ANTIVIRAL THERAPY

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Since 1910, when Ehrlich devised salvarsan for the treatment of syphilis, the science of antimicrobial therapy has progressed by a series of major steps at intervals of 10-20 years. The next such advance was the introduction of sulphonamide by Domagk in the 1930's, followed by the development of penicillin in the 1940's and the opening of the floodgates to a great wave of new antibiotics. The era of antiviral therapy can be said to have started in 1950, when Hamre and coworkers described the inhibition of vaccinia in chick embryos and mice by a thiosemicarbazone compound (Hamre *et al.*, 1950) but it was not until the 1960's that Bauer and his colleagues reported the prophylactic effect of methisazone (isatin-β-thiosemicarbazone) in smallpox contacts (Bauer *et al.*, 1963). This drug however became redundant with global eradication of the disease by vaccination at the end of the last decade. Recently, 20 years after the first use of thiosemicarbazone, we have witnessed the next advance in the form of drugs active against certain herpes viruses; this step is of great significance because it coincides with and derives support from the current expansion in our knowledge of molecular biology in general and of viral replication in particular.

Although these exciting developements give hope that we are now seeing the dawn of the age of antiviral therapy, the way ahead abounds with difficulties. Table 1 shows that the number of virus infections at present amenable to chemotherapy is still very limited and that progress has been slow by contrast with that in the field of bacterial infections. The reason of course is that bacteria, replicating largely independently, can be attacked at several points without seriously interfering with the metabolism of their hosts; these vulnerable activities include cell-wall synthesis, cell membrane function and synthesis both of polypeptide and of nucleic acid. By contrast, viral replication is intimately related to that of the host cell, so that interference with one without affecting the other is a difficult and sometimes seemingly insoluble problem. Before considering specific antiviral agents it is therefore necessary to give a brief generalized description of the way in which viruses reproduce themselves.

VIRAL REPLICATION

Viruses consist of a core of *nucleic acid*, either DNA or RNA, coding for the genetic information needed for replication and contained within a protective shell of protein units known as the *capsid*, the whole forming a *nucleocapsid*; this may or may not be enclosed within an outer *envelope* derived from the host cell. The complete assembly is termed the *virion.*

The virus must first attach to the host cell, usually by means of specific receptors on the latter; it is then taken by pinocytosis into the cytoplasm where host, or occasionally virus-specified enzymes strip off the outer protein capsid. This

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TABLE 1. — *Availability of chemotherapy for virus infections in 1984.*

	Available	Not available
DNA viruses	*Herpesviruses* + + + herpes simplex + + varicella-zoster ± cytomegalovirus ± Epstein-Barr virus *Poxviruses* + + variola *Hepadnaviruses* ± hepatitis B	Adenoviruses Papovaviruses Parvoviruses
RNA viruses	*Orthomyxoviruses* + + influenza A *Picornaviruses* + rhinoviruses ± hepatitis A	Arenaviruses Bunyaviruses Coronaviruses Paramyxoviruses Reoviruses Retroviruses Rhabdoviruses Togaviruses

"uncoating" paves the way for the next step, which is fundamental to the whole process: the formation of viral messenger RNA (mRNA) from which virus-specified proteins can be translated on the host cell ribosomes. The nucleic acid of some RNA viruses can itself function in this way, but in most instances mRNA must be transcribed from the nucleic acid of the infecting virus. Early mRNA is mainly translated into transcriptases that catalyse the synthesis of more viral nucleic acid, whereas mRNA formed later in the cycle directs production of the structural proteins. Finally, the new virus nucleic acid is packaged into its shell of protein subunits and the progeny virus particles are then released from the cell. During replication, the host cell provides the energy and basic building materials for these complex processes and its own functions are inhibited to a greater or lesser extent depending on the type of virus.

A number of steps in replication are, potentially at any rate, amenable to interference by antiviral agents (table 2). It should be noted that the larger the virus, the more such functions are available as points of attack. As we shall see, the most successful compounds so far devised are those that specifically inhibit DNA synthesis in certain herpes viruses.

