THE CONTROL OF VIRUS INFECTIONS

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Virology is still in its infancy when compared with the now well-established parent study of bacteriology. When one remembers how slow to progress were the advances in bacteriology, which we now accept as commonplace, it is not so surprising that since the first discovery of a virus in the late nineteenth century there has been very little progress towards control of virus infections. But, let it be said at the outset, this is no detriment to the virologist - the subject is fraught with difficulties. The fact that viruses can only be grown in living media, and that to prove even their presence, let alone their identity, is a procedure laborious in the extreme, would be enough to discourage the average worker; but add to this the fact that each new discovery in the field seems to add to the complications rather than clarify the situation and one begins to see the immensity of the problem. There are even diseases which appear to be of viral aetiology where no agent has yet been isolated. However, one would not want to approach the subject of control of virus infections in too gloomy a light. Progress has been made and indeed continues to be made and the prospects are improving with the realisation that the control of the virus is a separate problem from the control of the bacterium, and the principles which have been applied with considerable success to the latter may not necessarily be those which will provide the answer to the former.
I propose to consider the subject along three main lines -

(1) the treatment of the actual clinical attack of a virus infection,
(2) prophylaxis,
(3) the wider subject of epidemiology and actual prevention of disease of viral etiology.

(1) THE CLINICAL ATTACK

Treatment of virus infections has been up to now largely on conservative lines, that is directed towards relief of symptoms, and there has been little available to direct against the virus itself. It is extremely interesting to note that the steroid hormones and corticotrophin which have been used, empirically, but with measurable success in such a wide variety of ailments, have found no use in the treatment of virus infections, and indeed are contraindicated in the majority of cases. They have been found to increase susceptibility to secondary bacterial and mycotic infections but they may be indicated in cases of great severity when the risk of death is high, in the prevention or control of specific complications (for example thrombocytopenia) or in shock. Steroids seem to be particularly dangerous in relation to varicella (chicken pox) infections. A number of fatal cases of varicella have been reported in patients who were on steroid therapy when they contracted the disease. Reduction of dose or withdrawal of steroids is advocated when a patient being thus treated is exposed to varicella; with the obvious exception of those patients having replacement therapy for adrenal failure. It must be added in
this connection that reports are conflicting and no conclusive evidence is available, due to the distinct lack of controlled trials.

There are, however, two therapeutic possibilities; the use of immune human serum or gamma globulin which has been successful in many cases (e.g. measles and infective hepatitis) and chemotherapy. It must be borne in mind that the majority of virus infections are not severe and rarely does one prove fatal. Thus if a substance was to be found to be a successful anti-viral agent, to achieve widespread use it would have to be well-tolerated by a maximum number of patients and have minimum toxicity. An agent having undesirable side effects would be useless in practice no matter how effectively virucidal it might prove to be. Toxicity in an antiviral drug would only be acceptable where the risk of permanent disability or a fatal outcome was high (compare the use of chloramphenicol in typhoid fever). Usually a single attack of a virus infection results in the host's acquiring life-long immunity to any further infection by that virus. This applies particularly to those virus diseases having a long incubation period (vide infra). An anti-viral agent must not interfere with the achievement of such immunity.

It might now be useful to define the term anti-viral agent as a substance which produces clearly detectable protective or therapeutic effects in a virus infected host. This could be due to a direct virustatic or virucidal effect or could occur indirectly as a result of enhanced anti-body formation or activity, improved non-specific resistance, depression of symptoms, or increased rate of recovery and decreased length of convalescent period. Anti-viral agents may act in a chemotherapeutic or chemoprophylactic manner. It is the former which interests us at this
point. Such an agent might act by inhibiting the synthesis of virus particles within the host cell, by increasing the host's resistance to the infection, or preventing the pathogenicity of the virus, or by enhancing the inherent defence mechanisms of the host - relief of clinical symptoms might be sufficient per se to enable the host to rid itself of the parasite. Any or all of these properties would, of course, have to be combined with the usual requirements for any therapeutic agent (high therapeutic index, minimum side effects, ease of manufacture, etcetera). An ideal agent would be one which, when administered after the diagnosis had been made, would modify the course of the disease without affecting the build up of natural immunity.

