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Antiviral Chemotherapy

The major part of infectious diseases of man is caused by viruses. In the fight against viral diseases, great advances have been made by the development of vaccines, e.g. vaccines against yellow fever, poliomyelitis, measles, rubella and more recently against hepatitis B. Despite these momentous achievements, the battle is going on. There are many virus infections for which a vaccine is not available. In fact, the prospect of developing of a vaccine against virus groups consisting of many serotypes (e.g. enteroviruses, rhinoviruses) is rather dim. Antigenic variation (e.g. influenza viruses) also complicates an effective use of vaccines. Further problems concern the immunocompromised patient, vaccination against latent virus diseases (herpes viruses) and slow virus diseases. For all these reasons, not to speak of the many people who missed the opportunity to be vaccinated, treatment of viral diseases by chemotherapy is badly needed.

It has been thought for a long time that antiviral chemotherapy might be principally impossible. Viruses are obligatory intracellularly multiplying agents which depend heavily on the metabolism of the infected host cell: building blocks, energy, the protein synthesizing machinery, etc.; they all are provided by the infected cell. The task of antiviral chemotherapy, however, is to inhibit virus replication selectively, i.e. without impairment of vital cell functions. Basic studies during the last 25 years have clearly established that there do exist virus-specific structures, e.g. virus-induced enzymes or other viral structural components, which occur only in the infected cell and may be the target of antiviral substances (1, 2).

Despite these fundamental achievements, however, antiviral chemotherapy is, as of now, limited to only a few diseases. The important studies by *D. Bauer* on the chemoprophylaxis of poxvirus infections by isatinthiosemicarbazones (notably methisazone) in the late fifties (3) have been superseded by the eradication of smallpox. We hope the drug will never have to be used for the control of monkeypox.

A further decisive step has been *H. Kaufman's* demonstration in 1962 of the treatment of herpes keratitis with 5-iodo-2-desoxyuridine (IDU). Since then, several other substances have been shown to be effective in the treatment of herpes simplex virus infections of the eye, a major cause of blindness in the developed countries (4).

A major advance has been the introduction of 1-adamantanamine hydrochloride (amantadine, Symmetrel[®]) and its derivative rimantadine for the chemoprophylaxis and treatment of influenza virus A infections in the mid-sixties. However, for reasons not to be discussed here, amantadine and rimantadine have not been used on a

wider scale, though this treatment may be a true alternative to vaccination, in particular when influenza virus A variants emerge for the first time in the population (5). More unnoticed by physicians have been the important studies by *C. Alford*, *R. Whitley* and their collaborators on such life-threatening diseases as herpes simplex encephalitis and neonatal herpes by adenine arabinoside (vidarabine, Ara A) (6-8). However, such conditions are relatively rare and treatment requires hospitalization. Furthermore, side-effects of treatment necessitate a careful dose regimen.

The first reports on the antiviral effects of acyclovir (acycloguanosine, Zovirax[®]) on herpes virus infections were greeted with considerable enthusiasm (9, 10). Not only are herpes simplex virus infections (herpes genitalis) wide-spread and painful, the drug apparently has only a few side-effects and can be administered also orally.

Today, the main indications for the use of acyclovir are herpes infections of the eye and primary herpes genitalis. The beneficial effects on recurrent herpes genitalis (or labialis) are less striking. There is no evidence of an effect of acyclovir on latent herpes. However, continuous treatment with acyclovir appears to suppress recurrences of genital herpes considerably (11, 12). The safety of long-term treatment remains to be established.

Treatment of zoster with acyclovir appears to be beneficial, particularly in immunocompromised patients (8-10). An efficacy against cytomegalovirus infections has not been demonstrated.

Acyclovir, like other anti-herpes agents, exploits the fact that in herpes virus-infected cells, viral enzymes phosphorylate the drug at a much higher rate to the active compound than in uninfected cells. Furthermore, the activated drug inhibits the viral DNA polymerase considerably more than cellular DNA polymerase. Hence the significant selectivity of acyclovir.

Due to our insight into herpes virus replication and nucleotide metabolism, acyclovir could be designed by something more than trial and error alone. This fact, the effect on a common and painful disease, the lack of serious side-effects and the possibility of oral administration are something novel in antiviral chemotherapy with rewards not only for the patient and the physician, but also for the producer. It is hoped, therefore, that this achievement will stimulate researchers and industry as well, and overcome the lethargy that often paralyzes the discouraged investigator.

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It would be naive, however, to ignore the many problems of antiviral chemotherapy to be solved. Design of new compounds requires a knowledge of viral replication mechanisms that is as yet too often scanty. Besides educated guesses, luck will still be an important factor.

The development of drug-resistant virus mutants has been described for several antiviral compounds, acyclovir included (2, 9). The importance of this problem in practical antiviral chemotherapy is presently not known. Only widespread use of these agents will uncover its true significance.

Many facets of the pathogenesis of virus diseases are as yet unknown. The implications for antiviral chemotherapy are obvious, not only for the problem of virus latency. It likewise touches the question of whether therapy via in-

hibition of virus replication is still in time with the onset of first symptoms.

With the advent of recombinant DNA technology, sufficient quantities of interferons in pure form will ultimately be available for the treatment of virus diseases. Rapid progress in this area is to be expected within the near future. The true value of interferon treatment, however, must be established (13). Furthermore, dosage problems, and optimum combinations of the various interferon types and subtypes have to be worked out, as well as possible side-effects recognized.

More than ever before, however, like in many other fields of present-day medicine, economic factors will be of utmost importance in a world of vanishing resources.

Antiviral chemotherapy is unfolding. We hope for flourishing blossoms.

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