MEDICAL PRACTICE

Occasional Survey

Antiviral Chemotherapy: The First Decade*

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In reading Dr. Milroy's suggestions for lecturers it is interesting to note his concern with diseases which are now known to be caused by viruses, though in those days even their contagious nature was still in doubt. Thus we find references to yellow fever, smallpox, measles, and "hydrophobia in the canine species." Control of these diseases has made great strides since those days, but much still remains to be done. There are also references to diseases now known to be of bacterial origin, such as plague, scarlet fever, and diphtheria, and here the present situation is entirely different. In fact, one could say that the problem of the treatment of bacterial infections has been virtually solved, whereas the specific treatment of virus diseases is still in its infancy. Antiviral chemotherapy has now been in existence for a decade, and it is therefore an appropriate time to examine the progress which has been made, the reasons why it has lagged behind the achievements of antibacterial chemotherapy, and the prospects for antiviral drugs in the future.

There has always been a great deal of scepticism about the possibility of the specific treatment of virus infections. In my days as a medical student any fairly acute condition of obscure aetiology was apt to be shrugged off as a virus infection, with the inevitable corollary that nothing could therefore be done about it. The same attitude prevailed about infections which were known to be due to viruses, probably because the clinical course in many cases is so brief that there is little time for specific treatment to be instituted. This is by no means always the case, however, and I propose first of all to review the various

types of infections of proved and possible virus aetiology and analyse them with regard to feasibility of treatment if effective drugs should become available.

Acute and Chronic Virus Infections

In the case of *acute virus infections* (table I)—for example, coryza, influenza, haemorrhagic smallpox, and rubella—the clinical course is very brief and by the time the diagnosis has been made death or recovery is on the way. A number of virus diseases, though classed as acute, have a more prolonged course. Adenovirus infections, chickenpox, and mumps can last for seven days or more, and zoster and infectious mononucleosis can last for weeks. Here there is plenty of time to make the correct diagnosis and institute specific treatment. In other acute infections with a prolonged course there is a prodromal period which is often sufficiently characteristic to enable the diagnosis to be made, as in measles, smallpox, central nervous system infections, and hepatitis.

TABLE I—*Acute Virus Infections*

Short Course:	Common cold Influenza Haemorrhagic smallpox Rubella
Protracted Course:	
No prodrome	Adenovirus Infectious mononucleosis Chickenpox Mumps Zoster Measles Smallpox
With prodrome	Echo meningitis Tick-borne encephalitis Infectious hepatitis Serum hepatitis Poliomyelitis

* The Milroy lecture delivered at the Royal College of Physicians of London on 15 March 1973.

The most favourable situation for treatment is afforded by the *chronic virus infections* (table II). Warts, molluscum, and herpes are very common chronic infections of the skin, and vaccinia

TABLE II—Chronic Virus Infections

Skin	Warts	..	..	..	..	Papovavirus
	Molluscum	..	..	..	..	Pox virus
	Vaccinia gangrenosa	..	..	..	..	Vaccinia
	Herpes	..	..	..	..	Herpes
C.N.S.	Subacute sclerosing panencephalitis	..	..	..	..	Measles
	Progressive multifocal encephalopathy	..	..	..	..	Papovavirus, SV40
	Kuru	..	..	..	..	Slow virus
	Creutzfeldt-Jakob disease	..	..	..	..	Slow virus

gangrenosa is a chronic fatal complication of smallpox vaccination. Certain chronic diseases of the central nervous system are known to be caused by viruses, and there are a number of other chronic conditions in which a virus aetiology is suspected (table III).

Other virus infections are ideal for topical treatment. These include infections of the skin, such as herpes, molluscum, measles, zoster, vaccinia, warts, chickenpox, and smallpox, and infections of the eye caused by herpes, adenovirus, vaccinia, and zoster viruses. The condition is visible from the outset, can be diagnosed with certainty, and the antiviral drug can be applied direct to the site of infection.

