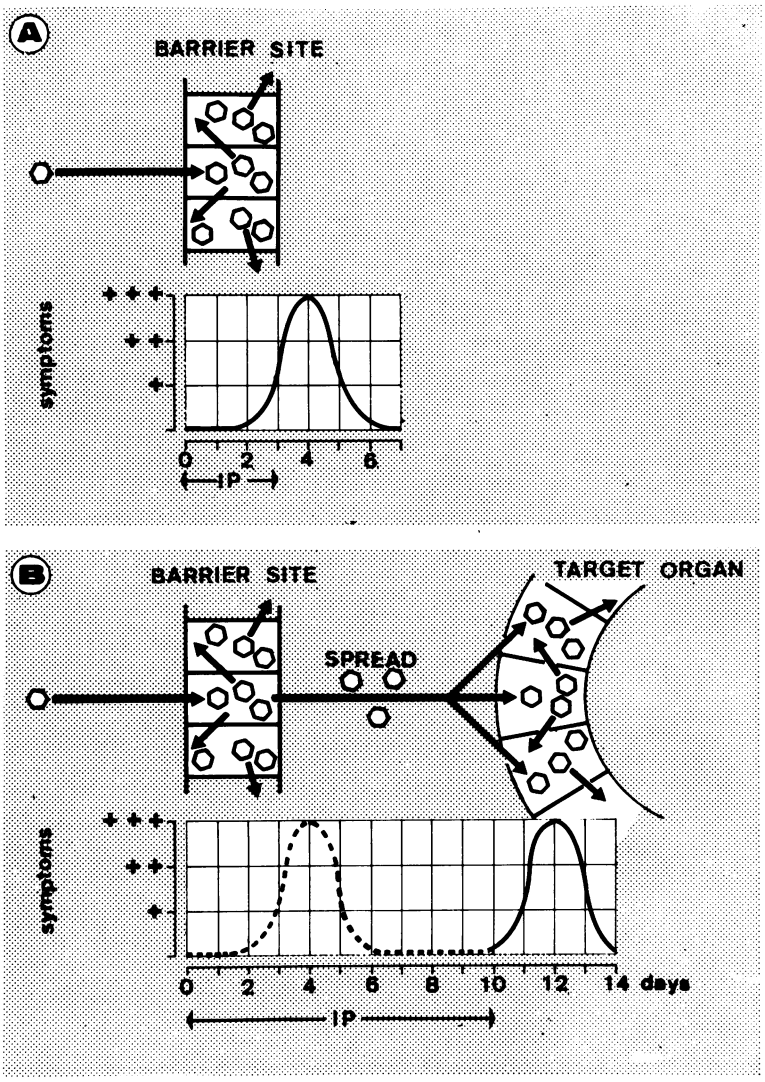

FIG. 3. Viral infection with short (*A*) and long (*B*) incubation period (I.P.) (see text).

damage, eliminate the virus, and prevent both further spread of virus and reinfection. However, host responses may also be deleterious. Indeed, symptoms often appear only when viral replication is already declining and must be attributed, at least in part, to the host's "defense" mechanisms. For instance, inflammatory edema in response to virus infection may not only be painful but have serious consequences (e.g., in viral encephalitis). Virus-antibody complexes can lead to immune complex disease (e.g., glomerulonephritis). Finally, cellular immune responses play a major part in viral disease patterns. Indeed, the classical clinical presentations of some viral diseases such as hepatitis, post-infectious encephalitis and exanthematous diseases are mainly due to cellular immune responses; viral damage *per se* may be minimal. This fact can be demonstrated in animal models in which immunosuppression may prevent symptomatic disease in some viral infections [10]. It has also been suggested that alterations of cell surface properties by viral replication, may initiate immune reactions leading to autoimmune disease [11].

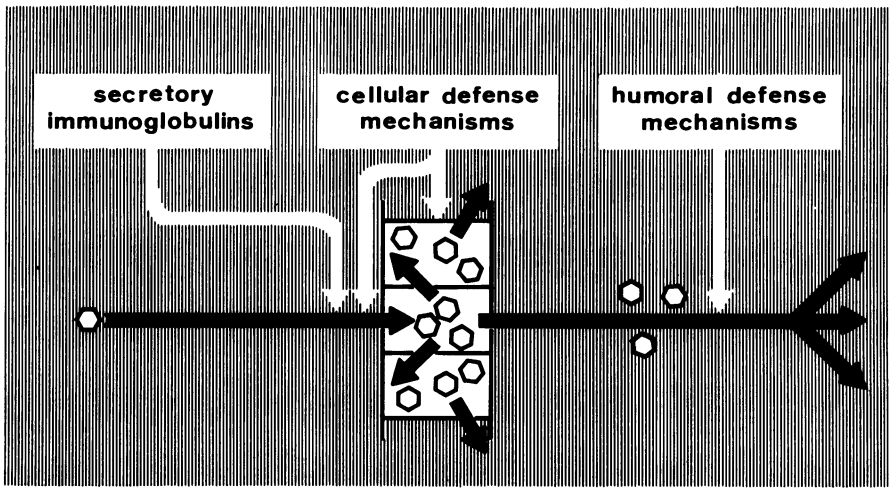

FIG. 4. Host immune defense mechanisms to viral infection.

Recovery is usually associated with total elimination of the virus. However, some viruses such as herpes viruses and "slow" viruses, may remain latent in certain tissues after primary infection and become the source of (recurrent) disease after a latent period.

General aspects of antiviral therapy

Taking into account the above considerations about the pathophysiology of viral disease, the following points should be considered, whenever planning to apply antiviral therapy.

Intracellular penetration of antiviral drugs: As viral replication occurs intracellularly, an ideal antiviral drug should be able to penetrate the cell membrane. Drugs whose action is limited to the extracellular space must be administered before the virus reaches the cells of the target organs, that is, in most instances, early during the incubation period.

Timing of antiviral therapy: Even when using drugs which are able to penetrate the cytoplasmic membrane, timing may be difficult. Indeed, ideal antiviral therapy should be applied before viral replication has caused widespread, possibly irreversible, cytopathic effects. Moreover, when clinical symptoms occur, viral replication has often reached its peak. At that time specific therapy may have little additional action on its further decline. Unfortunately treatment with antiviral agents is usually considered relatively late in the illness when non specific measures have failed or when the clinical situation is desperate. In most situations the chances of success at this stage are very small.

