secondary cellulitis. Involvement of nerve roots later in the disease produces an entirely different type of referred pain.

Conclusions

Pain referred from the female pelvic organs will often bear little relation to any causal lesion. Acute pain, though essential for the accurate diagnosis of ectopic pregnancy, may sometimes be due to a minor disorder of function, and cyclic menstrual pain may vary within extreme limits for little apparent reason.

Chronic and recurrent pelvic pain is extremely common and, though there is evidence to suggest this may be referred from some congestive state, its exact mechanism remains unproved. Probably the pain is caused by environmental stress, and the resulting anxiety may often be treated by nothing more than sympathetic reassurance. A hysterectomy in these patients should be delayed until the various social and emotional factors have been considered and associated conditions such as colon spasm have been excluded. Surgery should eventually be advised only when it is clear that the pain comes from the uterus, especially when there is associated menorrhagia. Many pathological reports will show unsuspected adenomyosis, and most patients, if carefully selected, will be permanently cured and extremely grateful.

Growing Points in Medicine

Success and Failure in Human Virus Diseases* III—Chemotherapy

SIR CHARLES STUART-HARRIS

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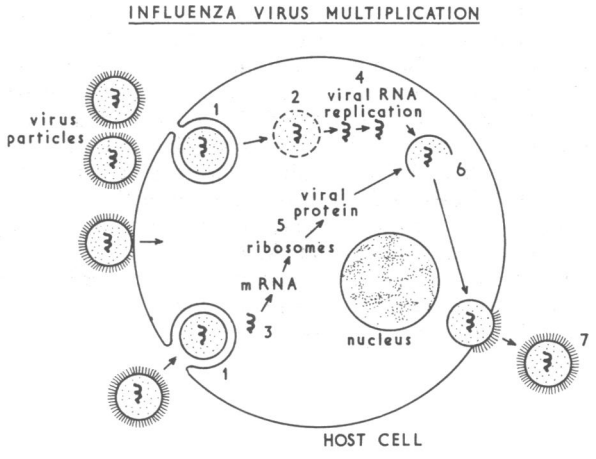
The ability to recover viruses from specimens stands in striking contrast to present-day inability to treat the patients therapeutically. There are many reasons for this failure. Viruses are intracellular parasites capable of taking over the metabolism of their host cells and are protected during their multiplication by the cell walls which surround them. They must therefore be attacked by inactivation before entry or during transport from infected to non-infected cells or prevented from penetrating the cell wall. Other modes of action are by interference at one or more of the various phases of virus multiplication, including uncoating of intracellular virus, transcription of virus nucleic acid, coding for virus protein, and release from the host cell (see Fig.). Many thought that such intracellular action would never be attained without harming the host cell, yet certain substances are now known which can bring this about safely.

That which seemed most promising of all because of its natural origin and broad antiviral spectrum—interferon—is still of great interest in the laboratory. But it has yet to be shown that it can have a practical role in therapy. The induction of interferon within the cells of the virus-infected host, though experimentally possible in animals, remains only a theoretical possibility in man, for it awaits the discovery of a safe non-toxic inducer.[1]

The list of antiviral chemical substances active in tissue cultures is now formidable. Unfortunately, most of these fail to exert a similar action in the intact animal, presumably because of failure to reach the virus-infected site before becoming metabolized. There is also the problem that virus infecting man may have passed its peak of multiplication before the patient has developed symptoms and reported to his doctor. Antiviral substances have their best chance, therefore, when used prophylactically during the incubation period. Though this is practicable in conditions such as the exanthemas which have a long period of incubation after infection, it is clearly difficult in the case of respiratory infections which have quite short periods between infection and symptoms.



Phases of influenza virus multiplication

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University of Sheffield
SIR CHARLES STUART-HARRIS, M.D., F.R.C.P., Professor of Medicine

Amantadine

Because of all these considerations the instances of antiviral activity that can be quoted will be limited to four. Firstly, amantadine (Symmetrel) seemed to have great promise soon after the empirical discovery of its inhibitory action on influenza A viruses in tissue cultures, eggs, and mice. Its potency in the laboratory is good but not prodigious, and though originally thought to prevent virus penetration it may also act at the stage of uncoating of the virus particle.[2] Amantadine has had several clinical trials, some of which, such as that carried out by Galbraith *et al.*[3] which was a rigorously controlled study, showed definite prophylactic value against influenza A2. Its subsequent failure in a similar family trial against A2/Hong Kong influenza in 1968/9[4] may indicate that it is chiefly active in the presence of a background of antibody. A trial in Finland[5] did, in fact, show significant prophylactic action against Hong Kong virus in persons with some pre-existing antibody. With regard to its suggested use in the treatment of influenza, the trial conducted by Hornick and others[6] indicated a slightly more rapid defervescence compared with the duration of untreated influenza. As amantadine is relatively non-toxic it will probably continue to be used, but it is inactive against influenza B and other respiratory viruses except for some parainfluenza virus strains.

Isoquinoline

A more logical approach to the development of anti-influenza drugs was that adopted in Pfizer's laboratories at Sandwich by Larin *et al.*,[7] who sought compounds inhibitory to the virus enzyme neuraminidase. Two such compounds—substituted isoquinolines—exhibited definite activity against influenza viruses in the laboratory and in the prevention of influenza in volunteers[8] and of natural influenza in the field.[9] Both memotine (U.K. 2371) and famotine (U.K. 2054) were thus able to limit attack by influenza virus B, and memotine is also marginally active against influenza A2.[10] Famotine also has antirhinovirus action in the laboratory, but it has none in man.[11]

IUDR

5-Iodo-2 deoxyuridine (IUDR) is a much more toxic chemical. It competes with the utilization of thymidine during the synthesis of deoxyribonucleic acid and consequently is inhibitory to mammalian cells, particularly those in the bone marrow. IUDR has been used topically in the treatment of experimental herpetic keratitis,[12] and though it has an undoubted therapeutic action in man in the same condition it fails to benefit the deep stromal reaction which appears to be important in the human disease. IUDR also has some action when given intravenously or intra-arterially to patients with herpetic encephalitis. Only a few individual patients have yet been treated,[13-16] but in this fatal condition it is worth taking a chance at success if the diagnosis is proved by the characteristic E.E.G. or by brain biopsy.

Methisazone

Finally, Marboran (methisazone; methylisatin β-thiosemicarbazone) has now had several prophylactic trials in smallpox contracts. The drug is active in mice infected with the neurovaccinial strain.[17] It is unfortunately toxic and causes nausea and vomiting, but this does not seem to have prevented its successful use in India.[18,19] It has thus reduced the attack rate after contact with virulent smallpox in unvaccinated as well as recently vaccinated subjects. The analogous thiosemicarbazone (M & B 7714) is also active experimentally in mice but has failed in similar prophylactic human trials.[20] Marboran has also been used to treat eczema vaccinatum. Individual patients with this serious and sometimes gangrenous and chronic disorder have been treated by Daly and Jackson,[21] Adels and Oppé,[22] and Van Rooyen *et al.*,[23] all of whom have reported favourable effects.

Clearly from what has been said there is no absolute bar to the development of antiviral chemotherapy. Yet it is impossible not to be disappointed with what has been achieved. It is particularly the need for activity against respiratory viruses which should spur the drug firms and research workers everywhere. Broad rather than specific antiviral activity is required, for prophylactic immunization is unlikely ever to be the answer for the common respiratory disorders.

[Part IV of this lecture will be published next week.]

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