It has been found that the broad spectrum antibiotics are effective against the psittacosis-lymphogranuloma venereum group of viruses but have no static or cidal effect against the smaller viruses. There is some doubt as to whether these larger organisms should be classed as viruses or included with the Rickettsiae, and certainly in this respect they differ markedly from the smaller viruses. They will not be considered further.

Resistance of viruses to the known antibacterial agents is probably due to differences in metabolic mechanisms. Viruses multiply in their animal host by means of their peculiar ability to take over the enzyme systems of the host cell and use these for the synthesis of virus nucleic acid and protein. It is this most intimate connection between the virus and the host that creates the largest therapeutic problem. Finding a virucidal agent is by no means the greatest difficulty, it is finding one
which is specific for the virus and non-toxic for the patient which is the stumbling block. The onset of symptoms and signs, the appearance of pathological lesions, and the maximum titre of virus particles do not always coincide; it is difficult therefore to diagnose virus infections in the early stages, when anti-viral therapy would be most effective. Many of the substances so far investigated have shown anti-viral properties only when administered at the same time as, or very shortly after the virus was inoculated. Thus they have only prophylactic possibilities.

A good deal of difficulty has been encountered in finding an agent which will selectively kill the virus without damaging the host cell. It would help considerably if the mechanism of chemical specificity of the virus were known, for example the nucleotide sequence of its nucleic acid or the shape and constitution of its protein moiety. This would give a definite point at which an attack could be made. Inhibition of nucleic acid synthesis seems to be the most profitable time of approach. This might be achieved either by competitive inhibition of enzyme systems, or by incorporation of abnormal analogues into viral nucleic acid, leading to the synthesis of a non-functional entity. In the resting host cell there is a minimal turnover of deoxyribosenucleic acid (DNA) because the rate of cell division is very small. If such a cell were infected by a virus the rate of synthesis of viral DNA would be much in excess of that of host DNA and it might be assumed that an abnormal analogue would be selectively incorporated into the viral DNA. There is a large turnover of ribose nucleic acid (RNA) in all cells, so that this kind of approach is less satisfactory for RNA-containing viruses; but, since it is thought
that the DNA carries the information required for synthesis of RNA, it is possible that a cell might recover after an RNA containing virus which had parasitised it had been eliminated, provided the cell retained its content of DNA. The main disadvantage of this approach is that any abnormal analogue would be incorporated into molecules essential to the host, such as enzymes. A similar approach to inhibition of protein synthesis using amino acid analogues is less likely to be successful owing to the brief time interval between the addition of the protein moiety onto the nucleic acid core and the release of the virus particles from the cell. So far substances investigated have reduced the rate of virus synthesis but have not inactivated the infective properties of the virus. It has been concluded that they have acted by inhibition of host cell processes. We shall go on now from this general discussion to consider some of the anti-viral agents which have been investigated.

Thiosemicarbazones

The effectiveness of thiosemicarbazones against vaccinia and variola viruses was first noted in 1950. N-methylisatin beta thiosemicarbazone proved effective prophylaxis against small pox in mice when given during the incubation period of the disease. In 1962 it was tried in a small pox outbreak in Great Britain with indications of success but no confirmatory evidence. In 1963 a controlled trial of methylisatin beta thiosemicarbazone was conducted amongst small pox contacts in India. The incidence of disease was reduced by 98% in 1101 treated patients, with a control group of 1126 untreated contacts. The prophylactic effect was independent of vaccination history, and was more effective than revaccination or antivaccinial gamma globulin, even when given late in the
incubation period. The only side effects were some slight nausea and vomiting. These very encouraging results have led to the use of thiosemicarbazones in cases of vaccinia gangrenosum and eczema vaccinatum with some success. The high mortality rate of these conditions makes controlled trials unethical. A fatal case of progressive vaccinia with hypogamma-globulinaemia has been reported in which there was no response to thiosemicarbazone or antivaccinial gammaglobulin.