Specificity of antiviral drugs: Until recently, toxicity has been a major problem in the use of antiviral drugs. As viral replication is so closely related to and dependant on cell metabolism, few antiviral drugs are really virus specific. The therapeutic margin is small. Therefore, when planning antiviral therapy, beneficial actions of a chosen drug have to be carefully balanced against possible toxic effects.

Spectrum of antiviral drugs: An ideal antiviral drug should have a wide antiviral spectrum, as it is often impossible to make an exact viral diagnosis on clinical or laboratory grounds early during a viral disease, when antiviral therapy is most likely to succeed. Due to their potential toxicity, antiviral drugs with a limited antiviral

spectrum cannot be given, before an (often time consuming) etiological diagnosis has been obtained.

Treating host or virus?: Considering these difficulties, it is reasonable to continue to treat most of the often harmless viral diseases by purely supportive measures, and by using analgesics and anti-inflammatory drugs. These latter may be beneficial, as host inflammatory reactions often aggravate the symptomatology of viral illnesses. However, anti-inflammatory drugs, especially corticosteroids [12] and even sometimes salicylates [13], may actually favor viral replication by diminishing host defense mechanisms. Therefore, unrestricted use of anti-inflammatory drugs should be avoided.

In spite of these restrictions, a small number of antiviral drugs, described in the following section, have been found useful in a number of well defined clinical situations.

The different modes of antiviral therapy and the possible side effects are described in Fig. 5.

ANTIVIRAL SUBSTANCES

Introduction

Many potential antiviral substances have been tested in tissue culture systems but only a small number have reached the level of animal experiments and even fewer are possibly useful in clinical practice. The main problem in achieving specific antiviral therapy lies in the fact that viral multiplication is so closely associated with cellular metabolism that most antiviral drugs also affect cell function. However, close examination of viral replication (Fig. 2) reveals a number of potential sites for selective inhibition. Adsorption (step 1), penetration (step 2), and uncoating (step 3) are all apparently unique to the virus. Little is known about step 4 (transport). Synthesis of virus components (steps 5, 6 and 7) depend heavily on the use of cellular enzymes, rendering selective inhibition often impossible. However, some viruses induce new virus-specific enzymes and these may be selectively inhibited. Finally, there is some evidence that assembly (step 8) and release (step 9) can be adversely affected. Table 1 summarizes the probable sites of action of some of the most commonly mentioned antiviral agents. In this section the use of immunoglobulins, amantadine, nucleoside analogs, methisazone and interferon will be described in detail. The other drugs mentioned in Table 1 are either too toxic (HBB, guanidine, actinomycin D) or too inactive (rifampicine) to be considered clinically useful, or have not yet undergone enough clinical testing (phosphonoacetic acid, isoprinosine).

Immunoglobulins

General aspects: The use of immune serum globulin (ISG) in the treatment of viral disease has several advantages over other modes of antiviral therapy. ISG, acting as "neutralizing" antibody, is highly effective in the prevention of extracellular dissemination of virus. Furthermore, ISG does essentially not harm the host, imitating a normally occurring host response. This therapeutic approach is especially useful in patients in whom normal immune responses are not elicited. However, ISG has a major disadvantage in that it does not pass the cytoplasmic membrane. Thus the virus is only vulnerable during extracellular spread, which in most instances is during hematogenous dissemination. Therefore, ISG has to be given before occurrence of viremia and infection of the target organ. Thus, in most instances, the moment of exposure must be known and ISG should be administered shortly thereafter. In fact,

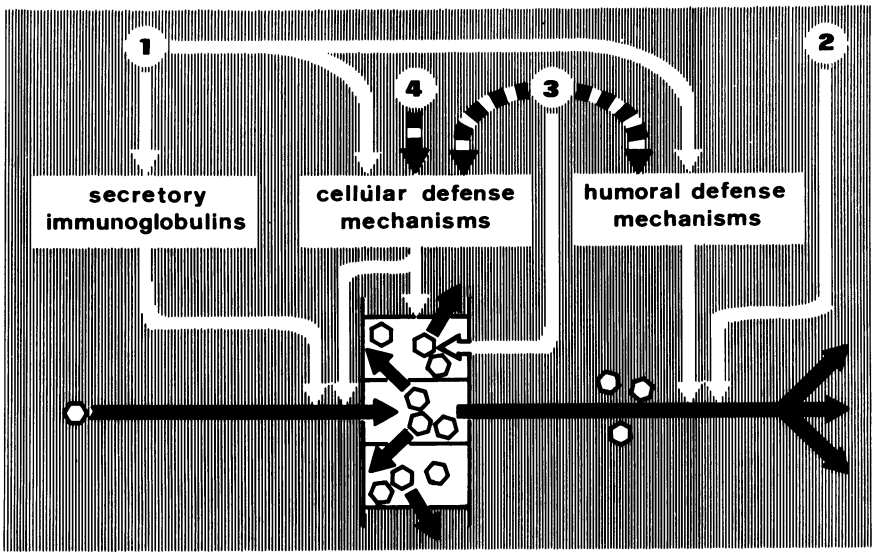

FIG. 5. Possible modes of antiviral therapy: 1. active immunization (antiviral prophylaxis); 2. passive immunization by immunoglobulins; 3. antiviral drugs; 4. antiinflammatory drugs.

treatment with ISG may be considered as an extension of antiviral prophylaxis ("postexposure prophylaxis"). It is also evident, that ISG postexposure prophylaxis is usually ineffective in viral infections limited to the barrier site, such as respiratory diseases.

Commercially available ISG contains primarily IgG antibodies at a protein concentration of 16 g/100 ml, an approximate fifteen-fold increase over the level of IgG in plasma. These preparations are obtained from pooled plasma of random blood donors. As such, they are representative of the general immunity of the donor population (herd immunity) and of broad current disease trends. In these "standard" ISG preparations, the level of specific antibody against a given viral disease is often too low for adequate protection. Hyperimmune serum globulin (HISG) preparations, obtained from patients recovering from or vaccinated against certain diseases, contain a much higher content of specific antibodies, and are therefore often more appropriate for postexposure immunization. The supply of these preparations is limited and costs are high.

