Hypothesis:

"Limbic Predilection in Alzheimer Dementia: Is Reactivated Herpesvirus Involved?"

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SUMMARY: *In the brains of patients with senile dementia of the Alzheimer type (SDAT), the quantitatively pathognomonic neuronal lesions (tangles, plaques, granulovacuolar degeneration, Hirano bodies, and nerve cell loss) are predisposed to occur especially within the limbic system. Anatomical and physiological studies indicate that fibres from the trigeminal ganglia innervate meninges and vessels within the middle and anterior cranial fossae, especially in the same subfrontal and mesial temporal regions preferentially afflicted in acute herpes encephalitis. These limbic regions are critical for normal memory processing and recall. Explantation and cocultivation techniques have recently demonstrated Herpes simplex virus in many human trigeminal ganglia, which also reveal a life-long lymphocytic infiltration in the absence of any pathological changes in the sensory neurones. These lymphocytes may represent a histological marker of latent herpes virus, which when reactivating is well-established as the ganglionic source of recurrent herpes labialis. It is suggested that reactivation of the same dormant viral material travelling centripetally instead might be the cause of the "degenerative" lesions typical both of Alzheimer's Disease and of the normal aged human brain.*

RÉSUMÉ: *Dans le cerveau des patients atteints de démence sénile du type Alzheimer, les lésions charactéristiques des neurons se trouvent principallement dans le système limbique. Des études anatomiques et physiologiques montrent que les fibres du ganglion trigéminal innervent les méninges et vaisseaux dans les fossés crâniens médians et antérieurs, surtout dans les mêmes régions sous-frontales et médio-temporales atteint préférentiellement d'encéphalite herpes aigu. Ces régions limbiques sont essentielles pour le procès normal de la mémoire. Les techniques d'explant et de culture conjointes ont récemment démontré que le virus d'Herpes simplex se trouve dans plusieurs ganglions trigéminaux humains. Ces derniers montrent aussi une infiltration chronique des lymphocytes en l'absence de changements pathologiques. Ces lymphocytes peuvent représenter un signe histologique du virus herpes latent qui est la source d'herpes labialis répétitive. On suggère que la réactivation du même virus latent voyageant dans la direction centrale peut être la cause des lésions "dégénérées" qui sont typiques et de la maladie Alzheimer et du cerveau des gens âgés normaux.*

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INTRODUCTION

The particular affliction of the grey matter of the limbic system by the "degenerative" lesions of senile dementia Alzheimer type (SDAT) has been well-documented. Reviewing the early literature on senile (neuritic) plaques, neurofibrillary tangles, granulovacuolar degenerative, and neuronal loss, Corsellis (1970) concluded that the amygdaloid nucleus, uncus and hippocampal region are "particularly liable to degenerate" in Alzheimer's Disease. A semiquantitative study in patients with Alzheimer's Disease surveyed frontal, temporal and cingulate cortex; hippocampus and entorhinal cortex; amygdala; septal nuclei; mamillary bodies; and fornices (Hooper and Vogel, 1976). Compared to two mentally normal aged controls, the 9 demented patients' brains showed a constant and very severe involvement of the limbic structures, especially hippocampus and amygdala. Hooper and Vogel (1976) consequently suggested that this pattern of predilection might justify the special term, 'limbic dementia'.

A computer-assisted image analysis to quantify neuronal populations in Alzheimer's Disease has found no more depletion of most size-classes of nerve cells in the neocortical areas sampled than occurs with normal ageing (Terry et al., 1977; Terry, 1979). However, our own morphometric investigation of the hippocampal population with a semi-automated sampling-stage microscope has shown that the neuronal fall-out accompanying senile dementia Alzheimer type is five times worse than in normal ageing (Ball, 1977). Another reason for believing the limbic system is of paramount importance is because the pyramidal layer of the mesial temporal lobe is the only

region of cerebral cortex wherein all five characteristic lesions may be observed together (tangles, plaques, granulovacuoles, Hirano bodies and nerve cell loss). Moreover, Tomlinson (1970) has suggested that by the tenth decade of life, all people will show at least some neurofibrillary tangle formation in their hippocampi, though this has not been noted in other regions.