TABLE III—Possible Chronic Virus Infections

Burkitt's lymphoma	..	..	..	..	..	E.B. virus
Multiple sclerosis	..	..	..	..	..	Measles
Guillain-Barré syndrome	..	..	..	..	..	Scrapie
Alzheimer-Pick disease	..	..	..	..	..	Echovirus
Amyotrophic lateral sclerosis	..	..	..	..	..	? Slow virus
Paralysis agitans	..	..	..	..	..	? Slow virus

Virus infections which cannot be diagnosed with certainty on clinical grounds will always present difficulties for chemotherapy. They include the multitude of upper respiratory infections and the febrile illnesses due to arboviruses which are encountered in the tropics. These infections will be susceptible to chemotherapy only if a drug with a wide antiviral spectrum becomes available.

From this brief review it is evident that a considerable number of virus diseases will be amenable to treatment once active drugs have been discovered. The field of antiviral chemotherapy is much wider than this, however, since there are special features of virus infections which make them very suitable for control by chemoprophylaxis. Unlike most pathogenic bacteria, which present a continual risk of infection, virus infections occur in epidemics, often with case-to-case contact, which clearly identifies those at risk. Treatment with an effective drug during the incubation period will suppress an infection before it becomes clinically manifest. Chemoprophylaxis has a particularly valuable advantage since the protection conferred by a drug is immediate, whereas protection conferred by vaccination takes a considerable time to become effective and is generally valueless in protecting a contact who is already in the incubation period. The acute exanthemata, respiratory infections, and hepatitis can be diagnosed with a fair degree of certainty and enough is known about their modes of dissemination to identify the persons at risk and offer prophylactic treatment. In recurrent herpes the existence of the infection in the individual is known from the history, and in rabies the history establishes that there is a risk of infection sufficiently great to require treatment.

There are also certain special cases of virus infections where an effective chemoprophylactic agent would be of great value, such as exposure to rubella during the first trimester of pregnancy in a woman who has not had rubella and has not been vaccinated against it. Reactivation of cytomegalovirus infections may occur during treatment with immunosuppressive drugs and might be prevented by prophylactic treatment with one of the drugs which are effective against herpes virus infections.

Antiviral Drugs in Clinical Use

There are four first-generation drugs—methisazone, idoxuridine,

cytarabine, and amantadine hydrochloride—and one second-generation drug—vidarabine—is about to come into use.

The properties of those antiviral drugs which are available are reviewed first.

FIG. 1—Structural formula of methisazone.

Methisazone (fig. 1).—The development of methisazone followed from the discovery, made in 1951, that certain thiosemicarbazones which were effective in the treatment of tuberculosis were also able to inhibit the multiplication of vaccinia virus.¹ These were the first antiviral compounds ever to be discovered, and like nearly all advances in therapeutics their discovery came about entirely by chance. In subsequent development related compounds were selected which had increased antiviral activity and lower toxicity, and methisazone was finally selected for trial in man.² Its antiviral spectrum (table IV) is very wide, covering smallpox, adenoviruses, and varicella among the DNA viruses, and a wide range of RNA viruses. Its use in man has so far been restricted to the DNA viruses.

TABLE IV—Antiviral Spectrum of Methisazone and Analogues

Nucleic Acid	Group	Virus
DNA	Poxvirus	Vaccinia, smallpox, cowpox
	Adenovirus	Adenovirus
	Herpesvirus	Varicella, herpes ?
	Picornavirus	Poliomyelitis, echovirus, rhinovirus, FMD
RNA	Reovirus	Reovirus 3
	Arbovirus	Rift Valley fever, Bunyamwera, Semliki
	Myxovirus	Influenza A, B
	Paramyxovirus	Parainfluenza 1

FIG. 2—Structural formula of idoxuridine.

Idoxuridine (fig. 2) is a synthetic nucleoside which was first used without much success in the treatment of leukaemia.³ It is a thymine antagonist, and it is not surprising that it was found on purely empirical grounds to be active against DNA virus infections (table V).

TABLE V—Antiviral Spectrum of Idoxuridine

Nucleic Acid	Group	Virus
DNA	Poxvirus	Vaccinia
	Adenovirus	Adenovirus
	Herpesvirus	Herpes, varicella-zoster, pseudorabies, bovine rhinotracheitis, cytomegalovirus
RNA	Papovavirus	Polyoma
	None	None

FIG. 3—Structural formula of cytarabine.

