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EDITORIAL

Scrapie and Alzheimer's disease[1]

Alzheimer's disease (AD) is the most common form of dementing illness in both the presenile and senile age-groups (Marsden & Harrison, 1972; Tomlinson *et al.* 1970). Predominantly a disease of old age, it manifests itself as a slowly progressive mental deterioration over a period of several years, leading eventually to profound dementia. As the proportion of the population in the older age-group increases, it becomes more important to understand the underlying causes of this distressing disease (Roth, 1982). This priority has recently led to an expansion of research on AD and related topics but one of the limitations in these studies has been the lack of satisfactory experimental models. There are no direct analogues of AD in laboratory animals, although senile plaques, a characteristic neuropathological change in AD, are seen in small numbers in very old animals of a few mammalian species (Wisniewski & Terry, 1973).

In recent years a number of parallels have been recognized between AD and scrapie, an infectious neurological disease of sheep and goats (Dickinson *et al.* 1979; Bruce & Dickinson, 1982). Like AD, scrapie follows a slowly progressive and unremitting course. Pathological changes in each disease are confined to the central nervous system and are degenerative, with little or no evidence of inflammatory reaction (for reviews of the pathology of AD and scrapie, see Corsellis (1976) and Fraser (1976) respectively). Most important, using certain scrapie models it is possible to reproduce some of the characteristic pathological features of AD, particularly the occurrence of amyloid-containing plaques and a selective loss of neurons in the hippocampus.

Scrapie is the best understood representative of a group of diseases which also includes Creutzfeldt–Jakob disease and kuru in man and transmissible mink encephalopathy (Marsh, 1976). These diseases are caused by similar replicating agents of an, as yet, unknown molecular nature. Although their unusual physico-chemical properties set them apart from conventional viruses (Millson *et al.* 1976), they can be regarded as small virus-like organisms in that they replicate and carry information. Scrapie has been transmitted to a range of laboratory animals by injection of infected tissue (usually brain) and has been studied most extensively in mice and hamsters.

Serial passage in mice of isolates from diverse natural sheep sources has so far led to the identification of 15 different strains of scrapie, distinguished from each other primarily on the basis of the highly repeatable incubation periods produced in particular mouse genotypes (Dickinson & Fraser, 1977); incubation periods in the various mouse models range from 140 days up to the animal's lifespan. A range of changes is seen in the brains of scrapie mice, the relative extent and distribution of which depend mainly on the scrapie strain, mouse strain and route of infection; in other words, there are many murine scrapie models, each with its own characteristic pattern of pathological change (Fraser, 1976). The most typical lesion is a spongy vacuolar degeneration which is targeted to different areas of brain in different models.

With certain combinations of scrapie strain and mouse strain a prominent feature is the occurrence of many small amyloid foci or plaques (Bruce & Fraser, 1975). These are analogous in structure to senile or neuritic plaques, a major diagnostic feature of AD (Terry & Wisniewski, 1970), consisting of a core of extracellular fibrils of amyloid protein surrounded by degenerating neuronal processes and microglial cells. Infection with scrapie is the only known experimental method for producing this type of lesion, although small numbers of senile plaques are associated with 'normal' ageing in a number of species, including humans (Tomlinson, 1979) but not mice (Dayan, 1971; Bruce & Fraser, 1982).On the other hand,neurofibrillary degeneration, the other characteristic feature of AD

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pathology (Kidd, 1964), has not been identified in any of the scrapie models. This lesion, in which tangles of 'paired helical filaments' accumulate and eventually replace neuronal cell bodies, is also seen in a number of other human neurological diseases (Iqbal *et al.* 1977) and in most non-demented old people (Tomlinson, 1979). However, as paired helical filaments have not been identified in any non-human species, their absence in scrapie-infected mice is perhaps not surprising.

The occurrence of amyloid plaques in various scrapie strain/mouse strain combinations ranges from a high frequency in some to a complete absence in others (Bruce *et al.* 1976). In general, plaques tend to be more abundant in combinations with comparatively long incubation periods (over 300 days for the best plaque models). The great advantage of these models is that lesion development can be traced from a known starting point, the date of injection, to the precisely known clinical scrapie end-point. Although small numbers of plaques may be seen comparatively soon after injection, plaque production is much more active towards the end of the incubation period (Bruce, 1981).