THE SEARCH FOR ANTIVIRAL COMPOUNDS

Until recent years, antiviral drugs were sought on a largely empirical basis, by screening large numbers of compounds for activity against a range of viruses

TABLE 2. — *The main steps in viral replication.*

Absorption and entry to host cells.
Uncoating.
Transcription of nucleic acid to mRNA.
Translation of mRNA into early and late proteins.
Assembly.
Release from host cell.

propagated in animals, chick embryos or cell cultures. Considerable resources were devoted to such experiments; but although some substances showed promise in the laboratory, the number with any practical value was small, mainly because they proved too toxic for use in man. Nowadays however, the emphasis is on screening compounds against specific viral enzymes isolated in cell-free systems; this method has already yielded substances with considerable potential.

A quite different approach to the problem, which must be mentioned even if only in parenthesis, is the use of interferon. This term refers to several species of low molecular weight glycoproteins induced in cells in response to stimulation by viruses, some bacteria and certain macromolecules. Interferon in turn stimulates production by neighbouring cells of an antiviral protein that is active against a wide range of viruses. Since interferon is naturally produced and relatively non-toxic, its discovery was hailed as the ideal solution to antiviral therapy; but this optimism proved unfounded in practice and the value of interferon for treating infections, even in large doses, seems very limited. It inhibitis hepatitis B virus replication, but only temporarily, so that its value for treating the chronic forms of this infection is doubtful (Thomas *et al.*, 1980). There is some evidence that it is effective in healing warts if injected directly into the lesions (Scott and Csonka, 1979). Its use for treating herpetic keratitis (Jones *et al.*, 1976) has now been superseded by chemotherapy.

I shall new briefly describe those antiviral agents that are licensed for use in the United Kingdom, or that show promise in clinical trials.

COMPOUNDS ACTIVE AGAINST R.N.A. VIRUSES

This group of viruses has not so far proved as amenable to chemotherapy as some of the DNA viruses. The most promising results have been obtained with influenza A.

Amantadine (1-aminoadamantadine)

This compound and the closely related rimantidine inhibit the replication of influenza A – but not influenza B – by a mechanism that is not clearly understood. There are claims that it acts at the entry or uncoating stages but doubt has been cast on this by Indulen and Kalninya (1980) and by Oxford and Patterson (1980). It certainly inhibits an early event, possibly transcription of RNA.

Amantadine possess both therapeutic and prophylactic activity. In the latter role, it has proved a useful supplement to vaccine prophylaxis: in the USSR, the protection rate with the two combined proved significantly better than with vaccine or drug used separately (Obrosova-Serova *et al.*, 1979, cited by Oxford and Patterson, 1980).

Virazole (1-β-D-ribofuranosyl-1,2,4,-triazole-3-carboxamide)

This is a synthetic nucleoside analogue which in laboratory tests inhibitis a wide range of viruses, both RNA and DNA. There is a considerable body of literature on laboratory and clinical trials of this drug, reviewed by Smith and Kirkpatrick (1980). A measure of success is claimed for its use in influenza A, hepatitis A and herpes simplex and zoster. The drug, known in the USA as "Ribavirin" is not licensed in the United Kingdom. Although its antiviral activity was first described 12 years ago, the fact that it has not come into more general use suggests that its value in clinical practice is not as great as the encouraging results of laboratory tests would suggest.

The benzimidazoles

These compounds have been extensively tested both in the laboratory and in volunteers for activity against rhinoviruses, with limited success (Reed, 1980; Tyrell *et al.*, 1983). There are however indications that they can be moderately toxic, and it seems at present that there is no ready cure for the common cold just around the corner.

The bichlorinated pyrimidines

Compounds of this type have been tested against poliovirus, mainly by Italian workers. The margin between antiviral activity and toxicity is small, and none have been subjected to clinical trial. Nevertheless, these substituted pyrimidines are of interest since, unlike most other antivirals, they appear to act very late in the replication cycle, i.e. by preventing assembly of the nucleic acid and structural proteins. It is probable that a drug with this sort of action would act synergistically in combination with another affecting an early stage in replication.