Cytarabine (fig. 3) is another compound of the same class, which was introduced for the treatment of leukaemia.⁴ Its antiviral spectrum covers the same DNA viruses as idoxuridine but it also has some in-vitro activity against rabies.

FIG. 4—Structural formula of amantadine.

Amantadine hydrochloride (fig. 4) differs from the previous three compounds in that its activity is entirely restricted to the RNA viruses, mainly influenza type A2.

FIG. 5—Structural formula of vidarabine.

Vidarabine (fig. 5) belongs to the same class of compounds as idoxuridine and cytarabine and has a similar spectrum of activity. It is coming into use at the present time and may have certain advantages over the older drugs.

Indications for Use of Antiviral Drugs

POXVIRUS INFECTIONS

Smallpox

Prophylaxis.—Persons who have been in contact with smallpox infection are vaccinated routinely, but if they have not been vaccinated at some time in the past the development of immunity is too slow to protect them against developing the disease. Such persons can be protected by giving methisazone during the

incubation period. In a study carried out in Madras⁵ methisazone was given to 2,610 smallpox contacts. Of these, 18 (0.69%) subsequently developed smallpox and four died. Among a comparable group of 2,710 untreated contacts from similar environments 113 (4.2%) developed smallpox and 21 died. The treatment thus brought about a reduction in incidence of about sixfold. The drug was given by mouth in various schedules ranging from 3 to 24 g over periods of one to four days. Almost complete protection was obtained with two doses of 3 g.

Treatment.—Methisazone is ineffective in the treatment of smallpox, but good results have been obtained recently in a series of nine cases with cytarabine given by infusion.⁶

Alastrim

Prophylaxis.—Methisazone is equally effective in the prophylaxis of alastrim, a mild form of smallpox occurring in Brazil. The drug was given to 215 contacts, 8 (3.7%) of whom developed alastrim, whereas in a control group of 267 contacts there were 42 (15.7%) cases.⁷

Vaccinia

Smallpox vaccination is an artificial infection of the skin with vaccinia virus. This is usually self-limiting and passes off uneventfully, but in certain instances the infection may get out of hand and require treatment.

Ectopic Primary.—By autoinoculation or heteroinoculation the virus may be introduced to a dangerous site, such as the face, nasal cavity, or orbit. If the person has not been vaccinated before a primary vaccination lesion will develop in these areas, leading to extensive tissue damage and severe general illness. These conditions respond well to systemic treatment with methisazone.

Vaccinal Keratitis.—Virus which enters the conjunctival sac may give rise to corneal ulceration, leading to opacities and possible perforation. It responds to treatment with eye-drops of idoxuridine.⁸

Moderation of Primary Reaction.—The local and general reactions to primary smallpox vaccination can be very severe, and if it must be carried out in the presence of some contraindication such as unsuitable age or unsuitable medical history it is possible to modify the reactions by oral treatment with methisazone combined with injection of antivaccinal gammaglobulin.⁹

Eczema Vaccinatum.—It is usual not to vaccinate persons suffering from eczema, since they are liable to develop a generalized infection with vaccinia virus which produces a disease which closely resembles smallpox and is not infrequently fatal. This may occur even if eczematous lesions are not present at the time, and is often seen in eczematous children who have been withheld from vaccination but have acquired the infection from a vaccinated parent or sibling. The course of the disease is very variable, and assessment of the results of treatment is necessarily based on clinical impressions, but the condition usually responds to treatment with methisazone.¹⁰

Vaccinia Gangrenosa.—In the presence of a deficiency in the mechanisms of immunity the lesion of primary smallpox vaccination may fail to heal. Satellite and metastatic lesions appear elsewhere in the body and steadily increase in extent. Death results from the effects of skin destruction and involvement of internal organs. Two types may be recognized—the infantile, occurring in young children with congenital hypogammaglobulinaemia, and the adult, occurring in patients suffering from reticuloses in whom the immune response has been depressed by therapeutic measures. The mortality can be reduced from 100% to 50% by treatment with methisazone,¹⁰ and it may be necessary to repeat the course more than once.

