Review Article

Recent advances in the understanding of dementia

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Progressive intellectual decline acquired in late life constitutes a major challenge to public health, in terms both of the medical and community services required to support an intellectually and physically frail population, and the physical and emotional strain on patients and their carers. Although the first scientific breakthrough occurred 80 years ago, with Alzheimer's description, using a new silver staining technique,¹ of characteristic neuropathological changes in dementia, it is in the last two decades that there has been a resurgence of research interest, with major advances in the neurochemistry, histopathology and molecular biology of the disorder.

Definition and causes of dementia

Dementia may be defined as an acquired, multidimensional cognitive decline, occurring in the absence of clouding of consciousness, which distinguishes it from confusional states due to metabolic, infective or other insults. The intellectual decline is required to be sufficient to interfere with normal social functioning,² and the stipulation that it is acquired distinguishes it from developmental retardation. Using such a definition, the reported annual incidence rates vary between 0.3 and 2.5% of the population aged 65 years or over.³ The magnitude of the problem will clearly increase in parallel with the predicted increase in the number of elderly people.

Any condition in which there is widespread disruption of normal neuronal architecture within the cerebral cortex, particularly if there is disruption of cortico-cortical association tracts, would be expected to cause dementia. The commonest causes are Alzheimer's disease (AD),

and multi-infarct dementia, although other conditions should be considered, (Table I), particularly in younger patients, or those with atypical features.

A precise diagnosis of the cause of dementia in a given patient is often not achieved, so a clinical classification can be more helpful than an aetiological one. A clinical distinction between cortical and subcortical dementias has been proposed,⁴ on the basis of the type of intellectual deterioration in progressive supranuclear palsy and Huntington's disease (Table II). The absence of aphasia, apraxia and agnosia in these diseases was contrasted with the cortical dementias, as exemplified by Alzheimer's disease.

This article will deal initially with Alzheimer's disease, the commonest and most intensively studied of the dementias, and will then consider other causes.

Alzheimer's disease (AD)

Alzheimer¹ described a patient with severe progressive memory loss, dysphasia, and dyslexia, in whom the new silver staining method allowed the first demonstration of the neurofibrillary tangles, that together with senile plaques, are considered diagnostic of the disease. Sixty years later, this technique was used to demonstrate a quantitative relationship between the plaque count post-mortem, and the severity of the dementia.⁵ A significant association between clinical severity and neurofibrillary tangle (NFT) count has also been recently described.⁶ The presence of both these histopathological abnormalities in AD implies a disruption of neuronal circuitry, either as a cause or a consequence of the cellular changes.

Classically, neuropsychological deficits are related to the area of cortex damaged, for example, Broca's aphasia is a specific clinical syndrome associated with a dominant frontal lobe lesion. While such a

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Received: 15 September 1987

Table I Differential diagnosis of dementia

<i>Primary cerebral degenerations</i>	<i>Vascular</i>	<i>Cerebral infection and inflammation</i>	<i>Neoplasm and hydrocephalus</i>	<i>Toxic/metabolic</i>	<i>Storage diseases</i>	<i>Psychiatric</i>
Alzheimer's disease	Multi-infarct dementia	Encephalitis	Meningioma	Alcohol	Adrenoleucodystrophy	Depressive pseudodementia
Parkinson's disease	Binswanger's	Neurosyphilis	Gliomas	Hypothyroidism	Metachromatic leucodystrophy	Hysterical pseudodementia
Huntington's disease	Congophilic angiopathy	Multiple sclerosis	Parapituitary lesions	Wilson's disease	Kuf's disease	Ganser's syndrome
Pick's disease	Cranial arteritis	Whipple's disease	Subdural haematoma	Hypoglycaemia	Cerebro-tendinous xanthomatosis	
Multisystem atrophy	Other vasculitides	Granulomatous diseases	Midbrain tumour	Porphyrria		
		Jakob-Creutzfeld disease	Aqueduct stenosis	Drugs		
		Multifocal leuko-encephalopathy	Communicating hydrocephalus	Heavy metals		
		AIDS-dementia		Chronic uraemia/dialysis		