COMPOUNDS ACTIVE AGAINST D.N.A. VIRUSES

The use of thiosemicarbazone for the prevention of smallpox was referred to in the Introduction and needs no further consideration since it is now only of academic interest. The drugs at present most relevant to gynaecology and obstetrics are those that inhibit herpesviruses, particularly herpes simplex.

Anti-herpes drugs

The herpesviruses affecting man are herpes simplex, types 1 and 2 (HSV-1, HSV-2); varicella-zoster (VZV); cytomegalovirus (CMV); and Epstein-Barr virus

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(EBV). Of these, HSV-2 and to a lesser exestent HSV-1 are liable to affect the genital tract.

With the exception of sodium phosphonoformate, all the drugs now to be described are nucleoside analogues that inhibit the replication of DNA.

Phosphonoformic acid

It is interesting that the antiviral activity of phosphonoformic acid (PFA) was discovered by tests in a cell-free enzyme system (Helgstrand *et al.*, 1980). *In vitro*, this simple compound and its trisodium salt inhibit DNA polymerases of HSV-1, CMV and hepatitis B, an RNA polymerase of influenza A and the reverse transcriptases of some animal tumour viruses; furthermore, the ratio of inhibition of viral nucleic acid to that of the host cell is relatively high. Both in guineapigs and in man, topical application inhibits the lesions of herpes simplex. Unfortunately however the compound in its present form cannot be given systematically since it is readily bound to bone and cartilage. It is to be hoped that this problem will be overcome because PFA inhibitis DNA synthesis by a mechanism differing from that of the nucleoside analogues; and as Öberg (1983) pointed out, a combination of drugs acting differently against the same enzyme – or inhibiting different enzymes – might well diminish the chances of development of drug-resistance.

Idoxyuridine (5-iodo-2′-deoxuridine)

This compound was first devised as an anti-tumour drug but was later found to be active against HSV and, to a lesser degree, VZV. Since it is incorporated into both virus and host DNA it is too toxic for systemic use. Applied locally, it is very effective for treating the dendritic form of HSV keratitis and is also useful for skin application in herpes zoster. The prolonged treatment necessary for some ophthalmic infections may give rise to hypersensitivity.

Vidarabine (adenosine arabinoside)

Like IDU, this purine nucleoside is effective in HSV keratitis. It can also, however, be given intravenously and has proved of some value in treating varicella (Whitley *et al.*, 1982a) and herpes zoster (Whitley *et al.*, 1982b) in patients with impaired immunity. The drug was only of limited value in treating HSV infection of the newborn, mainly because it failed to avert sequelae in infants with generalized infections (Whiley *et al.*, 1983). Vidarabine must be used with caution in patients with impaired renal function. It may cause side effects in the gastrointestinal tract, or less frequently, in the central nervous system; tremor has been reported, and this drug should be avoided in patients with Parkinsonism.

Bromovinyldeoxyuridine

The efficacy of this compound was recently reviewed by de Clercq (1983). It resembles IDU in its structure and also possesses activity against HSV-1 and VZV, but much less against HSV-2; so much so that BVDU sensitivity can be

used to type HSV strains. It appears to be highly selective in its action on virus as opposed to host DNA and is thus much less toxic than idoxyuridine; but although a number of open studies have yielded promising results, the final evaluation of this drug must await the outcome of controlled trials.

Acyclovir (9-{2-hydroxyethoxymethyl} guanine)

The action of acyclovir (ACV) against certain herpesviruses was reported by Gertrude Elion and her Colleagues in 1977.

