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EDITORIAL

Viruses, brain and immunosuppression[1]

There are a number of viruses which affect the central nervous system in a variety of ways. One group, which includes rabies virus and the agents of the arthropod-borne encephalitides, causes brain disease as its primary effect. Another group, including polio virus, affects the brain secondarily to more generalized infection in certain individuals. An encephalitis may result directly from invasion of the brain by virus, but it may also occur in the absence of such invasion following infection of other organs with certain viruses (including measles, rubella, cytomegalo virus and many respiratory viruses). There is also a group of viruses, including the herpes viruses and the human papova viruses BK and JC, which establishes persistent or latent infections in the host, and it is this group of viruses that is of greatest importance with regard to the immunocompromised individual.

Obvious immunodeficiency can be induced by prematurity, inborn defects (such as severe combined immunodeficiency, thymic hypoplasia and ataxia-telangiectasia), neoplasias and malnutrition. Normal states, such as the neonatal period, pregnancy and old age, also alter the immune state of the individual (Oleske & Minnefor, 1980). There is also an increasing number of individuals who are being therapeutically immunosuppressed in the course of their treatment for leukaemia, or after receiving transplanted organs, and it is with this group that we have been most concerned.

Many viruses take advantage of a host's impaired immunity. For example, herpes viruses, vaccinia and wart viruses are commonly found in cell-mediated immunodeficient states, while picorna viruses, hepatitis 'B' and influenza viruses are more influenced by poor antibody-mediated immunity. Viral infections themselves may significantly depress the host's defence system, and concurrent viral infections have been associated with more severe or prolonged infection in such individuals. This is illustrated by the fatal dual infections with adeno virus and influenza virus that have been reported in some children (Oleske & Minnefor, 1980) and recurrent HSV1 infections with colds.

Immunosuppression not only makes the host more susceptible to viral infection but, by inhibiting the immune mechanisms of the host, creates conditions suitable for the persistence of virus in the central nervous system. Indeed, viruses that produce latent or persistent infections are the ones most frequently associated with illness in the immunocompromised patient.

The human papova viruses BK and JC, originally isolated from transplant recipients, are infrequent but important hazards in the management of the immunocompromised. BK virus establishes latent or persistent infections in the kidneys, and excretion of the virus, often accompanied by ureteric stenosis, is a frequent occurrence following renal transplantation. JC virus is believed to establish latent infections in the brain, and when reactivated in a immunocompromised host may give rise to the relentless degenerative disease progressive multifocal leukoencephalopathy. Mercifully, this disease is rare, with an incidence of only one per million of population per year. It has recently been reported in two people suffering from Acquired Immunodeficiency Syndrome (Miller *et al.* 1982; Bedri *et al.* 1983).

Members of the herpes virus group are those most frequently diagnosed as causing serious disease in the immunocompromised individual, and include cytomegalo virus, varicella-zoster virus, herpes simplex virus (HSV) types 1 and 2, and Epstein–Barr virus. However, with regard to central nervous system involvement, HSV1 is of most interest.

The idea that recurrent herpetic disease involves reactivation of latent infection in the sensory ganglia is not new; indeed, such a model was proposed by Goodpasture in 1929. There have since been many demonstrations, using the methods of co-cultivation and explantation, that HSV can be harboured in the sensory and autonomic ganglia of man (Warren *et al.* 1977, 1978; Baringer,

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1974) and of other animals (Knotts *et al.* 1973; Puga *et al.* 1978; Tenser *et al.* 1982). Similar techniques applied to central nervous system tissue have shown the incidence of latent infection following experimental infection in animals to be much lower than in the peripheral nervous system (Plummer *et al.* 1970; Knotts *et al.* 1973; Cook & Stevens, 1976; Cabrera *et al.* 1980; Tenser & Hsiung, 1977). However, DNA–DNA hybridization studies in this laboratory showed that HSV1 DNA sequences were detectable in the brain tissue of patients with chronic (but not acute) psychiatric disease, and also in mice six months after infection with HSV1 (Sequiera *et al.* 1979). Other workers have since confirmed the presence of HSV1 DNA sequences in the brains of humans (Fraser *et al.* 1981) and of mice after experimental infection (Cabrera *et al.* 1980; Rock & Fraser, 1983).

Experimental immunosuppression in mice, after infection with HSV1, results in reactivation of the virus (Openshaw *et al.* 1979), and Kastrukoff *et al.* (1981) found that such reactivation in the brain was accompanied by transient neurological signs. In man, such effects cannot be investigated experimentally, but brain tissue from patients with illnesses such as acute leukaemia, where the disease itself and its cytotoxic treatment involve immunosuppression, can be studied. To this end, we examined specimens of post-mortem brain tissue from such patients using *in situ* hybridization (Saldanha *et al.* 1986). In patients in whom reactivation of HSV1 infection occurred in life, and in whom there was serological evidence of past HSV1 infection, HSV1 DNA sequences were detected in temporal lobe tissue. Such sequences were not found in patients without antibodies to HSV1. In two patients, the presence of HSV1 sequences was not confined to neuronal cells, but included adjacent endothelial cells. Since latent infections are established in neurones following intra-axonal spread from the site of primary infection (Hill *et al.* 1983), this suggests that, during a productive infection, virus had spread from neuronal cells to endothelial cells.

Although none of the immunosuppressed patients in our study had suffered any neuropsychiatric illness, it seems likely that, at least in some circumstances, low level HSV1 infection of the CNS due to immunosuppression could result in neurological or psychological disease. We have examined brain tissue DNA from elderly subjects suffering from a range of such diseases, including Alzheimer's disease, schizophrenia and depression. Half of the samples from Alzheimer's brains proved to be positive for HSV1 when tested with an HSV1 DNA probe by dot–blot hybridization, compared with a third, or less, of samples from schizophrenics, depressives and age-matched controls (Gannicliffe, 1985). It should perhaps be mentioned that Taylor *et al.* (1984) failed to detect HSV DNA by dot–blot hybridization in brain tissue from 8 cases of Alzheimer's disease and from 9 controls.

It is possible that those elderly control subjects in whose brain tissue we detected HSV1 DNA had previously harboured the virus and that immunosuppression due to their advanced age led to reactivation and sufficient replication for it to be detectable by the technique used, but not for any deleterious effect to be manifest. In contrast, those elderly people who developed Alzheimer's disease may be those in whom reactivation of HSV1 in brain may have combined with a genetic predisposition to the type of damage that could result from such a reactivation. Alternatively, they may have suffered more frequent episodes of reactivation as a response to stress, or the site of latent infection may have been in a more sensitive region.

Drawing the strands together, we believe that the results from our experiments may represent points on a continuum. Immunosuppression, either naturally or therapeutically induced, may allow localized reactivation of HSV1 already latent in the brain. In most cases this reactivation would be very limited, perhaps affecting only the cell harbouring the latent genome. However, in certain cases, such as those elderly people who may be immunodeficient, a more productive or widespread infection could occur and, if there were a genetic predisposition to specific brain damage, neuropsychiatric disease may result. This could be due to the death of 'key' cells and the subsequent atrophy of synaptic connections with other cells, or from disturbance of neurotransmitter function following blockage of neurotransmitter receptor sites by virions (see Shaskan *et al.* 1984, for review).

Our results, especially those concerned with Alzheimer's disease, are preliminary and much work

remains to be done. However, we believe that further investigations are warranted into the possible link between viruses and neuropsychiatric disorder.

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