Neuropathology of Dementias

Introduction
Dementia is a problem worldwide, not only for patients but also for carers; it affects some 5% of the elderly population over the age of 65 years and the incidence increases with age. Clinically, dementia is defined as a syndrome of progressive cognitive decline to a degree that interferes with work, personal relationships and social functioning in the absence of delirium or major psychiatric disorder. Impairment of memory, language, perception, problem solving ability and personality are all features of dementia. There are different clinical syndromes of dementia that correlate with the pathological features in the brain, although there is often some overlap between syndromes and with normal ageing. In this account, we outline the general pathology of dementias and then concentrate on Alzheimer’s disease to review the pathology, some of its possible causes and how immunotherapy is developing as a new treatment for Alzheimer’s disease.

General pathology of dementias
The pathological features of dementias are diffuse and affect multiple areas of the brain, thus cerebral atrophy may be the only change seen macroscopically in the post mortem brain and on MRI. A common feature seen microscopically is the accumulation of insoluble proteins and peptides, firstly in the extracellular spaces and in blood vessel walls and secondly within cells. The presence of vascular lesions, infarcts due to cerebrovascular disease, is a further remarkably common finding. These features are summarised in the table.

Extracellular proteins accumulate in the cerebral cortex and other areas of grey matter, as plaques and in artery and capillary walls as Cerebral Amyloid Angiopathy (CAA). Chief among these proteins is Amyloid-β (Aβ) in Alzheimer’s disease. Aβ is formed in the brain throughout life by cleavage of a 700 amino acid transmembrane amyloid precursor protein (APP) encoded by a gene on chromosome 21. APP is cleaved by a series of secretases, resulting mainly in the production of a 42 amino acid Aβ (Aβ 1-42) and a more soluble Aβ 1-40. In Alzheimer’s disease insoluble Aβ 1-42 is predominantly found in plaques in the cerebral cortex (Figure 1a) and Aβ 1-40 within blood vessel walls (CAA). Aβ and other proteins, such as Cystatin and AβRI (in the British type of dementia), accumulate in the brain and in blood vessel walls as CAA in a range of familial dementias that are associated with genetic mutations. In Creutzfeld-Jacob disease, insoluble deposits of protease resistance prion protein (PrP) (Figure 1b) accumulate in cerebral and cerebellar grey matter and are associated with spongiform change in neuronal dendrites and with substantial loss of neurons and gliotic scarring.

The intracellular proteins are mainly tau and synuclein; they accumulate as insoluble deposits in neurons (Figure 1c & d) and in their processes (forming dystrophic neurites), and in some cases in glial cells. Both tau and synuclein are associated with ubiquitin which suggests that there is failure of disposal of tau and synuclein through the proteosome system. Tau has a role in axoplasmic transport and is normally associated with axonal microtubules. The hyperphosphorylated form accumulates with ubiquitin in neurons in dementia, forming the neurofibrillary tangles (NFTs), typical of Alzheimer’s disease (Figure 1c). Synuclein is a protein associated with synapses in the brain and accumulates with ubiquitin in spherical Lewy bodies in neurons (Figure 1d), usually in the substantia nigra and in temporal cortex in Dementia with Lewy Bodies. In Huntington’s disease, deposits of the protein huntingtin accumulate within nuclei of neurons and there is selective loss of neurons from the basal ganglia.

Dementias mostly occur in elderly patients over the age of 65 years, although early-onset familial dementias with mutations in genes encoding tau, APP, synuclein and the presenilins affect people in their 50s.

Enzymic degradation of Aβ (Fails with age)

Absorption of Aβ into blood (Fails with Age)

Normal pathways for the elimination of Aβ from the brain

Failure of elimination of Aβ in Alzheimer’s Disease

Aβ plaques – diffuse Neurotic Tau – Neurofibrillary tangles

Perivascular elimination of Aβ (Fails with age & Vasc Disease)

Blood vessel

Cerebral Amyloid Angiopathy

Figure 1. Accumulation of proteins in dementias
a. Aβ immunohistochemistry in the cerebral cortex in a case of AD, magnification x 10. Arrow, a non-neuritic plaque. Insert, a neuritic plaque x 40. White arrow head central core of amyloid, black arrow head surrounding dystrophic neurites.
b. PrP immunohistochemistry in the cerebral cortex in a case of new variant CJD, magnification x 10. Insert, a PrP plaque x 40.
c. Tau immunohistochemistry showing neurofibrillary tangles in the cerebral cortex in a case of AD, magnification x 40. Arrowhead, tangle. Arrow, nucleus of cortical neuron.
d. Synuclein immunohistochemistry showing intracytoplasmic Lewy bodies in the cerebral cortex in a case of DLB, magnification x 40. Arrowhead, Lewy body. Arrow, nucleus of cortical neuron.

Figure 2. Elimination of Aβ in Normal brains and in Alzheimer’s Disease.

In normal brain (upper panel), Aβ produced by neurons is eliminated enzymatically, perivascularly and into the blood. All three pathways fail with ageing.