It seems that the action of the thiosemicarbazones is highly specific. N-methylisatin beta thiosemicarbazone was virustatic in mice against vaccinia, rabbit pox, alastrim, variola major and cow pox, but inactive against ectromelia (mouse pox). A substitution product N-methylisatin beta dimethyl thiosemicarbazone reversed this finding. A number of substitution products were investigated (Bauer et al. 1962) and it was found that increasing the chain length of the alkyl substituent decreased the antiviral activity and altered the specificity. Protection against death was due to inhibition of virus multiplication and not to any non-specific effect such as suppression of the inflammatory response. The fact that changing substituents alters the virus specificity of the drug indicates that the action is a direct one against the virus and not on the host cell. The specificity might be due to a difference at the molecular level with a constituent of the virus particle with which the compound interacts.

5-iodo 2-deoxyuridine

5-iodo 2-deoxyuridine (IDU) inhibits the incorporation of thymidine into DNA and also inhibits the DNA polymerase system. It has been used in experimental animals and also in humans against herpes simplex and
vaccinia infections of the eye. In a series of experimental infections in rabbits, IDU eliminated signs of keratitis in all cases and completely eliminated the virus in fifty per cent of cases. It was effective several days after the appearance of the clinical lesion, when corneal ulceration was far advanced. Clinical improvement preceded elimination of virus. IDU eye drops have been used in human patients. The use of cortisone to suppress the inflammatory reaction and so preserve the eye while the IDU is taking effect is a vexed question. In vitro steroids enhance the growth of the virus and inhibit interferon production (q.v.), and some workers have reported them to be definitely dangerous when used in herpetic keratitis. Experiments indicate that IDU has a specific antiviral effect.

IDU is relatively insoluble but rapidly dehalogenated once absorbed. This makes it useless for systemic administration but highly suitable for topical application. The cornea, being avascular and hardy, as well as accessible, is an excellent site for experiment with this agent. Local toxic effects were inapparent and rapid metabolism prevented any systemic side effects. In a trial of iododeoxyuridine in herpetic dendritic corneal ulceration in fifteen human patients in 1962 resolution of ulceration was achieved in all cases, and at the time of reporting no cases of early recurrence had occurred but it was too soon to make a confident statement as to the elimination of the virus. In some of the patients where IDU therapy had been prolonged there was corneal ulceration which did not respond to further doses of IDU but cleared on withdrawal of the drops. This was thought to be due to the action of the IDU on the corneal cell metabolism.
Virugon

Anhydrobishydroxyethyl biguanide hydrochloride combined with methscopalamine or methatropine and called virugon has been studied but reports so far available are conflicting to say the least. Virugon is stated to have both virustatic and virucidal properties. In 1960 virugon was investigated in a series of acute upper respiratory tract infections thought to be of virus aetiology. Prophylactic and therapeutic effectiveness was reported in cases of Asian influenza; but there have also been reports of complete lack of success with virugon in influenza. In a controlled trial with patients and contacts in the winters 1959-60 and 1960-61 no prophylactic or therapeutic effect of virugon was found. In 1962 Brown et. al. conducted a comparative study of virugon and penicillin V in cases of measles. They found no significant difference in the two groups of patients with regard to reducing the severity or duration of the illness or the occurrence of complications.

These reports indicate that further study of virugon as an anti-viral agent might meet with success. Certainly in a field such as this no stone showing the smallest possibility of success must be left unturned.

Guanidine

Guanidine has been found to have an antiviral effect against poliomyelitis virus and other enteroviruses in tissue culture, shown as an inhibition of the cytopathic effect. It has proved effective in monkeys, although it was apparently difficult to distinguish clinically between the effects of infection with the virus of poliomyelitis, and the toxic effects of guanidine. Assessment of the efficacy of the drug was based on study of sections of spinal cords of experimental animals. Guanidine was
specific for the enteroviruses, and more effective when administered orally than by the intramuscular route. The effect was due to guanidine itself and not to any substitution product. Unfortunately the drug is too toxic for human trials.

