SESSION 1

CLINICAL SPECTRUM OF HERPES SIMPLEX VIRUS INFECTIONS

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Herpes simplex virus infections

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WITHOUT writing a lengthy monograph it is impossible to cover all aspects of herpes infections in man, and I shall not attempt it. Rather, I want to make a few generalizations which may be controversial, but which touch on matters which may be relevant to the question of antiviral chemotherapy.

The herpesviruses form a large group of DNA viruses, with very similar morphological characteristics, with biochemical and serological similarities and differences. One of the most fascinating characteristics of the members of the group is that each has a natural host. Fish, birds, swine, horses and monkeys have their own herpesviruses, and man is host to at least four: herpes simplex, varicella-zoster, cytomegalovirus and Epstein-Barr virus. Some of these viruses can be transmitted to other species; herpes simplex virus (HSV) will infect a variety of other mammals such as the rabbit, guinea pig, rat and mouse. But its behaviour in these animals does not in every respect reflect what happens in man, and there are dangers in concluding that what will happen in one species will necessarily be reflected in another. B virus is probably no more harmful to the monkey than HSV is to man, and yet, if by accident it gets into man, an unnatural host, the result can be catastrophic, with a very high probability of a fatal myelo-encephalitis developing. Some herpesviruses, of which varicella-zoster virus is an example, appear to be confined to one species. So far attempts to transmit the virus to other mammals have been unsuccessful (though anecdotal accounts will have it that a chimpanzee has caught chickenpox from a child in a family where it was kept as a pet).

Normally, the herpesvirus has come to terms with its host. Herpes simplex virus invades its natural host, usually during childhood, and more often than not the event, the primary infection, is so trivial that it goes unnoticed, at least in children between the ages of 6 months and 10 years, as Knox showed so

well (Knox, 1968). The symptoms are often trivial, 'sore throat', 'teething', 'mild stomatitis', etc. and the diagnosis usually missed. After the primary infection the virus stays in the host during the life-span of the latter. As you will know it is still uncertain precisely where and in what form the virus hides, but it can be detected by the presence of antibody. Following the primary infection no more may be seen of the virus clinically. During the period April 1964-October 1968 we screened all our new clinical students at Oxford for HSV complement-fixing antibodies. Of 131 British-born students 32.8% had antibody, and of eighteen German and eight African, Indian or Chinese students 61.1 and 61.5% respectively had antibody. In both the British and German groups less than a third (27.9 and 27.3%) of those with antibody gave a history of recurrent cold sores or other manifestations of recurrent HSV infection. In the overseas group none gave a positive history. You will notice, however, that the incidence of antibody in the British-born Oxford student was very low, only half of that in the German and overseas students (all of the same age, about 24). The difference was probably accounted for because the German students had been born about the time of the end of the last war when social conditions were at a low ebb in their country. But the sheltered background of the British-bred Oxford medical student is a doubtful advantage, at least so far as the herpesviruses are concerned. They get their HSV (and incidentally varicella-zoster and EB virus) infections when they as young adults come into contact with infection in the hospital, and we see often very fierce primary attacks in them—whether as gingivostomatitis, as herpetic whitlows, or as generalized HSV infection.

What I am proposing is that we may be watching yet another example of how man has upset nature's balance by raising the general standard of living and the level of hygiene, postponing the day when the

first exposure to very common micro-organisms takes place. Yoshino *et al.* (1962) and Smith, Peutherer & MacCallum (1967) found that the level of antibody in those between the ages of 1 and 30 rose more slowly than had been the case in earlier surveys, such as that of Holzel *et al.* (1953) and Buddingh *et al.* (1953).

It is obviously not in the best interest of the virus to kill the host during the first attack. If it happened every time, the survival of the species would be threatened, and I am suggesting that severe and lethal herpes simplex virus disease is 'accidental'. Provided the primary infection takes place in the young and provided that the child has a normal defence mechanism and does not suffer from under-nourishment (Kipps *et al.*, 1967), the host is very unlikely to come to much harm and recurrent disease will only be a minor nuisance. The neonate is normally protected against Type 1 virus by passively transferred antibody from the mother, but one could foresee that as the number of women in their twenties who have been infected decreases, more neonates would be at risk, as they are to Type 2 virus infection. One cannot help speculating that infection of the CNS with HSV in man is an accidental happening; the virus has reached a site it was not intended to invade. If virus reaches the brain, it appears more likely to do so by neural routes via infection of the endoneural Schwann cells or fibroblasts and rarely via the blood stream, although the latter may happen in babies of non-immune mothers. It is remarkable that the virus apparently fails to spread to the brain from corneal lesions in man although this frequently happens in the rabbit and other animals infected on the scarified cornea. Herpes simplex virus encephalitis is a serious illness at any age, but after the immediate neonatal period it is more likely to be severe in adults than in children as herpesvirus disease in other sites. It is therefore likely that if the standard of living continues to rise and the moment of the primary infection continues to be put off we shall see more severe cases of HSV encephalitis and other severe HSV infections, not least because the majority of cases of necrotizing encephalitis appear to be primary infections.