The particular interest of this, the most recently licenced antiviral drug in the UK, lies in its specificity of action and lack of toxicity. Like vidarabine, acyclovir is active only when converted to the triphosphate. The initial phosphorylation to the monophosphate is mediated by a thymidine kinase (TK) specified by the virus, so that ACV is active only in infected cells; the next two phosphorylations are carried out by cellular TK. Antiviral activity is further enhanced by the ability of the compound to enter herpes-infected cells more readily than uninfected cells, and to inhibit viral DNA synthesis much more readily than that of the host cell (Elion, 1983).

ACV is highly active against HSV-1 and rather less so against HSV-2. In cell cultures, VZV isolates are about 10 times less sensitive than HSV. There is some activity against EBV, but little or no inhibition of cytomegalovirus (Collins, 1983). The relative inefficacy of ACV against the latter two viruses is not surprising, since neither codes for TK, and all phosphorylation has to be carried out by the inefficient medium of the host cell TK alone.

ACV is available as an intravenous infusion of the sodium salt, as 200 mgm tablets, as a 5% skin cream in polyethylene glycol and as a 3% ophthalmic ointment. There is now a voluminous literature on the use of ACV given parenterally, orally or topically for various herpesvirus infections and there is space here only to summarize briefly the more important applications, with emphasis on infections of the genital tract and newborn infants with HSV. Much useful information will be found in the proceedings of two recent symposia on acyclovir (King and Galasso, 1982; Field and Phillips, 1983).

Genital and other mucocutaneous infections

In descending order of severity, infections with HSV-1 or 2 can be categorised as "primary" in patients with no previous experience of the virus, "first episodes" in those partially immune from a previous infection with the other serotype, or "recurrent", the result of reactivation of a latent infection. Although recurrent attacks are less in degree and duration than initial infections, they may, if at all frequent, cause serious sexual disability and distress.

There is general agreement that ACV, given early enough by an appropriate route, shortens the duration of symptoms, healing time and virus shedding in the acute phase of all 3 types of infection. Recent evidence (Straus *et al.*, 1983) suggests that prolonged administration of ACV by mounth substantially reduces the number of recurrences of genital herpes. Since the drug could not act on non-re-

plicating virus in the latent state within the dorsal root ganglia, it seems reasonable to assume that reactivation actually takes place, but that subsequent replication in the related area of skin is inhibited by ACV before vesiculation can occur.

In genital infections, both intravenous and oral therapy appear more effective than topical treatment (Corey *et al.*, 1982). Intravenous administration is clearly inappropriate in the vast majority of patients with this type of infection, but oral treatment is useful in dealing with both initial and recurrent attacks, the benefit being greater in the former. Local treatment may be helpful for shortening recurrent attacks, particularly in men, if application started in the prodromal phase; but it should be noted that the ointment is relatively expensive, and may cause pain when applied to raw areas of skin or mucosa.

The question has been asked whether ACV might be given to women suffering from genital herpes in late pregnancy, with the object of protecting the infant at the time of birth. Although there is no evidence that ACV would harm either mother or fetus, the manufacturers suggest caution in prescribing it in pregnancy, pending further experience; nevertheless, there appears to be no *prima facie* case for withholding it in the face of a very serious infection.

Although the pharmacokinetics of ACV in neonates seem satisfactory (Yeager, 1982; Hintz *et al.*, 1982), the results of treating disseminated disease of the newborn are, like those with vidarabine, disappointing (Whitley *et al.*, 1983); this is perhaps not surprising in view of the heavy load of infection.

Other herpesvirus infections

ACV is at least as effective as idoxyuridine for treating *herpes simples keratitis* (Falcon, 1983), especially the dendritic form, and is less liable to cause hypersensitivity in prolonged use. Its value in herpes encephalitis is now being assessed in the United States.

ACV may be used with advantage for treating severe varicella/zoster infections, particularly in immunocompromised patients (Balfour *et al.*, 1983), the dose used for herpes simplex infections being doubled to take account of the lesser sensitivity of VZV. There is some evidence of efficacy in cytomegalovirus infections, but it is not as yet clearcut. ACV has little or no influence on the course of infections wih Epstein-Barr virus.