In general, ISG cannot be given intravenously because anaphylactic reaction may occur, due to IgG aggregates formed during the fractionation procedures [14]. ISG, given by the intramuscular route, reaches only about 40% of the maximal levels of equivalent doses given intravenously and this peak is only attained after several days [15]. This delay may be critical in the treatment of viral disease. ISG prepared for the intravenous route have in general either less immunologic properties or are excreted much more rapidly than intramuscular preparations [14]. Recently developed plasmin treated ISG does not seem to have these disadvantages [16]. However, HISG of this type are not yet available.

Post-exposure immunization in viral disease:

a. *Rabies:* Rabies has such an exceptionally long incubation period that vaccine-induced active immunity may be elicited even after exposure. Pasteur first made use of this fact in 1882 when he actively immunized a patient bitten by a rabid dog [17]. However, subsequent attempts to prevent clinical disease by postexposure vaccina-

TABLE I
Probable Action Sites of Some Antiviral Substances

Site of Drug Action		Antiviral Substance
Attachment		Immunoglobulins
Penetration		Amantadine HCl
Uncoating		Immunoglobulins
Nucleic acid replication	RNA viruses	2 (alpha-hydroxybenzyl) Benzimidazole (HBB)
		Guanidine
		Photodynamic dyes
	DNA viruses	Nucleoside analogs
		Photodynamic dyes
		Phosphonoacetic acid
Protein synthesis	Transcription	Actinomycin D
		Interferon
	Translation	Thiosemicarbazones (Marboran)
		Interferon
		Isoprinosine (?)
Assembly		Rifampicin

tion have not been uniformly successful, especially when the incubation period was short (e.g., when rabid bites were located in the head region [18]). In experimental animal rabies (where the incubation period is shorter) immune serum has an additional protective effect, especially after a high virus challenge dose [19,20]. In man, the beneficial effect of passive immunization (in addition to the vaccine) was demonstrated after a devastating attack by a rabid wolf in Iran in 1953 [18]: addition of rabies immune serum dramatically reduced the mortality in the patients bitten in the head region. Later studies in the same country showed that mortality rates after rabies exposure were reduced from about 20 percent to less than 1.5 percent by postexposure treatment with rabies hyperimmune serum globulin [21]. Therefore, both vaccine and serotherapy are clearly indicated, if there is heavy exposure to rabies.

Unfortunately, the simultaneous administration of ISG with the vaccine interferes with the stimulation of active immunity [22,23]. Therefore, the vaccine must be applied repeatedly and for a prolonged period [24]. Furthermore, the Pasteur type vaccines, derived from nervous tissue, may cause severe side effects [25]. Non-nervous vaccines, especially duck embryo vaccine, are safer [26], but less immunogenic [27]. Vaccines produced in tissue cultures, e.g., human fibroblasts, elicit a high antibody response, and are exempt from severe secondary reactions [28–30].

The occurrence of serum sickness in more than 40% of the adult recipients of heterologous (horse) serum [31] can now be avoided by the use of human rabies HISG, prepared from immunized volunteers [32,33].

b. *Measles (rubeola):* Standard ISG or rubeola HISG can prevent or attenuate clinical measles if given within the first five (or more?) days after exposure [34,35]. Since the "incubation period" of vaccine (attenuated) measles is shorter than that of the natural disease it is possible to prevent the disease by active immunization during the first 48 hours after exposure [36].

c. *Rubella (German measles):* Only about 15 percent of the adult population are susceptible to rubella. Rubella causes malformations in 10 to 50% of the offspring of

susceptible pregnant women who become infected during the first trimester. Since rubella virus probably reaches the fetus by hematogenous and transplacental routes, it is theoretically possible to prevent fetal infection by giving ISG. Clinical manifestations of and seroconversion to rubella can be prevented by the use of high titered rubella HISG [37] in volunteers. Unfortunately, controlled field trials [38], particularly in pregnant women exposed to rubella [39], have failed to show evidence of protection by rubella HISG. These failures may be due to the fact that rubella HISG is rarely given early enough after exposure. The exact time of exposure is difficult to ascertain as an infected person sheds virus one week before and up to two weeks after the appearance of the rash [40].

d. *Varicella-zoster:* Chickenpox, usually a mild childhood disease, may be a serious threat to patients with congenital, acquired or drug induced immune deficiencies. Recurrent varicella-zoster virus infection in the form of shingles (herpes zoster) may also be severe and generalized in immunosuppressed patients. Standard ISG in high doses may attenuate but not prevent chickenpox in a normal population [41]. High titered zoster HISG (prepared from patients recovering from herpes zoster) can prevent varicella in normal children [42] and is likely to attenuate the disease in immunosuppressed patients [43–45]. There is no evidence that zoster HISG is of any effect once the rash has appeared [46].

e. *Mumps (epidemic parotitis):* Although the incubation period of mumps is more than two weeks, administration of HISG after exposure is not always successful in preventing the illness [47]. Some [48–51], but not all [52], controlled trials indicate that the incidence of mumps orchitis, but not that of encephalitis [49], may be decreased by administration of high dose mumps HISG, even after parotitis has appeared.

f. *Smallpox (variola) and smallpox vaccination complication (vaccinia):* After smallpox contact, the disease may be prevented or attenuated by vaccinia HISG [53,54]. The effect of simultaneous (re)vaccination is doubtful, but it is indicated as a public health measure [53]. Once the rash has appeared, immunotherapy is unlikely to be effective [53]. There are only uncontrolled data to show the value of vaccinia HISG in the treatment of vaccinia complications. No effect has been demonstrated in the treatment of post-vaccinial encephalitis [55]. Eczema vaccinatum and ocular inoculation vaccinia are generally regarded as indications for the use of hyperimmune globulin [53,55,56]. Vaccinia gangrenosa is a frequently lethal complication of vaccination occurring in patients with impaired immunity [57]. Vaccinia HISG alone, although indicated, is rarely effective [55].

g. *Hepatitis A and B:* The data about the efficacy of immunoglobulins in postexposure immunization of viral hepatitis are conflicting. This confusion is in part due to the facts that in the older literature anicteric hepatitis was not detected, hepatitis A and B could not be differentiated, and the content of specific hepatitis B antibody in the preparations, which may vary from one batch to another [58], was not known. At present, it is well established that non-parenterally transmitted hepatitis A may be prevented by low dose standard ISG [59–63]. Passive immunization may be effective as long as one to two weeks after exposure [62]. Standard ISG is probably not effective in the prevention of hepatitis B unless it contains some antibody against this virus [64–66]. Hepatitis B HISG may have a favorable prophylactic effect in people at high risk of acquiring hepatitis B [67–71]. However, protection is neither complete nor uniform. In one study of medical workers accidentally (by needle puncture) exposed to hepatitis B, it was found that the disease could be delayed but not prevented [72]. Clearly much more information is needed before recommendations

can be given about the clinical effects, indications, dosage, possible time interval after exposure, etc., of hepatitis B HISG.