Thus on the one hand the protection, at cellular and humoral level, acquired by the natural host through the primary infection, tends to be achieved later and later, and the first infection is likely to be increasingly severe. On the other hand, man's inter-

ference with other disease processes may disturb the acquired equilibrium. Although diseases affecting the lymphatic system in particular (such as lymphatic leukaemia, multiple myeloma, Waldenström's syndrome and Hodgkin's disease) may lead spontaneously to disturbance of immune mechanisms and cause severe local or generalized HSV or varicella-zoster disease in patients who harbour the virus, steroid and cytotoxic treatment have created additional new problems, both in these patients and in others with normal immune mechanism who are being subjected to immunosuppression, for instance because they are undergoing organ transplantation.

It might be argued that the majority of the disease manifestations caused by HSV are so trivial that they do not merit specific treatment. Genital herpes, so often due to Type 2 HSV, though usually relatively trivial, may nevertheless be important to treat. Not only does it occasionally affect the CNS in the primary attack (primarily in neonates, but sometimes also in adults), but it may be that the postulated association with cervical carcinoma will be confirmed. There can be no argument that the severe types need every help we can give them, and of all HSV lesions the necrotizing encephalitis is perhaps the nastiest. You will hear a good deal in this symposium about many aspects of the disease and about its treatment. Many of us have worked with chemotherapy of herpesvirus for a good many years. Herpesvirus infections can be unpredictable and tiresome, and in assessing the effect of chemotherapy it is vitally important not to be misled by clinical impression which too often is biased by wishful thinking. There are at present three chemicals which *in vitro* are effective against HSV: idoxuridine (IUdR, 5-iodo-2'-deoxyuridine), cytarabine (Ara-C, cytosine arabinoside), and vidarabine (Ara-A, adenine arabinoside). Among many other substances they have alone turned out to have a level of toxicity that can be tolerated in man.

Idoxuridine has been shown to be of benefit in herpetic eye lesions, in recurrent skin lesions, and in herpetic whitlows. As a single example to show that it works I will quote the case of a 46-year-old man whose primary herpetic whitlow was treated promptly with continuously applied 40% idoxuridine in DMSO. The pain went within 48 hr and the lesions healed quickly. You will see from Table 1 that he failed to produce more than minimal amounts of

TABLE 1. Complement fixing and neutralizing antibody in case of treated herpetic whitlow infected 2 February 1968—clinical signs 7 February 1968. Treatment begun 7 February 1968

	8 Feb. 68	12 Feb.	29 Feb.	11 Sept.	15 Sept.	22 May 69	3 Nov.	18 July 70	13 Jan. 71
CFT	< 1/4	< 1/2	1 : 16	< 1/4	< 1/4	< 1/4	< 1/4	< 1/4	< 1/4
NA	< 1/2	1/4	1/4	1 : 2	1 : 2	< 1/2	1:1-< 1:2	1 : 2	1 : 2

(Juel-Jensen & MacCallum 1972).

TABLE 2. Clinical and virological results in some patients with severe HSV infection treated with systemic cytarabine

Sex	Age		Site	Response		
				Clinical	Virological	
M	22	HSV (Type 1)	Primary generalized	Excellent	Good	(4)
M	28	HSV (Type 1)	Primary generalized + eczema herpeticum	Excellent	Good	(5)
M	27	HSV (Type 1)	Primary generalized	Good	Poor	(20)
M	19	HSV (Type 1)	Rec. eczema herpeticum	Excellent	Excellent	(3)
F	64	HSV (Type 1)	Rec. stomatitis	Excellent	Excellent	(3)
F	67	HSV (Type 1)	Rec. stomatitis + pneumonitis	Excellent	Excellent	(2)
M	47	HSV (Type 1)	Rec. stomatitis	Excellent	Good	(4)
M	56	HSV (Type 1)	Rec. stomatitis	Good	Good	(4)
M	27	HSV (Type 1)	Primary stomatitis + skin	Excellent	Good	(5)
M	20	HSV (Type 1)	Primary encephalitis	Excellent	Virus isolated from brain biopsy only	
F	19	HSV (Type 2)	Primary severe genital	Excellent		Good (5)
F	24	HSV (Type 2)	Primary generalized	Excellent		Poor (≥ 12)