One of the aims of studies on amyloid plaques is to identify treatments which will prevent or reverse plaque formation. Such treatments might suggest possible therapeutic approaches to AD, in which a correlation has been reported between the degree of dementia and senile plaque counts (Blessed *et al.* 1968). It is known that some experimental variables introduced at the time of initial infection, such as route of inoculation and dilution of inoculum, greatly influence the eventual frequency of plaques and their distribution in the brain (Bruce & Fraser, 1981). However, these variables also exert a considerable influence on the dynamics of agent replication during scrapie pathogenesis; treatments which modify plaque production independently of these effects have yet to be identified.

Plaques in scrapie are frequently seen in the white matter, suggesting that nerve terminals are not necessarily involved in plaque formation and therefore that amyloid deposition is the primary event (Bruce & Fraser, 1981). Amyloid is defined on the basis of its fibrillar structure and staining properties, characteristics which are known to be displayed by a range of otherwise unrelated proteins which accumulate in peripheral organs in a number of pathological conditions (Glenner, 1980). Amyloid cores from senile plaques have already been partially characterized by amino acid analysis and were found to differ from previously analysed amyloids (Allsop *et al.* 1983). A major objective is therefore to identify the chemical nature and origin of the amyloid in scrapie and to establish its relationship with the various other types of amyloid.

In AD a diffuse loss of neurons has been recognized in the cerebral cortex (Terry *et al.* 1981). Although such widespread neuronal loss is not obvious in mouse scrapie, some cases show a profound, sometimes almost total loss of pyramidal neurons in the hippocampus, accompanied by an intense glial reaction (Fraser, 1976). A similar type of hippocampal pathology is seen in many patients with AD (Corsellis, 1970). In scrapie this hippocampal sclerosis is particularly common with certain combinations of scrapie strain and mouse genotype, although there is often great variation in its severity between the individual mice of an experimental group (Scott & Fraser in preparation). These models tend to be ones in which vacuolar degeneration develops in the hippocampus at a relatively early stage in the incubation period, neuronal loss only becoming apparent some time later. In other models a severe gliosis, probably associated with neuron loss, is seen in the ventral nucleus of the thalamus, also apparently following on from an earlier vacuolar lesion (Fraser, 1976). Because severe vacuolation is often seen in other areas of brain without obvious neuron loss or gliosis, it seems likely that neuronal death occurs only when vacuolar lesions are targeted to particularly vulnerable nuclei. It may be relevant that hippocampal pyramidal neurons and neurons of the ventral nucleus of the thalamus are highly vulnerable to a range of insults, for example, hypoxia (Brierley, 1976). It is not clear how these results relate to AD, in which vacuolar degeneration is not a prominent feature.

It is well established that, in AD, there is a severe deficit in the activities of choline acetyl transferase (CAT) and acetylcholinesterase, enzymes involved in the cholinergic neurotransmitter system (Davies & Moloney, 1976; Bowen *et al.* 1976). This reduction is particularly severe in the cerebral cortex, amygdala and hippocampus, areas in which senile plaques and neurofibrillary tangles are also frequent. There is some evidence that the cholinergic deficit results from a selective

loss of neurons in one of the subcortical nuclei of the forebrain, the nucleus basalis of Meynert, which provides most of the cholinergic innervation of the neocortex (Whitehouse *et al.* 1982). A reduction in CAT levels has also been found in a number of murine scrapie models, including some which do not produce plaques (McDermott *et al.* 1978), but it has not been established whether this is a selective cholinergic lesion, or whether there is any loss of neurons from the nucleus basalis in these models.

The parallels that have been recognized between AD and scrapie obviously raise the possibility that an unconventional infectious agent might be involved in AD. However, attempts to transmit AD to laboratory animals have either failed or have been inconclusive (Goudsmit *et al.* 1980), whereas Creutzfeldt–Jakob disease (CJD), a known analogue of scrapie in man, has been experimentally transmitted on numerous occasions (Gibbs & Gajdusek, 1978). AD and CJD are usually distinguishable on clinical and neuropathological criteria, but there remain some cases which show characteristics of both. Spongy vacuolar degeneration, of the type seen in most, but not all, cases of CJD and scrapie, is not a feature of AD. Furthermore, the most consistent finding among scrapie and related diseases is the presence of characteristic filaments (scrapie-associated filaments or SAFs) in brain extracts (Merz *et al.* 1981); such filaments have not been found in extracts of Alzheimer brain (P.A. Merz & R. A. Somerville, personal communication). On balance, therefore, it seems unlikely that AD is caused by a scrapie-like agent. The similarities between the various scrapie models and AD might simply reflect the fact that both involve a slow progressive degeneration of the CNS. Even if AD does not have an infectious aetiology, scrapie still provides valuable models for this type of degenerative pathology.

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