The occurrence of transfusion transmitted hepatitis B has been greatly reduced by screening of donor blood for hepatitis B-antigen (HBsAg). In spite of this, post-transfusion hepatitis still occurs. It is probably due neither to hepatitis A nor B virus [73,74]. In a preliminary study the incidence of non A, non B hepatitis was reduced by administration of ISG during transfusion [75].

Synthetic antiviral drugs

Amantadine: Amantadine (1-Adamantanamine hydrochloride) (Fig. 6A) inhibits the replication of certain strains of influenza A and C viruses and some paramyxoviruses [76,77]. In high doses it protects tissue cultures from rubella and respiratory syncytial viruses, but it has no effect on influenza B [77].

Amantadine prevents virus penetration through the cytoplasmic membrane by an unknown mechanism [76]. In therapeutic doses it has no effect on virus or host cell DNA, or on protein synthesis [76]. In tissue culture, the drug is inactive when administered as short as five minutes after infection [76]. However, mice are protected if the drug is given even 48 hours after challenge [78]. Drug resistance can be induced in vitro [77].

In man, amantadine has been shown to be effective in the prophylaxis of influenza A. In experimental [79–81] as well as in epidemic field studies [82,83], the incidence of infection, the severity and duration of symptoms and the duration of virus shedding were significantly reduced by the drug. Some reports [84–87], but not all [79,88] have also demonstrated some therapeutic activity of amantadine when given shortly after apparition of symptoms. In most trials no side effects have been observed [80,83,85,86]. However, central nervous system symptoms, such as dizziness, nervousness, insomnia or even hallucinations may occur [82].

Rimantadine (α-methyl-1-adamantanemethylamine hydrochloride) a close analog of amantadine has been shown to be more effective against influenza A infection in tissue culture and animals [89,90]. There is less tendency for virus resistance to occur with rimantadine than with amantadine. Amantadine resistant viruses remain sensitive to rimantadine but the converse is not true [90]. In man, rimantadine is at least equally active as amantadine [86,91].

Nucleoside analogs: Nucleoside analogs act on purine and pyrimidine metabolism either by competitive inhibition or by incorporation as "false" subunits into nucleic acids. As a result, nucleic acid synthesis may be altered as well as metabolism of protein and carbohydrates [92].

Theoretically, a nucleoside analog may have a selective antiviral effect if one of two conditions are fulfilled: 1. The agent may be modified by virus induced enzymes into an active compound. This will result in a higher concentration of the inhibitory principle in infected cells. 2. The virus may code for an enzyme which is more easily inhibited by the drug than the corresponding enzyme of the host cell [93].

a. *5-iodo-2'-deoxyuridine (IDU)* (Fig. 6B): The thymidine analog IDU was the first antiviral drug to be used successfully in man by Kaufman et al. in 1962 [94] and has since become standard treatment for herpes simplex keratitis.

Its antiviral action is complex. IDU is a competitive inhibitor of thymidine kinase. Furthermore, it is incorporated into DNA [95]. Thymidine kinase activity although sometimes enhanced by viral multiplication [96] is an important cellular enzyme. Thus, a dose sufficient to arrest viral multiplication is likely to impede cell metabolism as well. In other words, the therapeutic margin is narrow.

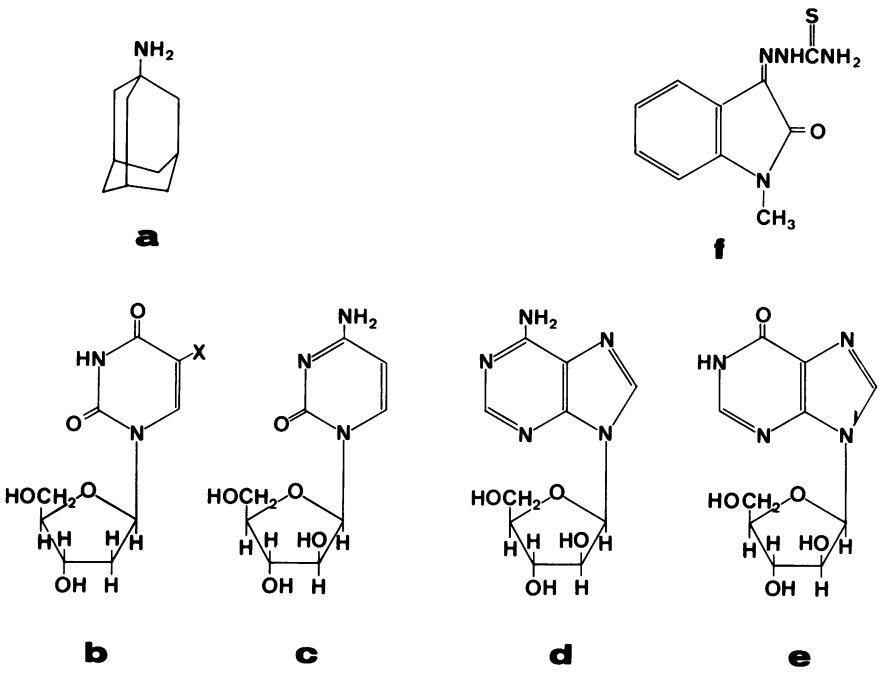

FIG. 6. Synthetic antiviral drugs: (*a*) 1-Adamantanamine hydrochloride (Amantadine); (*b*) Nucleoside analogs (X = CH_3: thymidine; X = H: 2-deoxyuridine; X = I: 5-iodo-2'-deoxyuridine (IDU); (*c*) 1-β-D-arabinofuranosyl-cytosine (ara-C); (*d*) 9-β-D-arabinofuranosyl-adenine (ara-A); (*e*) 9-β-D-arabinofuranosyl-hypoxanthine (ara-Hx); (*f*) N-methylisatin β-thiosemicarbazone (Marboran).