Anatomical Considerations

Anatomical studies in both primates and man have indicated that meninges in the middle and anterior cranial fossae are supplied by fibres derived from the trigeminal nerve (Davis and Johnson, 1979). Centripetal branches, including the nervus tentorii from the ophthalmic division, the nervus meningeus medius and nervus spinosus from maxillary and mandibular divisions form perivascular plexuses around meningeal vessels and possibly contribute to the pial nerve twigs (McNaughton, 1937; Penfield and McNaughton, 1940). Experimental studies of the proximal middle cerebral and of the anterior cerebral artery during investigation of pain-sensitive intracranial structures (Ray and Wolff, 1940), as well as clinical trials using anesthetic injections into the Gasserian ganglion for relief of intracranial pain (Feindel et al., 1960) have added weight to such evidence that fibers from the trigeminal ganglion do innervate structures in the middle and anterior fossae, concentrated in those basal areas corresponding to the anatomical predilections of (acute) herpetic encephalitis, which characteristically is localized to the subfrontal and mesial temporal regions (Baringer, 1978).

At the same time, clinical observations have suggested that bilateral limbic lesions, especially of the hippocampi, may cause severe memory deficits (Glees and Griffith, 1952; Penfield and Mathieson, 1974; Scoville and Milner, 1957; Victor, 1969; Victor et al., 1961), in agreement with numerous physiological experiments reporting the behavioural role of the hippocampus and related limbic regions, particularly for learning and memory processing (Greene and Stauff, 1974; Mishkin, 1978). While precisely which portion of the limbic system subserves memory may still be debated (Horel, 1978), there can be little doubt from both anatomical and clinicopathological reports that the hippocampal formation and its very extensive limbic connections are critical for higher cognitive function, especially memory recall (Meissner, 1967; Raisman et al., 1965; Raisman et al., 1966; Swanson, 1979; Van Buren and Borke, 1972). Significant impairment of this function is an essential criterion for the diagnosis of Alzheimer's Disease.

Virological Considerations

Studies of the clinical phenomenon of herpetic skin eruptions repeatedly occurring in the distribution of the same sensory branch of the trigeminal nerve provide an emerging body of evidence that the ganglion serves as the site for latent herpes simplex virus (HSV), and as a reservoir for the recurrent infections (Baringer, 1978; Stevens, 1975). By in vitro cultivation of human Gasserian ganglia, Baringer showed it is possible to recover herpes simplex from a high proportion of ganglia obtained at necropsy from unselected cadavers (Baringer and Swoveland, 1973), though not from the trigeminal nerve or root of the same patients. Warren et al. (1978) isolated HSV type 1 in explanted and cocultivated trigeminal ganglia, and found it in 22 of 44 American and 7 of 29 Japanese cadavers, as well as in 3 of 15 superior cervical and one vagus ganglion (Warren et al., 1978). These investigators noted an extensive lymphocytic infiltration of the trigeminal ganglia in 8 of the 10 American cases examined for this mononuclear cell presence; a similar incidence of lymphocytes has been seen in Japanese cadavers. No neuronal inclusion bodies were found, however, and electron microscopy has failed to detect virus particles. One intriguing possibility is that the lymphocytes, rather than the ganglionic nerve cells themselves, harbour the virus during long incubation periods. Studies from Bloom's laboratory have confirmed that resting lymphocytes are essentially nonpermissive for a variety of lytic RNA viruses, but rapidly acquire the capability of replicating these viruses after appropriate antigenic or mitogenic activation (Bloom et al., 1978). Epstein-Barr, a DNA virus, is already believed to be harboured by infected B lymphocytes (Pattengale et al., 1974). If the same were true for other DNA viruses, latent herpes material might well be present in trigeminal ganglionic lymphocytes. Some lymphocytes are extremely long-lived cells; nonreplicating human lymphocytes marked via radiation-induced chromosome aberrations have been reported to persist for more than 20 years without division (Buckton et al., 1967). Examination of 64 pairs of trigeminal ganglia from autopsied patients aged 2 months to 81 years has recently revealed that the chronic inflammatory infiltrate, which is chiefly lymphocytic, is present virtually from the 1st year of life, and is pronounced and apparently ubiquitous in North American cadavers (Ball et al., 1982). Acquired ability for virus dormant in such lymphocytes to replicate would explain the not uncommon onset or worsening of senile dementia which shortly follows some specific clinical event potentially causing antigenic activation and/or immune dysfunction (e.g., after trauma, hypotension, anesthesia). Lymphocytes have not been described in non-human ganglia (Ball et al., 1982), and it is interesting that tangles and plaques are exceedingly rare except in human brain.

