Comment

The ability of this patient's serum to bind complement to red cells at physiological temperatures is consistent with the clinical picture of severe haemolysis. Although agglutination was not demonstrable above 32°C IgM molecules were presumably bound in sufficient numbers to initiate efficient complement activation even at 37°C. The results of the absorption experiment clearly show independent specificities for the cold agglutinin and the mycoplasma antibody, and are therefore at variance with the suggestion that these cold agglutinins are cross-reacting mycoplasma antibodies.[2 3]

We thank Dr Hillas Smith for permission to report on one of his patients.

[1] Dacie JV. *The haemolytic anaemias. Part II. The autoimmune anaemias.* 2nd ed. London: Churchill, 1962.
[2] Janney FA, Lee LT, Howe C. Cold haemagglutinin cross-reactivity with Mycoplasma pneumoniae. *Infect Immun* 1978;**22**:29-33.
[3] Deas JE, Janney FA, Lee LT, Howe C. Immune electron microscopy of cross-reactions between Mycoplasma pneumoniae and human erythrocytes. *Infect Immun* 1979;**24**:211-7.
[4] Harboe M. Cold auto-agglutinins. *Vox Sang* 1971;**20**:289-305.

(*Accepted 24 September 1980*)

Haematology Division and Lister Unit, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex HA1 3UJ
G N SMITH, MB, MRCPATH, consultant haematologist
W R C WEIR, MB, MRCP, senior registrar

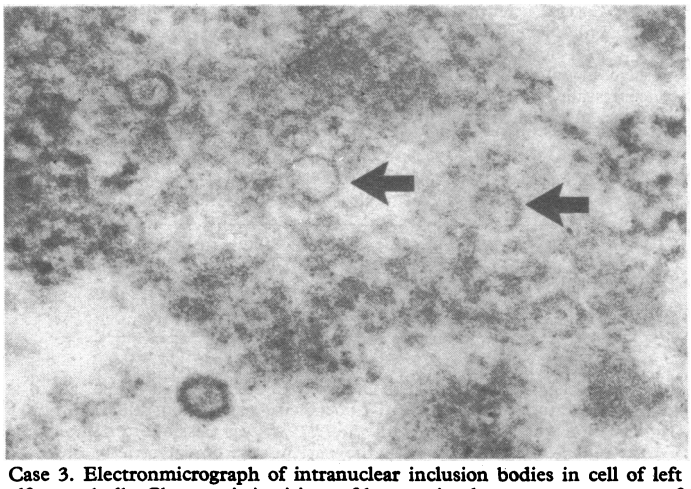
Transolfactory spread of virus in herpes simplex encephalitis

Unlike most encephalitides, acute necrotising encephalitis caused by *Herpesvirus hominis* type I exhibits several unique features, including a tendency to affect the limbic system, often asymmetrically and resulting in maximal damage to one or other temporal lobe. In a recent case[1] herpesvirus was especially prevalent throughout the limbic system and in the necrotic olfactory bulbs, suggesting that transolfactory spread of virus may be important in pathogenesis. The next three cases were therefore similarly investigated.

Case reports

Case 1—A 78-year-old man was admitted in coma after three days of rapidly progressive confusion and drowsiness. Examination showed neck stiffness, fever, and hypertension. The cerebrospinal fluid contained 25×10^9 red cells/l (25 000/mm^3) and 82×10^6 white cells/l (82/mm^3) (48% lymphocytes); normal glucose and protein concentrations; and negative Gram and Ziehl-Neelsen. He developed prolonged seizures, deteriorated, and died after five days.

Case 2—A 66-year-old woman was admitted in coma after three weeks of gradually progressive dementia, right-sided weakness, and convulsions.



Case 3. Electronmicrograph of intranuclear inclusion bodies in cell of left olfactory bulb. Characteristic virions of herpes simplex are present, some of which (arrowed) show unusual swelling, loss of nucleic acid core, and partial fragmentation of thin nucleocapsids, presumably resulting from adenine arabinoside. ×26 000 (original magnification).