*The figures in brackets indicate the number of days during which virus could be isolated (Juel-Jensen & MacCallum, 1972).

antibody, presumably because very little antigen was left: he is otherwise immunologically competent. Like Dr Hall, who will speak later, we have by now had extensive experience of the use of systemic cytarabine in severe HSV and zoster infections, and our results have been favourable. The drug is well tolerated. In most patients with HSV infections positive virus cultures have been obtained for a much shorter time than one would normally expect in the conditions treated, for instance in herpetic stomatitis, as Table 2 shows. We have found that cytarabine given in a patient with a normal bone marrow causes few side-effects. At ≤ 3 mg/kg/day by single daily intravenous injections there has been no significant depression of WBC, platelets or reticulocytes, and only transient macrocytosis. We have used much higher doses in three patients with HSV encephalitis where we felt that the severity of the disease justified every attempt to get a therapeutic level of drug to the virus. The patients received 10 mg/kg for 1 day, 8 mg/kg for 4 days, and 6.5 mg/kg for a further 2. They all had depression, first of reticulocytes, then of platelets and WBC, but all rebounded spontaneously in the second week after the start of treatment. Figures 1, 2 and 3 show the similarity of the response. Two of the patients recovered with minimal residual damage. In the third chemotherapy made little immediate difference; it was started late, extensive destruction of neurones had already taken place, but the patient subsequently recovered.

Our experience with vidarabine is still modest. It looks promising and may be of particular value in patients with a depressed marrow, but we are currently trying out the drug (for review of the three drugs see Juel-Jensen & MacCallum, 1972).

FIG. 1. Reticulocyte response to cytarabine.

FIG. 2. Platelet response to cytarabine.

FIG. 3. WBC response to cytarabine.

FIG. 4. Patient on admission with severe generalized herpes and eczema herpeticum.

We shall mainly be hearing about necrotizing encephalitis and I am personally greatly looking forward to the contributions from so many distinguished colleagues. We are dealing with a very nasty disorder, but one of great variability. It may kill within a few days, or may drag on for weeks. Tomlinson & MacCallum (1970) in their analysis of

108 cases cited 55% deaths, 22% survivors with considerable disabilities, and 23% who were said to have made a full recovery. We recently looked at the published reports of sixteen cases treated with idoxuridine (Juel-Jensen & MacCallum, 1972). Of these six (or 38%) died, and half of the survivors had gross residual defects, half minimal sequelae. The marginally lower mortality may be false, a selection may have taken place because the most fulminating cases died before treatment could be contemplated. I know of six well-documented cases of HSV encephalitis treated with cytarabine. Three survived with minimal defects, one with gross defects, and two died. Clearly these figures are too small to be significant.

It may be that the far more soluble cytarabine is superior to the very insoluble idoxuridine in reaching the replicating virus in the brain. We shall hear about the relative results of the two drugs in animal experiments, but ultimately we shall have to do properly controlled trials in man. No single centre will have enough cases to produce valid results and I sincerely hope the outcome of this symposium will be

FIG. 5. Patient after 4 days treatment with cytarabine.

a co-operative trial between centres in this country and centres across the waters. The data we have suggest that there are benefits, however marginal, from chemotherapy, and it is no longer ethically defensible to do nothing for those unfortunate patients. Many problems will arise: it will be necessary to alert colleagues, to make physicians aggressive diagnosticians, for unless a diagnosis is made as early as possible no amount of drug, however good, will restore dead cells to life. But it could be that we might be able to do for patients with necrotizing encephalitis what it is possible to do for those with generalized herpes. The two photographs (Figs. 4 and 5) show a 28-year-old undergraduate with severe generalized herpes and eczema herpeticum as he looked on admission and as he looked 4 days after treatment with cytarabine had been instituted when virus could no longer be isolated. If we can do as well for our patients with encephalitis much will have been gained.

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