Latency involves 3 separate though related processes - establishment, maintenance, and reactivation. Eight weeks after corneal inoculation of herpes simplex virus into mice, during the latent phase, Cabrera et al. (1980) found that HSV could be reactivated by explantation and cocultivation from 95% of the trigeminal ganglia but from only 5% of the brain tissue explants; yet using DNA reassociation techniques, herpes simplex DNA sequences were detectable in 30% of the brains of mice harbouring the latent virus in their ganglia. Virus might not be eliminated from brain tissue, but maintained in a state which cannot be reactivated by certain explanation techniques (Marsden, 1980). Such differences in methodology perhaps account for the apparent failure by Middleton et al. (1980), utilizing nucleic acid hybridization, to

show significantly increased herpes DNA genome equivalent in brains of 3 demented patients with apparent Alzheimer's Disease. In their solution hybridization technique, extraction of huge amounts of human cellular DNA may have severely diluted any viral DNA present, obscuring detection of the latter.

That reactivated Herpes can travel centrifugally down the trigeminal branches to a site of "cold sore" is indisputable. Could the same virus ascend centripetally into the CNS? It has been postulated HSV could travel from superior cervical ganglion along postganglionic fibres to the cerebral hemispheres to result in acute herpes simplex encephalitis (Warren et al., 1978). If there were partial organ resistance to such virus, however, could the resulting lesions be "degenerative" rather than necrotic? Insidious "degenerative" CNS lesions are the histological hallmark of subacute sclerosing panencephalitis (SSPE), in which a variant of measles virus, now believed to be the causative agent, has been isolated from lymphoid tissue (Horta-Barbosa et al., 1971) as well as from brain (Horta-Barbosa et al., 1969). Tangles and granulovacuoles have, in fact, been reported in SSPE (Mandybur et al., 1977).

Clinicopathological Considerations

Intraneuronal neurofibrillary tangles identical to those of SDAT are pathognomonic in the substantia nigra of post-encephalitic Parkinsonism, a "degenerative" process occurring many years after an apparent viral encephalitis (Hirano, 1970). Neuritic (senile) plaques are said to have been induced by inoculating mouse brain with the scrapie virus agent (Wiesnewski et al., 1975). If Alzheimer's Disease were to represent the chronic form of an herpetic CNS infection, and necrotizing encephalitis the acute form, it is reasonable to expect an intermediate type of affliction to occur in some brains. Such a subacute encephalitis has, in fact, been well-described in which the grey matter of the limbic system bears the brunt of the inflammatory process, with no necrosis or hemorrhage and a clinical course lasting several months (Brierley et al., 1960). Its topography and histopathology are highly suggestive of herpes virus causation.

The amyloid which is deposited both in the cores of senile plaques and in some intraparenchymal vessel walls in SDAT, and which may be derived from amyloid B, said to be a complex of light chains of immunoglobulins (Glenner et al., 1973), might indicate virally induced immunological dysfunction. Immunoglobulins have been identified in plaque amyloid (Ishii and Haga, 1976). It has even been suggested that the correlation claimed between increasing impairment of cognitive function and progressive decrease in serum IgG attests to the role of aberrant immune function in Alzheimer's Disease (Eisdorfer and Cohen, 1980). Immune dysfunction, which has been well-established in Down's syndrome, could also be postulated as operating in the CNS of mongols, in whom the neuropathological lesions of SDAT are virtually inevitable past the third decade of life (Whalley and Buckton, 1979).

Senile dementia Alzheimer type is an extremely common disorder, probably afflicting between 5% and 10% of all senior citizens (Wang, 1977). Rather than persisting in the so far futile efforts to demonstrate the presence of some extremely rare kuru-like or Creutzfeldt-Jakob type agent in brain tissue from SDAT (Gibbs and Gajdusek, 1978), perhaps we should be turning much more attention to the very common Herpes simplex virus. If not reactivated after years of dormancy in the Gasserian ganglion to cause incapacitating Alzheimer type dementia, this agent might nevertheless be venturing forth in subclinical strength to evoke identical neuronal lesions typical of normal ageing, which, in the human brain, apparently differs only quantitatively, but not in its limbic topography, from senile dementia (Ball, 1978).

The above hypothesis would also explain the recent suggestion of Whitehouse et al. (1982) that selective degeneration of nerve cells in the nucleus basalis of Meynert within the basal forebrain underlies the cholinergic deficiency of neocortex in Alzheimer's disease. This nucleus, situated just inferior to the pallidum, lies within a few millimeters of the trigeminal ganglion, and the meninges of the anterior perforated region are heavily traversed by striate branches of the internal carotid-middle cerebral artery supplying the substantia innominata of which this nucleus is a part. Moreover, herpes simplex virus passing intra-axonally within the trigeminal system can be propagated across synaptic junctions even to a third order of neurons (Kristensson et al., 1982).

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