The few compounds mentioned will have served to indicate how wide is the scope of antiviral therapy and how difficult the task of finding and investigating antiviral agents. There seems to be no guiding principle or common property to indicate whether or not a given compound might have anti-viral activity, so the research must go on by trial and error with the ever present hope that sooner or later some fact will come to light which will enable some basic principle to be drawn up on which research workers can base their hypotheses. The fact that no such principle has been found with regard to antibacterial agents is not encouraging!

Antiviral agents will find uses not only in chemotherapy and prophylaxis of infections but also in the preparation of killed vaccines and in sterilisation of blood and blood products, which would at least remove serum jaundice from the clinical scene.

**Interferon**

Interference is a property peculiar to the viruses, whereby infection with one virus (the interfering virus) protects the cell from infection with another (the challenging virus). There are a number of theories as to the mechanism of this property. It is possible that the interfering virus occupies or destroys all the available receptor sites on the cell, or that it gains control of the enzyme systems and nucleic acid synthesis of the host cell so that no metabolic processes are available for the challenger or that the mechanism of escape of the interfering virus is blocked, thus
preventing invasion by the challenger. None of these explanations seems complete for the property of interference is retained by the killed virus and is also possessed by a purified extract of virus given the name interferon. This is most probably a protein. It is a smaller particle than the original virus, is non-toxic and non-antigenic, not neutralised by antiviral sera and stable over a pH range 2 - 11. Interferon seems to be linked with the phenomenon of cellular immunity. It inhibits the intracellular growth of viruses in a non-specific manner and is effective against a wide range of viruses. Thus it is not an antibody, and indeed in a virus infested host interferon can be shown to develop before antibodies are detectable. It inhibits growth of viruses in vivo only - it has no effect in vitro.

The possibilities of using interferon or even harmless interfering viruses in treatment of viral infections have been entertained. Trials so far have shown interferon to be effective when administered at the same time as the experimental inoculation of virus, or a short time after. The fact that interferon is produced naturally in the host in viral infections is a point in its favour as a possible antiviral agent for clinical use. It has been shown that failure to produce interferon may prove fatal, and certainly in such cases therapeutic use of interferon would be highly effective. Work on these lines has only recently been begun and no evidence is yet available.
(2) PROPHYLAXIS

Prophylaxis is the prevention or preventive treatment of disease (Dorland's medical dictionary). The earliest method of prophylaxis was quarantine, that is the isolation of the patient until he was proved to be no longer infectious, and of his contacts until they had passed through the period of incubation of the disease without developing clinical symptoms. This of course made no provision for the protection of the community against dissemination of viruses by people suffering from subclinical infections or by healthy carriers. There are at present in force international quarantine regulations for smallpox, yellow fever, and epidemic typhus. These include, in addition to limitation of freedom, enforced sanitary practices, disinfection or decontamination and vaccination of affected or exposed persons. While such measures are obviously necessary and desirable in the case of such serious diseases as those mentioned, they are not practicable for the control of milder viral diseases in the local community.

When an epidemic of a viral disease strikes a community, immunisation of the population at risk is the most satisfactory way of protecting that community against the rapid spread of the disease with resulting loss of man-hours to the general disadvantage of the community as a whole. Immunisation may be achieved passively, by the administration of immune serum or human gamma globulin, or actively by the process of vaccination. Which method is used will depend on the circumstances. In an actual epidemic passive immunisation of direct contacts of clinical cases, and mass vaccination of the rest of the population would achieve control.
Passive immunisation has the advantage of being immediately effective, but provides protection for a matter of weeks only, whilst with vaccination immunity develops gradually over days or weeks, but is much longer lasting (several years to a lifetime). There are some diseases against which no effective vaccine has yet been developed, and for these the use of immune serum either prophylactically or therapeutically (that is after exposure) is an important and valuable procedure.