IDU is effective in vitro against most DNA viruses. However, in vitro resistance is readily observed and is due to viral mutants which fail to induce thymidine kinase [97]. IDU is active in animals infected by herpes simplex, particularly as a topical agent in keratitis [98]. IDU does not easily pass the "blood-brain barrier" [99,100] and is rapidly metabolized to inactive compounds [101]. Therefore, little effect can be demonstrated on experimental herpes simplex encephalitis [99,102,103].

In man, success rates of topical IDU in the treatment of superficial herpes simplex keratitis vary from 68 to 85% [104–106]. IDU is not active in the deeper (stromal) keratitis. Furthermore, resistance to the drug has been observed [94].

There is no convincing evidence that IDU is effective in recurrent cutaneous herpes simplex. Whether IDU treatment is more effective (and safe) after addition of dimethylsulfoxide (DMSO) [107] remains to be confirmed. Multiple case reports and small uncontrolled series have suggested a favorable action of IDU in herpes simplex encephalitis. The only prospective study to date had to be interrupted because of unacceptable toxicity [108].

Systemically administered, IDU may have, at least theoretically, not only immediate, but also long lasting serious side effects. It is incorporated into DNA and may therefore induce mutations [109]. Furthermore, IDU has been shown in vitro to activate "dormant" tumor viruses [110]. Thus, the use of IDU should be restricted to topical ophthalmic treatment.

b. *Cytosine arabinoside (1-β-D-arabinofuranosyl-cytosine, ara-C)* (Fig. 6C): Ara-C blocks DNA synthesis, partly by inhibiting DNA polymerase [111] and partly by competing with the phosphorylation of deoxycytidine [112]. Ara-C is incorporated into DNA but does not depend on this for its antiviral action [111]. In experimental in vitro and animal studies, the drug is effective against DNA viruses [113]. However,

cellular DNA synthesis is also impeded [113,114]. Furthermore, ara-C exhibits local toxicity when used in experimental herpetic keratitis [115].

In man, the drug is rapidly deaminated to an inactive compound (1-β-D-arabinofuranosyl-uracil (ara-U) [116,117], and must therefore be given by continuous intravenous infusion. Clinically, the drug has been used in herpes virus infection, mainly in uncontrolled studies. The few placebo controlled prospective double blind studies in disseminated [118,119] or localized [120] zoster infections in immunosuppressed hosts and in variola [121], showed that toxicity was greater than the beneficial action. Although active on herpetic keratitis (and particularly on IDU resistant strains of herpes simplex) its effect is hampered by the appearance of glittering corneal deposits [115,122]. Ara-C has probably no further clinical use as an antiviral agent.

c. *Adenine arabinoside (9-β-D-arabinofuranosyl-adenine (ara-A)* (Fig. 6D): Ara-A is a potent antiviral agent against DNA viruses (with the exception of adenoviruses) [123,124]. Its mode of action is not completely understood, but includes inhibition of DNA polymerase [125]. Small amounts of ara-A are incorporated into DNA [126]. Tissue culture and animal experiments with ara-A have demonstrated a much higher therapeutic margin than with ara-C and IDU [124]. Resistance is rarely observed. Furthermore, ara-A is active against IDU resistant herpes simplex strains [127]. The effect on experimental herpetic keratitis is similar to that of IDU [128]. In animal studies, herpes simplex encephalitis reacts favorably to ara-A [123,128], probably because ara-A or its metabolites (see below) easily pass the "blood-brain barrier" [129,130].

Like other nucleoside analogs, ara-A is rapidly metabolized. However, the main metabolite, 9-β-D-arabinofuranosyl-hypoxanthine (ara-Hx) (Fig. 6E), also has some antiviral activity, and no major toxicity to host cells [130]. Blockage of deamination of ara-A to ara-Hx enhances the activity of ara-A [131].

Ara-A is not well absorbed if given per os and must therefore be given parenterally. In man, where the drug is also rapidly metabolized to ara-Hx, about 50% of ara-Hx is excreted in the urine [130]. In serum, urine, CSF, and vitreous humor, antiviral activity is almost exclusively due to ara-Hx [130]. The serum half life of ara-Hx is about 3.5 hours. CSF levels may reach about half of the serum levels [130].

At present, only a few controlled trials with ara-A are available. Herpes simplex keratitis responds to ara-A at least as well as to IDU [132]. Its activity on IDU resistant keratitis, and the beneficial influence on herpetic kerato-uveitis [133] when used parenterally are real advantages of ara-A over IDU. Recently, it has been shown that ara-A has a beneficial effect on the evolution of systemic herpes zoster in immunosuppressed patients [134].[1] Preliminary uncontrolled experiments suggest a favorable action in severe mucocutaneous herpes simplex infections [135] and in neonatal disseminated herpes simplex [136]. In most trials, few side effects were observed. However, when used in high dosage (20 mg/kg for several days) nausea, tremor and hematologic abnormalities may be observed [137]. Ara-A does not influence established smallpox infection [138] and is ineffective for cutaneous herpes simplex when used topically [139]. It has little or no effect on established cytomegalovirus infection [140,141].

At present, ara-A is the nucleoside analog with great promise of clinical efficacy.

[1] Ara-A, if given early, has very recently been shown to diminish significantly mortality and sequellae in noncomatose patients with biopsy-proved herpes simplex encephalitis (Whitley RJ, Soong S-J, Dolin R, et al: Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. N Eng J Med 297:289, 1977).

d. *Other nucleoside analogs:* It is likely that in the near future, other nucleoside analogs will be introduced. Several have already reached the level of clinical trials (e.g., trifluorothymidine in herpetic keratitis [142], ribavirin (virazole) which has a large antiviral spectrum [143], etc.). It is beyond this review to discuss these substances. For references see reference 92.

Thiosemicarbazones (Methisazone): In 1950, Hamre et al. [144] opened the era of antiviral therapy by demonstrating that a thiosemicarbazone derivative protects the chick embryo and mice from otherwise fatal vaccinia virus infection. Thiosemicarbazones, especially those substituted with an aromatic ring such as isatin (Fig. 6F) interfere with the multiplication of poxviruses and, at least in vitro, some other DNA and RNA viruses [145,146]. They act on "late" messenger RNA translation in polyribosomes without inhibiting host cell functions [147–149]. However, even though virus particles cannot be fully assembled, cytopathic effect by the virus is not prevented [147].