HERPESVIRUS INFECTIONS

Herpes

Herpetic keratitis can be effectively treated with eye-drops of idoxuridine¹¹ or cytarabine.¹² In recurrent infections the virus may develop resistance to these agents, however, and they are not effective in the presence of deep stromal involvement.¹³

Cutaneous Herpes.—A 5% solution of idoxuridine in dimethylsulphoxide is effective in shortening the course of cutaneous herpes,¹⁴ and severe generalized primary herpes can be treated with cytarabine¹⁵ given intravenously in doses up to 2 mg/kg daily.

Herpetic Whitlow.—Hospital staff frequently contract primary herpes infection of the skin in the form of a whitlow, which may take several weeks to heal. It resolves rapidly on treatment with 40% idoxuridine in dimethylsulphoxide applied on lint.¹⁶

Herpetic Encephalitis.—Idoxuridine¹⁷ and cytarabine¹⁸ are used in the treatment of herpetic encephalitis but the results obtained are far from satisfactory. The drugs are given by intravenous infusion, a typical dose being 1,000 mg/kg over a period of several days. Both compounds are rapidly inactivated by metabolism, and better results could be expected from vidarabine, which is metabolized to derivatives which retain antiviral activity.

Zoster

Keratitis.—Lesions may occur on the cornea in ophthalmic zoster. They respond to treatment with eye-drops of idoxuridine.¹⁹

Cutaneous Zoster.—Application of a 40% solution of idoxuridine in dimethylsulphoxide results in rapid disappearance of pain and drying of the lesions.²⁰ Generalized zoster may occur in patients receiving immunosuppressive therapy, and can be treated with intravenous idoxuridine.²¹

Varicella

Generalized varicella may occur as a serious complication in patients suffering from leukaemia and similar conditions. It responds to cytarabine given intravenously in a daily dose of 100 mg/m² (ref. 22).

Varicellar pneumonia may be similarly treated with cytarabine,²³ and good results have also been reported with methisazone.²⁴

Cytomegalovirus

Congenital infections with cytomegalovirus are not infrequently seen in young infants and may lead to retardation of development. Considerable clinical improvement has been obtained with intravenous idoxuridine in a total dose of 600 mg/kg given over a period of five days.²⁵

MYXOVIRUS INFECTIONS

Influenza

The only drug available for use in influenza at present is amantadine hydrochloride. Its antiviral activity is not very great, and the results obtained with it have not always been satisfactory. A good prophylactic effect was obtained in a collaborative general-practitioner study carried out in 1967-8 among home contacts of patients suffering from A2 influenza. The drug was tested against a placebo and treatment was continued for 10 days. There was a highly significant reduction in the incidence of contact cases in the amantadine group.²⁶ The prevalent strain of virus was A2/England/10/67. However, no effect was obtained in a similar trial carried out in 1969 when the prevalent strain was A2/Hong Kong/68.²⁷ Amantadine hydrochloride has also been used in the treatment of influenza, and some reduction in the febrile period was observed.²⁸

Future Possibilities

There are a number of treatments which have not come into use yet which offer possibilities of success within the present state of the art. These include the use of methisazone and idoxuridine and related compounds in the treatment of adenovirus infections, particularly conjunctivitis. Idoxuridine and the other nucleosides might be effective on theoretical grounds in the treatment of infectious mononucleosis and also in the prophylaxis of recurrent herpes. Another nucleoside, 6-azauridine, which is in the experimental stage, may be effective in measles and subacute sclerosing panencephalitis.