Effective vaccines are available against a number of viral diseases. Some of these will now be considered. In the case of smallpox immunisation is the principal method of prophylaxis. This is because of the rapid spread of the viruses by droplet infection and their ability to survive for long periods outside the animal host so that quarantine, while preventing spread of infection, could not bring about eradication of the disease, and also because the degree of immunity after vaccination (or after infection for that matter) is generally high and of long duration. It has been possible to eradicate smallpox completely from some countries and to protect against its reintroduction from elsewhere by maintaining the immunity of the population by revaccination at regular intervals and by enforcing stringent quarantine precautions and mass vaccinations whenever a case of clinical smallpox presents itself. World wide eradication of smallpox is a conceivable and practical possibility by these means. There have been many arguments about the ethics of compulsory vaccination but it seems to me that in the case of a disease as dreadful and as readily preventable as smallpox, no argument against the protection of the population as a whole can possibly be accepted.
The last few years have seen the development of two different vaccines for protection against poliomyelitis. The first was a killed vaccine, developed by Salk, which gave immunity against paralytic poliomyelitis to the vaccinated person, but did not prevent the virus from multiplying in the alimentary and respiratory tracts and so did nothing to prevent the wide dissemination of the virus. The later developed Sabin vaccine, consisting of living attenuated viruses, gives immunity and also increases the resistance of the cells of the alimentary and respiratory tracts to infection and multiplication of virus so that it also reduces the possibilities of spread of viruses from immune persons. It should be possible, by the use of this vaccine, to eliminate poliomyelitis completely. The Sabin vaccine has the additional advantages of oral administration, low cost, and ease of manufacture.

There is as yet no effective vaccine for influenza, but the facts of droplet spray spread, short incubation period, high infectivity, and world wide distribution of the virus leads one to suppose that immunisation would be the most effective means of prophylaxis. However, the viruses change their antigenic structure with such alarming regularity and rapidity that unless some method of rapidly detecting new antigenic strains and equally rapidly producing effective vaccines can be devised, immunisation prophylaxis of influenza seems an insurmountable problem.

Measles is probably the most infectious of all diseases. While in this country infection tends to be mild and uncomplicated, measles is regarded as one of the serious killing diseases of the world. Prophylaxis by immune serum or gamma globulin has until recently been the only means of control, but there is now under trial a living attenuated vaccine.
From the reports it would seem that the virus has not yet been sufficiently attenuated. After vaccination a mild febrile syndrome occurs, sometimes with a faint rash, recovery from which is associated with immunity to measles. The child is not contagious while suffering from this syndrome and children who do not develop the reaction have no immunity. In the U.S.S.R., this vaccination reaction has been accepted as a reasonable price to pay for immunity to measles, but it does seem possible that a further attenuated strain of the virus could be cultured which would confer immunity without producing a reaction. It must be remembered that the aim of immunisation is to produce a degree of resistance comparable to that achieved by a clinical attack, without harm to the recipient.

Chemoprophylaxis is also a feasible means of combating viral infections. Many of the agents already discussed as therapeutic agents could be used in a prophylactic manner if administered after exposure to infection. It might be possible by means of a chemical compound to inactivate the virus particle before it reaches the cell, to protect the cell against adsorption of the virus, to prevent the migration of viruses from infected cells to normal ones, or to inhibit the early stages of viral multiplication, as already described. The thiosemicarbazones are good examples of chemoprophylactic agents for smallpox.
(3) EPIDEMIOLOGY

Obviously, as in any form of disease, actual prevention of virus infections is more desirable than cure. This requires a more detailed study of the mode of transmission of an infection within the community, of the pattern of occurrence with regard to time, age and sex incidence, and so on; and from information thus gained investigation of possible means of eliminating the disease. Most of the viruses which cause disease in man have man himself as their natural host so that man is the only reservoir of infection. There are a few viruses which mainly parasitise other animals but which may on occasion be transmitted to man resulting in the sporadic outbreak of rare diseases. Thus there is a range of viral infections from isolated cases of rare diseases such as Q fever to the common diseases primarily of man, which result in epidemics and even pandemics which may decimate populations and change the course of history as smallpox and influenza, to take two extremes, have been seen to do in the past.