Reports of the efficacy of thiosemicarbazones in man are conflicting. Methisazone (5-methylisatin thiosemicarbazone, Fig. 6F) is the derivative which has been the most thoroughly studied. Early enthusiasm for methisazone in the treatment of smallpox during the incubation period [150,151] has been challenged by the results of placebo-controlled double-blind studies [152,153]. It is likely that the drug has some effect shortly after exposure, but is ineffective once the rash has appeared [154]. No controlled data are available on thiosemicarbazones in vaccinia gangrenosa or eczema vaccinatum [155,156].

Besides nausea and vomiting, which occur frequently, methisazone has no side effects [150,151].

Photodynamic dyes: Some antiviral drugs ("photodynamic dyes") exhibit their action only following interaction with light [157]. These compounds bind to the guanine bases of nucleic acids. Activated by ultraviolet light, they lead to the oxygenation of the base and consequently to a breakage of the nucleic acid [158]. In vitro, several RNA and DNA viruses, and particularly herpes simplex virus [159], are inactivated if treated with a photodynamic dye such as proflavin or neutral red, and subsequently exposed to ultraviolet or visible light. Experimental rabbit herpes simplex virus keratitis [160], has been successfully treated with photodynamic dyes, although the effect was inferior to the well established IDU treatment [161].

The use of photodynamic dyes in man remains controversial: 1. They are not selectively virucidal, but also destroy tissue culture cells [157]. 2. Experiments with hamster fibroblasts have shown that herpes simplex viruses, when inactivated by neutral red and light, may reveal their capacity to render cells malignant (transformation) [162]. Although this mechanism has never been demonstrated in vivo, too short a time has elapsed since the application of photodynamic dyes in the treatment of human herpes simplex skin lesions to exclude this potentially disastrous side effect. 3. Earlier published favorable results of the treatment of herpes simplex skin lesions by photodynamic dyes [163] have recently been challenged by carefully controlled studies [164,165].

Other approaches to antiviral therapy: interferon and interferon inducers

Interferon(s) (IF), discovered by Isaacs and Lindenmann in 1957 [166], is a naturally occurring glycoprotein with potent antiviral activity [167,168]. Human IF, although not homogenous, has a molecular weight of approximately 20.000 daltons [169]. IF formation (and release) is induced by viral infection. Furthermore, protozoal or bacterial products (e.g., endotoxin), double stranded RNA and synthetic

compounds may act as IF inducers [170]. IF has no direct action on viruses and does not inhibit adsorption, penetration, uncoating or release. It appears to act by inducing an antiviral protein within the cell which subsequently inhibits viral RNA or protein synthesis [171–173]. With some exceptions [174] IF is species or at least order specific, depending probably on specific IF receptors on the host cell membrane [175]. Its antiviral spectrum includes both RNA and DNA viruses. Some viruses, e.g., adeno- and herpesviruses, may be more resistant than others [176]. Although any cell may produce IF, lymphocytes appear to be a major source of IF. After immune stimulation, IF is released in conjunction with other lymphokines [177]. There are several facts which suggest that IF plays an important role in the recovery of viral disease: 1. Recovery is often associated with the early appearance of IF but not necessarily with inflammation or humoral immune responses [178,179]. 2. Immune suppressed patients in whom certain viral diseases are more serious, have delayed IF responses to viral infection [179,180]. Furthermore, animals treated with specific antibody to IF are highly susceptible to viral infection [181]. 3. Application of IF or IF inducers may inhibit viral damage and accelerate recovery not only in tissue culture but also in animals and in man (see below) [167,168]. Although IF has been considered non toxic, it has recently been found that it may inhibit DNA synthesis [182] and cell division [183,184]. Cellular [185,186] and humoral [187] immune responses may also be inhibited by IF. Furthermore, IF in high titers is toxic to newborn mice [188]. As IF is species specific and potentially antigenic, it has to be produced from human cells. The main source has so far been human leukocytes, but tissue culture cells may be another more easily available source [189]. After parenteral injection of IF, levels which are known to be antiviral in vitro, are reached in blood [190,191]. There is only irregular passage in urine and none into cerebrospinal fluid [190,191]. Serum half life is between 1½ and almost 5 hours after equal distribution has occurred. Some cumulation may be observed if IF is given repeatedly [190]. The few side effects observed (e.g., fever, and slight depression of the bone marrow [192] have not been serious.

There have been few clinical trials which allow assessment of the efficacy of human IF [193]. Respiratory infections can be prevented by intranasal IF [194,195]. IF, administered parenterally over a long period reduces the amount of hepatitis B-DNA polymerase found in serum; this, however, may not be a direct effect of IF [192]. Prospective studies in severe varicella-zoster infection are being conducted [193]. So far, the results of topical human IF in herpetic keratitis are rather disappointing [196]. Because of the difficulties of producing IF in high concentrations much work has been done using synthetic IF inducers [170]. Unfortunately, stimulation of IF by inducers becomes often refractory after repeated doses. Inducers which have been used in man include: synthetic polymerized double-standard RNA's such as polyriboinosinic acid-polyribocytidylic acid (poly I_R-poly C_R) [197] and substituted propanediamines [198–200]. The available data from man do not establish that the antiviral action of these substances is due to IF induction. Furthermore, some of these substances are considerably toxic.

In summary, although indications are not yet established, IF and IF inducers may become clinically useful. Like immunoglobulin, IF is a natural product with a broad antiviral spectrum and low toxicity. The use of potent and non toxic IF inducers would circumvent the difficulties and the cost of the production of IF from human cells.

ANTIVIRAL THERAPY

How many patients, especially in hospital, are allowed to recover from their viral infection without antibiotics? [201]

It is hoped that this section may serve as a guideline for specific antiviral treatment. Diseases for which no specific treatment is available (e.g., viral meningitis) will not be mentioned below. Furthermore, it is not within the scope of this review to describe merely supportive, albeit important measures (such as rehabilitation in poliomyelitis).