Toxicity and drug resistance

There are very few reports of toxic effects resulting from the use of ACV; possible marrow toxicity and neurotoxicity were mentioned by Wade *et al.* (1982) but these reactions occurred in marrow transplant patients who were seriously ill with cytomegalovirus infections and receiving unusually high doses. ACV is mostly excreted unchanged through the kidneys, and in those with impaired renal function the dose must be reduced in accordance with the manufacturer's instructions.

Although ACV-resistant strains of HSV lacking TK can be produced in the laboratory, they are less pathogenic than strains isolated from patients; drug re-

sistance has not so far proved a problem in clinical practice, although this position will obviously have to be kept under continuous review.

Future developments in antiviral therapy

Accurate prediction of trends in science is always difficult, especially now that the pace of technological advance is so rapid. Nevertheless, it is possible to make a guess at some of the developments that we may see within the next decade or so.

The exploitation of the techniques of molecular biology for studying the replication and structure of viruses will continue, as will the use of cell-free systems for testing the action of potential antiviral compounds on specific enzyme systems; but animals will still have to be used in the foreseeable future for examining pharmacokinetics, toxicity and teratogenicity. Synergism between compounds acting at different points in virus replication is a field that needs to be explored; and the use of aerosols and possibly liposomes to carry drugs more efficiently to infected organs may also be developed. In this connection, recent researches suggest that monoclonal antibodies may provide a means of delivering drugs to virus-infected cells with great precision and economy. As we have seen with influenza, combinations of drugs and immunological products may be useful in prophylaxis; indeed, we are now using a combination of acyclovir and immunoglobulin to provide maximum protection for children with impaired immunity who are inadvertently exposed to varicella.

We can be reasonably sure that, as has happened with bacteria, drug resistance will eventually rear its ugly and unwelcome head – and will in its turn provide yet another fertile field to research!

In conclusion, it must be emphasized that, to be successful, antiviral therapy must be applied early in the course of infection. This in turn depends on prompt diagnosis and here the possibilities of quick laboratory confirmation have been greatly extended by new techniques: rapid methods for detecting early antibodies are being supplemented or superseded by others for direct detection of virus antigens in clinical specimens by electron and fluorescence microscopy and by tests such as ELISA. I anticipate therefore that the antiviral therapist of the future will go into battle with as much support from the laboratory as is enjoyed by his bacteriological colleagues today.

REFERENCES

Balfour H. H., McMonigal K. A., Bean B.: *Journal of Antimicrobial Chemotherapy*, *12*, suppl. B, 169, 1983. – Bauer D. J., St. Vincent L., Kempe C. H., Downie A. W.: *Lancet, 2*, 494, 1963. – Collins P.: *Journal of Antimicrobial Chemotherapy, 12*, suppl. B, 19, 1983. – Corey L., Benedetti J. K., Critchlow C. W., Remington M. R., Winter C. A., Fahnlader A. L., Smith K., Salter D. L., Keeney R. E., Davis L. G., Hintz M. A., Connor J. D., Holmes K. K.: *American Journal of Medicine, 73*, 326, 1982. – De Clerq E.: "The chemotherapy of herpesvirus infections with reference to bromovinyldeoxyuridine and other antiviral compounds". In: *Problems of Antiviral Therapy*, p. 295, C. H., Stuar-Harris, J. Oxford (Eds.), Academic Press, London, 1983. – Elion G. B.: *Journal of Antimicrobial Chemotherapy, 12*, suppl. B, 9, 1983. – Elion G. B., Furman P. A., Fyfe J. A., de Miranda P., Beauchamp L. Schaeffer H. J.: *Pro-*