Table II Cortical and subcortical dementias

	<i>Clinical features</i>	<i>Causes</i>
Cortical	Memory disorders in combination with aphasia/apraxia/agnosia	Alzheimer's disease Pick's disease Down's dementia Jakob-Creutzfeld disease
Subcortical	Slowness in thinking and behaviour Apathy Motor disorders	Huntington's disease Parkinsonian dementia Progressive supranuclear palsy

localisationist approach may be most appropriate for focal lesions, such as tumours or strokes, it has been suggested that a more diffuse degeneration might be described more accurately in terms of damage to a neurotransmitter-specific subset of neurones. Such a system, not anatomically discrete, but consisting of neurones related by their similar neurotransmitter function, may be termed a 'pharmacosystem'.⁷

Despite the initial impression of widespread atrophy, there is evidence of both anatomical and biochemical selectivity of the neuronal disruption in AD. The hippocampus, temporal neocortex and cortical association areas are areas of anatomical

predilection for Alzheimer change. The most marked histopathological change occurs in the hippocampus, and this, together with the critical role of the hippocampus in memory,⁸ has led to the hypothesis that AD may be primarily a hippocampal disease.⁹ NFTs have been demonstrated in the cells of origin of the perforant pathway (the principal cortical input to the hippocampal formation), and in the termination zone of this pathway, in AD but not in controls.¹⁰ This effectively disconnects the hippocampal formation from the association and limbic cortices. However, the frequent occurrence of abnormalities throughout the neocortex suggests that to relate the clinical features solely to the hippocampus is insufficient. Within the areas of maximal damage, particular neuronal systems, for example cholinergic and glutamatergic, appear to be affected. The features that make a particular neuronal subset, or pharmacosystem, vulnerable to Alzheimer's change are unknown.

Neuropathological changes in AD

Normal neurones contain three major polymeric protein systems, microtubules, intermediate filaments, and microfilaments. These have important roles in maintenance of cell shape, cell motility, and movement of organelles through the cytoplasm.¹¹ Any abnormality of these elements, or

their interconnections, is likely to affect cell function adversely. Recent studies have highlighted the complexity of the neuritic and perikaryal changes that occur in the AD cerebral cortex.¹²

NFTs are argyrophilic intraneuronal inclusions found in a number of neurodegenerative disorders, including ageing Down's syndrome, post-encephalitic Parkinsonism and dementia pugilistica.¹³ They may be found in small numbers in the hippocampi of normal elderly people.¹¹ In AD, NFTs are found mainly in the cortex, particularly in the hippocampal and neocortical pyramidal neurones and in various brain stem nuclei.¹⁴ NFTs are composed of paired helical filaments (PHFs) wound around each other¹⁵ and their polypeptide composition appears to be different from that of neurofilaments and plaque amyloid.¹³ Accumulation of PHFs within the cytoplasm could disrupt neuronal architecture sufficiently to affect cell function, and possibly cause cell death, although the finding of NFTs in a variety of disorders suggests that they could be markers simply of cell damage.

Immunochemical studies have demonstrated a variety of antigens in association with PHF, but these may be secondary phenomena. Certain microtubule associated proteins, particularly tau proteins (which stimulate assembly of microtubules from tubulin),¹⁶ are important antigenic constituents of PHF¹⁷ and tau protein incorporated into PHFs is different from normal neuronal tau in that it is abnormally phosphorylated.¹⁸ This may affect the interactions of tau with other cytoskeletal proteins and cellular organelles, and there is evidence of abnormal microtubule assembly in AD.¹⁹

Senile plaques, the other major histological feature of AD, have also recently come under scrutiny. Amyloid filaments, with the same staining properties as the amyloid fibrils of systemic primary and secondary amyloidoses, are found in extracellular deposits in the centre of neuritic plaques, and the peptide sequence determined (see below). In addition, amyloid may be found in cerebral and meningeal vessels in AD brains. Ultrastructural studies in AD show thickened irregular capillary walls, without the perivascular neural plexus that normally invests the brain parenchyma.²⁰ Loss of this innervation might alter the structure of capillary walls, perhaps damaging the blood-brain barrier, and exposing neurones to toxins from which they are normally protected.