Hepatitis A and B: The following persons should receive low dose standard ISG (0.02 ml/kg i.m.) [202]: family members in contact with a case of overt hepatitis A, persons accidentally pricked by needles contaminated with blood from patients suffering from hepatitis A, personnel working and patients hospitalized in institutions where hepatitis A is endemic, persons exposed to a common source outbreak of hepatitis A and finally people travelling in endemic (tropical) areas. The dose may be doubled and repeated after 4–6 months, if the exposure is prolonged. For the moment, guidelines for indications and dosages of hepatitis B HISG are not yet fully established. The following persons may benefit from HISG: newborn infants of hepatitis B-antigen positive mothers [67], family contacts exposed to hepatitis B [70], medical personnel accidentally exposed to hepatitis B [70], and both patients and personnel in dialysis and oncology units [68,71]. If standard ISG is used, it should contain specific anti-hepatitis B antibody.

Herpes simplex: Reports of treatment of herpetic skin lesions should always be compared with the high "success rate" of placebo treatment which may reach more than 70% [203,204]. Indeed, there is no proof that any specific antiviral treatment (e.g., nucleoside analogs, photodynamic dyes, etc.) is of more value than simple disinfection. Furthermore, there is little hope that the recurrence of herpetic skin lesions may be influenced by any topical treatment because the "reservoir" of herpes simplex virus is likely to be situated in the sensory ganglia (trigeminal or sacral).

In the past, vaccination by vaccinia or inactivated herpes simplex virus has been proposed. In small, but controlled studies both these treatments have been shown to be ineffective [203,204]. Vaccination with inactivated herpes simplex should be abandoned for two other reasons: 1. there is no definite proof of an immune defect in persons prone to recurrent herpetic skin lesions and therefore, no strong argument for vaccination; 2. introduction of viral genetic material may be potentially hazardous due to the known oncogenic properties of herpes viruses.

Active genital herpes at the time of delivery exposes the newborn to a high risk of infection [205,206]. In these cases in which there are active lesions and on condition that the membranes have been ruptured for less than four to six hours, cesarian section has been recommended [205,206]. Preliminary reports indicate that ara-A may be effective if given early in established neonatal infection [136].

Skin and mucous lesions may become chronic and very painful in immunosuppressed patients. Preliminary studies show that parenteral use of ara-A may be helpful [135]. There have been many reports of successful treatment of herpes simplex encephalitis. These should be interpreted with caution because in many cases the etiology of encephalitis has not been firmly established and the spontaneous evolution of this disease is unpredictable [207]. IDU should be abandoned in this disease [108]. At present there are no reports adequate for judging the efficacy of ara-A in treating herpes encephalitis (see footnote 1).

If ara-A is given parenterally, the recommended doses are between 10 and 20 mg/kg/day for 5 to 10 days, given in a continuous infusion. At the higher doses,

side effects include nausea, vomiting, tremor and bone marrow toxicity [137]. [For the treatment of ocular infections, the reader is referred to references 208 and 209.]

Influenza and other respiratory diseases: It is particularly disappointing that no established antiviral treatment exists for one of the most common human syndromes, viral respiratory illness. Amantadine (or its close derivate rimantadine) is effective in the prophylaxis of some influenza A infections [79–83,86,91] and may alter the disease course if given almost immediately after appearance of symptoms [84,85,87]. No effect has been demonstrated in other respiratory infections of man. This selectivity, in addition to the difficulty of making an exact viral diagnosis early during a respiratory illness, and the necessity to give the drug immediately, limit the use of amantadine in medical practice. Furthermore, amantadine in the doses used (100 mg p.o. twice daily for ten days) is not always exempt of side effects such as dizziness, nervousness, insomnia or even confusion [82,210]. The drug is not metabolized. It is entirely excreted by the kidney and the dosage should be reduced in renal failure [211].

The topical use of interferon (and interferon inducers) is still experimental.

Measles (rubeola): Measles can (and should) be prevented by vaccine. There is some evidence that active immunization may prevent measles up to 48 hours after exposure [36]. During the first five days after exposure, passive protection using 0.2 ml/kg standard ISG intramuscularly should be given to all persons who have no immunity to measles (negative history of either immunization or natural disease) [212]. ISG or HISG are not effective in the treatment of encephalitis [213].

Mumps: Mumps live-attenuated vaccine provides a lasting immunity, but is not yet widely used. Mumps HISG may diminish the incidence of orchitis in postpuberty males even after appearance of parotitis [48–51]. Its use remains controversial [214]. Contrary to common belief, mumps orchitis never leads to impotency and only rarely to sterility [215]. In two prospective studies, it has been shown that steroids are no more effective in the management of mumps orchitis than simple analgesics [216,217].

Rabies: The prophylaxis of clinical rabies [218,219] after exposure is threefold: 1. wound care; 2. active and 3. passive immunization. The first aim is to reduce local load. The wound should be thoroughly rinsed with water, soap or alcohol immediately after exposure followed by a 1% quaternary ammonium base (after having carefully removed all traces of soap). These latter compounds have been shown to be virucidal in vitro and may, in addition, inhibit neural spread of the virus [220]. In cases of heavy exposure, rabies immune serum or HISG (see below) should be injected into and around the wound site. The wound should be left open. Simultaneously, duck embryo vaccine or, if available, human fibroblast derived vaccine [30] should be administered. Fourteen daily doses of the former vaccine are recommended. If serum or HISG is applied 21 doses should be given as either one dose daily for 21 days, or two doses daily for seven days followed by seven daily doses. Two booster doses after 10, 20 and 90 days respectively are necessary for a lasting protection (fewer doses are needed for human fibroblast derived vaccine). In heavy exposures, horse rabies hyperimmune serum (40 UI/kg, half of the dose into the wound site and half i.m.) or preferentially human rabies HISG (20 UI/kg) should be given. The indications of rabies prophylaxis are listed in Table 2.

Rubella (german measles): Rubella in children and nonpregnant adults is a harmless disease which does not need specific treatment. For reasons discussed earlier, postexposure immunization for pregnant women exposed to rubella is rarely effective. If it is attempted, it should be noted that the absence of clinical illness is not

TABLE 2
Guide for Postexposure Rabies Prophylaxis in Endemic Areas [218,219].

Nature of Exposure	Animal and Its Condition	Treatment
No lesion, indirect contact, licks on unabraded skin	Rabid	None
Licks on abraded skin or mucous membranes. Scratches, abrasions and minor bites	Domestic, healthy	None[1]
	Rabid, suspect[2] but escaped, unknown	Vaccine[3]
Deep or multiple bites, bites in head region	Rabid or suspect	Serum and vaccine[3]

[1] Hold animal for ten days. If any signs of disease, the animal should be killed, and the brain examined for evidence of rabies. If positive start vaccine.