ceedings of the National Acadamey of Sciences, USA, 74, 5716, 1977. – Falcon M. G.: *Journal of Antimicrobial Chemotherapy,* 12, suppl. B, 39, 1983. – Field H. J., Phillips I. (Symposium Editors): *The Journal of Antimicrobial Chemotherapy,* 12, suppl. B, Academic Press, London, 1983. – Hamre D., Bernstein J., Donovick R.: *Proceedings of the Society for Experimental Biology (N.Y.), 73,* 275, 1950. – Helgstrand E., Flodh H., Lernestedt J.-O., Lundström J., Öberg B.: "Trisodium phosphonoformate: antiviral activities, safety evaluation and preliminary clinical results". In: *Developments in Antiviral Therapy,* p. 63, L. H. Collier, J. Oxford (Eds.), Academic Press, London, 1980. – Hintz M., Connor J. D., Spector S. A., Blum M. R., Keeney R. E., Yeager A. S.: *American Journal of Medicine, 73,* 210, 1982. – Indulen M. K., Kalninya V. A.: "Studies on the antiviral effect and the mode of action of the anti-influenza compound rimantadine". In: *Developments in Antiviral Therapy,* p. 107, L. H. Collier, J. Oxford (Eds.), Academic Press, London, 1980. – Jones B. R., Coster D. J., Falcon M. G.: *Lancet, 2,* 128, 1976. – King D. H., Galasso G. (Symposium Editors): *American Journal of Medicine, 73,* (1A), Technical Publishing, New York, 1982. – Öberg B.: "Ihibitors of virus-specific enzymes". In: *Problems of Antiviral Therapy,* p. 35, C. H. Stuart-Harris, J. Oxford (Eds.), Academic Press, London, 1983. – Oxford J. S., Patterson S.: "Pulse labelling and electron microscope studies of the inhibition of influenza A viruses by amantadine". In: *Developments in Antiviral Therapy,* p. 119, L. H. Collier, J. Oxford (Eds.), Academic Press, London, 1980. – Reed S. E.: "The assessment of antirhinovirus compounds with clinical potential". In: *Developments in Antiviral Therapy,* p. 157, L. H. Collier, J. Oxford (Eds.), Academic Press, London, 1980. – Scott G. M., Csonka G. W.: *British Journal of Venereal Disease, 55,* 442, 1979. – Smith R. A., Kirkpatrick W.: "The pharmacology of ribavirin". In: *Developments in Antiviral Therapy,* p. 133, Academic Press, London, 1980. – Strauss M. L., Takiff H., Bachrach S., Di Giovanna J., Western K., Creagh-Kirk T., Liniger L., Alling D.: *Clinical Research, 31,* 543 A, 1983. – Thomas H. C., Bassendine M. F., Weller I. V. D.: "Treatment of chronic hepatitis B virus infection". In: *Developments in Antiviral Therapy,* p. 87, L. H. Collier, J. Oxford (Eds.), Academic Press, London, 1980. – Tyrrell D. A. J., Phillpotts R., Wallace J.: "Studies on two antirhinovirus substances - Dichlorobavan and Enviroxime". In: *Problems of Antiviral Therapy,* p. 265, C. H. Stuart-Harris, J. Oxofrd (Eds.), Academic Press, London, 1983. – Wade J. C., Hintz M., McGuffin R. W., Sprigmeyer S. C., Connor J. D., Meyers J. D.: *American Journal of Medicine, 73,* 249, 1982. – Whitley R., Hilty M., Haynes R., Bryson Y., Connor J. D., Soong S. J., Alford C. A.: *Journal of Pediatrics, 101,* 125, 1982 a. – Whitley R. J., Soong S. J., Dolin R., Betts R., Linnemann C. jr., Alford C. A. jr.: *The New England Journal of Medicine, 307,* 971, 1982 b. – Whitley R. J. and the NIAID Collaborative Antiviral Study Group: *Journal of Antimicrobial Chemotherapy,* 12, suppl. B, 105, 1983. – Yeagar A. S.: *American Journal of Medicine, 73,* 205, 1982.

TREATMENT OF COMMON INFECTIONS
IN PREGNANCY AND THE PUERPERIUM

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INTRODUCTION

The use of antimicrobial agents constitutes an important part of the management of infections in pregnancy and the puerperium. It is well documented that the prescribing of antibiotics is less than ideal and gynaecologists appear to be the

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