Where man is the only animal host transmission of the virus to a healthy person occurs by contact with the infected host or his contaminated environment. If this were the only means of transmission solution of the problem would be relatively simple, but the situation is complicated by the fact that apparently healthy people may harbour and disseminate viruses, such people being classed as healthy, incubatory, convalescent, or chronic carriers according to whether or not there is any relation between their carrier state and a clinical attack of the infection. Virus diseases may be contracted by inhalation of droplet spray, or by ingestion of contaminated
food or water. Diseases which are contracted from human sources are described as contagious. The infectious period may not coincide with the period of clinical illness. Non-contagious infections are those in which man shares the role of host with other animals and which are not characterised by case to case infection, that is, man is only an accidental participant in the chain of events leading to propagation of the virus. There are some intermediate diseases in which man is the natural reservoir but an intermediate vector, usually an anthropod, is necessary for transmission of infection. The vector may or may not also act as a host in which multiplication of virus can occur.

Most virus diseases have an incubation period between contraction of infection and appearance of clinical symptoms. The length of the incubation period depends on whether the virus can multiply at the site of inoculation (as in influenza) when it is short, or whether it has to travel through the tissues to its preferred site (as in infectious hepatitis). It may also depend to some extent on the size of the inoculated dose of virus. Knowledge of the length of incubation period of a particular disease is useful in determining the rate of spread through the community and also in finding the source of an epidemic. It is thought that there may be some relationship between length of incubation period and degree of immunity to an infection - a long incubation period may allow time for reactivation of immunity against a particular virus so that infection with that virus subsequent to the first infection, is never able to manifest itself clinically. It is not known whether immunity is associated with actual persistance or virus particles within the tissues, or whether there remains in the cell a model for reassembly of antibody against an antigen,
so that immunity can be reactivated should the antigen ever be reintroduced.

In order to study a particular disease in relation to a particular community it is necessary to assess the community susceptibility to that infection, that is the number of persons possessing a degree of immunity complete or partial. In the case of viral infections this has to be done by serological tests. There are no suitable skin tests such as are available for tuberculosis and diphtheria. Once knowledge of community susceptibility is available steps can be taken to make the population one hundred per cent immune, thus ensuring that viruses have no chance to spread, at least among the human members of the community. The best way of doing this is mass vaccination - where vaccines are available.

There are however a number of more general means of producing a degree of control. These are aimed at reducing the risk of disease and death without eradicating the subclinical immunising infections which most of us undergo without ever knowing anything about it. This aim at once presents a problem as has been illustrated in the case of poliomyelitis. In certain communities improvement in general hygiene and sanitation was followed by an increasing incidence of paralytic poliomyelitis which proved to be due to failure to contract subclinical but immunising infection in childhood, as had been the common occurrence when faecal contamination of water and food had been the rule rather than the exception. Obviously hygiene and adequate sanitation are desirable and indeed very necessary, and this situation serves to emphasise the fact that mass vaccination must be introduced.

In the case of anthropod borne infections it seems more sensible to direct an attack at the vector and source of infections rather than at the host himself. This is however not always possible. Yellow fever is a...
disease, primarily of monkeys, which may be transmitted to man by the bite of an infected mosquito. There are two types of yellow fever, classed according to the vector, the virus being the same. The urban type is carried by the mosquito Aedes aegypti which lives and breeds only close to human dwellings. In this case, eradication has been achieved by stringent anti-mosquito methods with vaccination as a supplementary procedure. The jungle type of yellow fever is transmitted by other species of Aedes mosquitoes. It is virtually impossible to control these forest mosquitoes and protection can only be achieved by vaccinating all people at risk. One hundred per cent vaccination, if maintained, could eliminate yellow fever as a human infection.

It has been possible only to touch in a superficial manner on the many aspects of control of virus infections. It must be emphasised again that virology is a young science, but one which is growing at a most encouraging rate. Perhaps if, in ten years time, another set of medical students are asked to write on this subject, they will be able to give facts where theories are all that is available at present, and positive results with confirmatory evidence where only the earliest research has been mentioned here. The trend is in that direction.

SUMMARY

The control of virus infections is considered from three broad viewpoints. Firstly, the treatment of the clinical attack, secondly prophylactic measures, and thirdly the epidemiology of virus diseases. Where possible statements have been accompanied by experimental evidence and results of trials.
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