Neck stiffness, right hemiplegia, and fever were present. CT brain scan was normal, and bilateral carotid angiograms showed brain swelling. Cerebrospinal fluid contained 40×10^6 white cells/l (80% lymphocytes) and 2·8 g protein/l; Gram and Ziehl-Neelsen stains, culture, and complement fixation tests for herpes, mumps, and measles viruses gave negative results. She died four days after admission.

Case 3—A 2½-year-old girl was admitted after a "febrile convulsion." She presented with pharyngitis, otitis media, fever, and a 12-hour history of left-sided facial twitching. The electroencephalogram and CT brain scan suggested encephalitis. Cerebrospinal fluid was normal. Viral studies, which included complement fixation tests on serum and cerebrospinal fluid, and culture of cerebrospinal fluid, throat, and rectal swabs gave negative results. Adenine arabinoside was started on the third day but she continued to deteriorate and died on the seventh day.

In each of these cases the brain showed all the features characteristic of acute necrotising encephalitis, including unilateral swelling and necrosis of the temporal lobe, panencephalitis without inclusion bodies, and abundant herpes simplex virus on electron microscopy. Herpes simplex virus was especially prevalent in the left and right temporal lobes and throughout the limbic system in cases 1 and 2, but in case 3 the virus was more evenly distributed throughout both hemispheres. Interestingly herpes simplex virus was found in the necrotic olfactory bulbs (figure). Necrotic cells containing herpes simplex virus were found in both right and left bulbs in each case and were associated with pronounced degeneration of myelinated fibres and prominent astrocytosis and gliosis in the olfactory tracts.

Comment

The route by which herpes simplex virus enters the brain in acute necrotising encephalitis is unknown. Haematogenous spread is the usual explanation, though in most cases no primary focus is found outside the nervous system. After the isolation of latent herpes simplex virus in various sensory ganglions,[2 3] a theory was formulated whereby virus supposedly reaches the floor of the cranial fossae via tentorial branches from the trigeminal ganglia.[4] My findings, however, would implicate a more direct route. The presence of herpes simplex virus in the necrotic olfactory bulbs, the degeneration in the olfactory tracts, and the distribution of the virus within the rhinencephalic areas suggest that the olfactory apparatus is the principal pathway in the pathogenesis of acute necrotising encephalitis in man.

[1] Dinn JJ. Distribution of herpes simplex virus in acute necrotising encephalitis. *J Pathol* 1979;**129**:135-8.
[2] Warren KG, Brown MS, Wroblewska Z, Gilden D, Koprowski H, Subak-Sharpe J. Isolation of latent herpes simplex virus from the superior cervical and vagus ganglions of human beings. *N Engl J Med* 1978; **298**:1068-9.
[3] Warren KG, Gilden DH, Brown SM, *et al.* Isolation of herpes simplex virus from human trigeminal ganglia, including ganglia from one patient with multiple sclerosis. *Lancet* 1977;ii:637-9.
[4] Davis LE, Johnson RT. An explanation for the localization of herpes simplex encephalitis? *Ann Neurol* 1979;v:2-5.

(*Accepted 19 September 1980*)

Department of Neuropathology, Central Pathology Laboratory, St James's Hospital, Dublin 8
JOHN J DINN, MD, PHD, consultant neuropathologist

Acute haemolysis and renal failure after nomifensine overdosage

Nomifensine is an antidepressant unrelated to the tricyclic or tetracyclic drugs. No serious toxicity has been reported after overdosage,[1-3] but we report a case of acute haemolysis and renal failure requiring haemodialysis in a patient with nomifensine poisoning.

Case report

The patient, a previously well 25-year-old woman was admitted two hours after allegedly taking nomifensine 2 g (80 capsules), nitrazepam 100 mg, and chlordiazepoxide 300 mg. She had been prescribed nomifensine six months before and had taken it regularly for three months and then intermittently. On admission she was unconscious although responding to stimulation, her blood pressure was 110/70 mm Hg, and her pulse was regular at 120/min. She regained consciousness after six hours but remained drowsy. Two days later she complained of bilateral loin pain and was noted to be pale and oliguric. Her plasma and urine were the colour of creosote and there was evidence of acute intravascular haemolysis. Her plasma haemoglobin concentration