[2] Carnivorous animals and bats are more likely to be infective than other animals. An unprovoked attack is more suspect than a provoked attack (e.g., attempts to feed).

[3] In case of domestic or captured animals, stop treatment if the animal remains healthy after five days or if brain examination of the killed animal is negative for rabies.

an index of successful prophylaxis: most of adult rubella infections are asymptomatic [221] but may still result in the fetopathy. Therefore, serum antibody titers against rubella have to be assessed before and after passive immunization. A significant titer rise means active infection with the known high risk to the fetus.

Smallpox: A person exposed to smallpox but not (re-)vaccinated during the past three years should receive human vaccinia HISG (0.1 ml/kg) [53,54]. The indication for methisazone given during the incubation period is controversial [150–153]. Once the rash has appeared, the treatment of smallpox is purely supportive. Antiviral drugs are ineffective [154,137].

Complications of smallpox vaccination (vaccinia): There are five major complications of smallpox vaccination: postvaccinial encephalitis, generalized vaccinia, eczema vaccinatum, vaccinia gangrenosa and inoculation vaccinia [56]. All, except encephalitis, can usually be prevented by strictly following the instructions for smallpox vaccination.

There is no specific treatment for vaccinia encephalitis. Generalized vaccinia, due to hematogenous spread of vaccinia virus, is not a serious condition and does not need specific antiviral treatment. Patients suffering from eczema who are accidentally vaccinated or inoculated by a close contact should receive vaccinia HISG (0.6 ml/kg i.m.) [53,55,56,222] (it should be given prophylactically in all patients with a history of eczema, who need vaccination). If there is no amelioration after repeated doses of HISG, methisazone may be tried (200 mg/kg as a loading dose, then 400 mg/kg p.o. in divided doses every 12 hours over the next two days [155,156]). Methisazone is not toxic, but nausea and vomiting occur frequently. Vaccinia gangrenosa is a life-threatening complication of smallpox vaccination in patients with deficient immunity. Vaccinia HISG (0.6 ml/kg i.m.) is not sufficient therapy in most cases. Methisazone (same doses as above) may be tried [155,156]. The transfusion of lymphocytes from a recently vaccinated donor may also be effective [55,223]. The application of vaccinia HISG [56] and topical IDU [224] has been advocated in patients inoculated accidentally in the eye.

TABLE 3
Summary of Antiviral Therapy (see text)

	RNA Viruses							DNA Viruses						
								Herpes viruses				Poxviruses		
								Herpes simplex				Vaccinia		
	Influenza A	Measles	Mumps	Rabies	Rubella	Hepatitis A	Hepatitis B	Eye	Encephalitis	Neonatal	Varicella zoster*	Eczema vacc.	Vacc. gangrenosa	Variola
Prophylaxis														
By vaccines	+	+	+	+	+	–	e	–	–	–	–			+
By immunoglobulins	–	+	(+)	–	–	+	(+)	–	–	–	–	+	–	–
Postexposure prophylaxis														
By vaccines	–	+	–	+	–	–	–	–	–	–	–	–	–	(+)
By immunoglobulins	–	+	(+)	+	(+)	+	(+)	–	–	–	+	+	(+)	+
Amantadine	+	–	–	–	–	–	–	–	–	–	–	–	–	–
IDU	–	–	–	–	–	–	–	+	–	–	–	–	–	–
Ara-A	–	–	–	–	–	–	–	+	+	e	+	–	–	–
Methisazone	–	–	–	–	–	–	–	–	–	–	–	(+)	(+)	(+)
Interferon and interferon inducers	e	–	–	–	–	–	–	e	–	–	e	–	–	–

\+ Antiviral drug has shown to be active in this disease—may be indicated (see text).

(+) Antiviral drug may be active in this disease, but studies not conclusive or results controversial (see text).

– Antiviral drug is not active in this disease and not indicated.

e Antiviral drug experimental in this disease (see text).

* In altered hosts

No controlled data concerning ara-A therapy in vaccinia are available.

Varicella-zoster: Chickenpox is usually a mild childhood disease which requires no treatment. In adults, varicella may be more severe, but the prognosis is good if there is no underlying disease. Therefore, in these situations, the treatment should remain supportive. However, in newborns and immunosuppressed patients, varicella (and generalized zoster) may constitute a serious, even life-threatening, disease.

When available, zoster HISG (5 ml i.m.) (or plasma) obtained from patients recovering from herpes zoster, should be given, whenever an immunosuppressed child (without a history of varicella) is exposed to a patient with varicella or zoster [225]. Newborns, whose mother contacted varicella within four days before delivery, may also be protected by zoster HISG. There is no evidence that zoster HISG has any beneficial action once the rash has appeared.

Ara-A, using the same dose as for HSV infections, is the only antiviral drug which may be of use in varicella and generalized zoster in altered hosts [134]. Ara-C should no longer be used since it is ineffective and toxic [118,119]. Interferon has been tried, but definitive conclusion about efficacy cannot yet be drawn [192].

Uncomplicated herpes zoster does not need specific treatment. Preliminary results of treatment with IDU in DMSO [226] need confirmation. Postherpetic pain may be a major problem, especially in patients over 60 years. The use of corticosteroids in this age group remains controversial. Although patients under longterm corticotherapy suffering from varicella and zoster have often a prolonged and serious course, there is no evidence that a short corticotherapy after appearance of the rash aggravates the disease. Corticosteroids had a beneficial effect on zoster pain [227,228] but there is no proof that other inflammatory drugs are not equally effective. Corticosteroids may therefore be tried, if the usual analgesics fail.

SUMMARY

Table 3 summarizes clinical use of antiviral therapy. Positive statements "+" should be interpreted in the sense that the drug may be indicated in some, but certainly not all patients. The reader should refer to the appropriate sections of the text. Viral illnesses in which there is no available treatment (such as enterovirus infection) or in which antiviral therapy is still at an early experimental stage have been omitted.

ACKNOWLEDGMENTS

The help of Dr G. Friedli, Miss F. Michaud, Miss M.R. Payne, Drs M.J. Levin, M.N. Oxman, D.H. Smith, F.A. Waldvogel and Mr M.A. Rychner was indispensable for the accomplishment of this review and is kindly acknowledged. This work was partly supported by a fellowship from the Swiss Academy of Medical Sciences.

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