In Alzheimer’s Disease (lower panel), Aβ accumulates as diffuse plaques (shown by arrow in figure. 1a) and neuritic plaques, with a central core of amyloid surrounded by structurally abnormal (dystrophic) neurites (as shown in the inset of figure 1a). Tau also accumulates intracytoplasmically in neurofibrillary tangles (see figure 1c). Cerebral Amyloid Angiopathy develops with accumulation of amyloid around blood vessels.
factor for dementias and is also a major risk factor for cerebrovascular disease. Patients with Vascular Dementia show widespread damage in the brain due to cerebrovascular disease with multiple small areas of infarction that may be recognised during life with MRI or by examination of the brain at post mortem. Such patients often have cardiovascular risk factors such as diabetes and hypertension and may show stepwise progression of cognitive impairment due to the occurrence of new infarcts in the brain. Most patients with Alzheimer’s disease also show evidence of cerebrovascular disease so that there is overlap between vascular dementia and Alzheimer’s disease both clinically and pathologically.

**Pathology of Alzheimer’s disease**
The classical pathology of Alzheimer’s disease was described 100 years ago; intraneuronal neurofibrillary tangles and the extracellular plaques of amyloid were visualised in histological sections stained with silver techniques. Today, the amyloid plaques of Alzheimer’s disease can be visualised in histological sections stained with silver techniques. pathologically.

**Pathogenesis of Alzheimer’s disease**
Over 90% of cases of Alzheimer’s disease are sporadic with no family history. Three major genes, those encoding APP, presenilin 1 and presenilin 2, are associated with inherited susceptibility in the very small number of families with familial Alzheimer’s disease. Apart from age, one major risk factor for sporadic Alzheimer’s disease is possession of the E4 isoform of apolipoprotein E (APOE). The 1-2% of the population who are homozygotes for APOE E4 have an eight to ten fold increased risk of developing Alzheimer’s disease and heterozygotes have a two to three fold increased risk.

The recent use of transgenic mice with mutations for human APP, presenilin and tau genes has illustrated much of the biology of Alzheimer’s disease. Cerebrovascular disease in the elderly interferes with the perivascular drainage of Alzheimer’s disease and in its clearance.

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**Therapy for Alzheimer’s disease**
As failure of elimination of Aβ from the ageing brain appears to be a major factor in the pathogenesis of Alzheimer’s disease, therapies that remove Aβ from the brain may be beneficial. Following reports that immunisation against Aβ1-42 eliminated plaques of insoluble Aβ from the brains of transgenic APP mice, clinical trials were instituted for immunotherapy in Alzheimer’s disease. The study of post mortem brains from patients who died following immunisation against Aβ showed not only clearance of insoluble Aβ plaques from cerebral cortex but also showed a reduction in the number of damaged neurites containing tau protein (Figure 2) that sur-

| Table: Pathology of Dementias as characterised by depositions of insoluble peptides and proteins within cells, in the extracellular spaces and blood vessel walls of the brain. |
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| **Dementia** | **Intracellular Deposits in Neurons** | **Extracellular Deposits** | **Cerebral Amyloid Angiopathy** | **Vascular disease - Infarcts** |
| Normal ageing | Tau | Aβ | Aβ | ↓ |
| Alzheimer’s Disease | Tau | Aβ | Aβ | ↓ |
| Vascular Dementia | ↓ | ↓ | ↓ | ↓ |
| Dementia with Lewy Bodies | Synuclein | Aβ | Aβ | ↓ |
| Frontotemporal Dementia | Tau | ↓ | ↓ | ↓ |
| Corticobasal Degeneration | Tau | ↓ | ↓ | ↓ |
| Multi System Atrophy | Synuclein in glial cells | ↓ | ↓ | ↓ |
| Creutzfeldt-Jacob Disease | Huntington (Intranuclear) | PrP | PrP (rare) | ↓ |
| Familial Dementias | Tau | Synuclein | Aβ, Cystatin; Aβ | Aβ, Cystatin; Aβ | ↓ |

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round Aβ plaques in Alzheimer's disease. However, there was no reduction in the amount of Aβ deposited in blood vessels as CAA and the drainage of interstitial fluid from white matter may also be impaired. In transgenic mice, the reduction of Aβ plaques in the brain in immunised animals is associated with a significant increase in CAA and with haemorrhages from the Aβ-laden vessels.

Conclusion
The neuropathology of the majority of dementias is characterised by the accumulation of proteins within cells, within the extracellular spaces and in blood vessel walls indicating failure of elimination of such proteins from the ageing brain. Overlying the protein accumulation are the effects of cerebrovascular disease both as a cause of infarction in the brain and as a probable factor in the failure of elimination of proteins such as Aβ from the extracellular spaces and from blood vessel walls. Therapies that facilitate the clearance of Aβ from the extracellular spaces and from blood vessel walls may prevent or ameliorate Alzheimer's disease. Immunotherapy may prove to be one such therapy.