Conclusion

That concludes a brief survey of the achievements of antiviral chemotherapy in its first decade. The subject, which did not exist when I was a medical student, has come into being and has made solid advances. Diseases which once threatened life and loss of sight can be effectively treated, but antiviral chemotherapy has as yet made no great impact on therapeutics comparable with that achieved by antibacterial drugs. There are several reasons for this. Antibacterial chemotherapy has been in existence for much longer and got off to a much more impressive start. It is no reflection on the genius of its pioneers to comment that "they never had it so good," since the first drugs to be found were highly effective against organisms of the greatest clinical importance. In contrast we who have devoted ourselves to antiviral chemotherapy have had to seize whatever chance discoveries have come our way and develop them within the limits of their clinical effectiveness. The situation which we brought about was rather as if antibacterial chemotherapy had begun with the discovery of drugs active against only anthrax and meningococcal meningitis. These would have been major advances in the history of medicine, but they would have made little impact on our management of the bacterial infections in general.

What of the future? Antibacterial chemotherapy is losing its impetus now that most infections have been brought under control, and we may never see again discoveries of the magnitude of penicillin or isoniazid. With antiviral chemotherapy much still lies in the future. The problem of DNA virus infections has been taken most of the way to its solution. It is an unfortunate fact of life, however, that most virus diseases are caused by RNA viruses, and the attack on this problem is only just showing signs of success. There is a need for a much more effective drug against influenza and drugs active against the many types of upper respiratory infections caused by viruses. Progress is already being made in this field, and it will form the major challenge to antiviral chemotherapy in its second decade.

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Scientific Basis of Clinical Practice

Hepatic Encephalopathy

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The Syndrome

In severe liver disease neuropsychiatric changes may occur and may progress to coma. These effects are termed hepatic encephalopathy. An early manifestation is defects of behaviour. Later there may be euphoria or drowsiness, confusion, ataxia, and a characteristic flapping tremor, before progression to coma. The course often fluctuates and may be arrested or reversed at any stage. The flapping tremor is characteristic but not pathognomonic of hepatic encephalopathy. It may also occur in severe heart failure, severe respiratory failure, or severe renal failure.^{1,2}

In hepatic encephalopathy there is a characteristic abnormality of the electroencephalogram consisting of paroxysms of bilaterally synchronous, symmetrical, high-voltage, slow waves in the delta range of 1½ to 3 per second interspersed with, or superimposed on, relatively normal alpha waves.³ Again, these changes are not pathognomonic of hepatic encephalopathy but may occur in other severe metabolic disturbances.

OBSERVATIONS

The mechanism of hepatic encephalopathy is not established, but any proposition must take account of the following observations:

(1) The liver is the only organ which can remove ammonia from the blood and convert it to urea.^{1,4,5}

(2) In liver disease, particularly if there is significant portal-systemic shunting of blood, the blood ammonia concentration may rise.⁶⁻⁹ Hepatic encephalopathy occurs in virtually all patients in whom the blood ammonia concentration exceeds 3 or 3.5 µg/ml,⁷⁻⁹ and in an individual patient as encephalopathy progresses the blood ammonia concentration rises. Perhaps 20% of patients with severe hepatic encephalopathy, however, have ammonia levels within the normal range.⁷⁻⁹

(3) In the absence of liver disease, encephalopathy may occasionally develop if there are appreciable portal-systemic communications due to extrahepatic obstruction in the portal venous system,¹⁰ but in most patients with encephalopathy there is evidence of both liver disease and portal-systemic communications.

(4) Several orally administered nitrogenous compounds have been shown to produce encephalopathy in susceptible subjects: ammonium chloride, ammonium-containing cation-exchange resins, diammonium citrate, urea,¹¹ and dietary protein.¹² These all yield ammonia in the gut and are associated with raised blood ammonia levels. However, methionine may provoke encephalopathy without causing a significant rise in blood ammonia concentration and this effect can be prevented by chlortetracycline.¹³

SUGGESTED MECHANISMS

Toxic products of bacterial degradation of nitrogenous material within the bowel are normally absorbed, pass into the portal vein, and are removed by the liver (fig. 1). In chronic liver disease, because of failure of removal by the diseased liver—and also because of direct access to the systemic circulation by collateral vessels, surgical shunts, or intrahepatic communications—these toxic products reach the brain, where they exert a deleterious effect.

There is suggestive evidence that ammonia is one of the toxic products responsible for hepatic encephalopathy, but

FIG. 1—Mechanism and methods of treatment of hepatic encephalopathy.

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