Neurotransmitter changes in AD

Since the discovery of a cholinergic deficit in AD,²¹ there has been a great deal of interest in the

neurotransmitter changes in dementia, although the initial hope for a treatable deficit – analogous to the dopaminergic deficit in Parkinson's disease – has not been realised. The relationship between the structural changes of neuronal loss, NFTs, neuritic plaques and neurochemical markers has been studied, allowing some insight into the biochemical selectivity of the diseased neuronal networks.

A reduction in the activity of the enzyme choline acetyl-transferase (ChAT) in selected brain regions in AD was first described in 1976.²¹ Since this biosynthetic enzyme is confined to acetylcholine neurones, it is a valuable marker of the cholinergic system. Reduced ChAT activity is reported in all areas of neocortex, particularly temporal cortex and hippocampus, but not all subcortical areas.²² The ChAT activity has been correlated with both the density of senile plaques and NFTs, and with the severity of dementia. More specifically, a recent biopsy study revealed a correlation between the severity of dementia, and the degree of pathological change in large cortical neurones, and with a reduction in acetylcholine synthesis.²³

Muscarinic cholinergic receptors are the predominant cholinergic receptors in the central nervous system, and the subtype M2, which is believed to be presynaptic, is reported to be selectively lost in AD.²⁴ This is confirmed *in vivo* by single photon emission tomography studies which show impaired muscarinic binding using iodine labelled QNB (3-quinuclidinyl-4-iodobenzilate, a muscarinic antagonist).²⁵ Relative preservation of post-synaptic (M1) receptors is an important observation since intact post-synaptic receptors would be necessary for cholinergic therapy. By contrast, significant reduction in nicotinic binding in AD is found in frontal, temporal and occipital cortex,²⁶ although the role of nicotine in cognition is unknown. The association of cholinergic cell loss with AD suggests that the ascending projections from the basal forebrain to the neocortex and hippocampus are associated with memory and other aspects of cognitive function. This view is supported by pharmacological studies that demonstrate impairment of memory and attention by cholinergic blockade.⁷ However, although the cholinergic abnormality is a major feature of AD, this is now seen within the context of a variety of neurotransmitter deficits (Table III).

Other ascending projections from the brain stem, namely noradrenergic and serotonergic, are involved, and loss of the chemical marker in the central nervous system can be related to loss of cells from the nucleus of origin. However, none of these changes can be related to the intrinsic cortical pathology of cell loss and NFT formation. A

Table III

<i>Neurochemical system</i>	<i>Neurotransmitter</i>	<i>Evidence for implication in AD</i>
Monoamine	Noradrenaline (projection to cortex from locus coeruleus)	(a) Reduced uptake of NA in synaptosomes prepared from biopsy samples. (b) Loss of cells from locus coeruleus (c) Loss of cortical noradrenaline. ²⁷
	Dopamine (projection to cortex and striatum from midbrain)	Reduced levels of 5-HIAA and HVA in CSF and striatum
	5 HT (projection to cortex from midbrain)	(a) Reduced 5 HT and 5 HIAA in cortex (b) Reduced 5 HT uptake (c) Reduced K ⁺ stimulated release of endogenous 5 HT
Amino acids	Glutamate/aspartate (major excitatory neurotransmitter used by pyramidal cells, which are involved in cortico-cortical association tracts)	(a) Distribution of plaques corresponds with termination of cortico-cortical association pathways (b) Predilection of NFTs for pyramidal cells (c) Glutamate binding reduced in hippocampus ²⁸ (d) Glutamate uptake sites reduced ²⁹
	GABA (major inhibitory neurotransmitter used by inter-neurons)	Reduced GABA concentration and reduced GABA uptake in cortex ²⁷
Neuropeptides	CCK/VIP (co-exist with GABA)	Unchanged in AD. ²⁷
	Somatostatin (co-localized to some GABA neurones)	(a) Reduced especially in temporal cortex (b) SLIR co-localised with neural plaques (c) Correlation in biopsy studies between SLIR and cognitive performance
	CRF	CRF-like immunoreactivity reduced in cortex ³⁰

Abbreviations. 5 HIAA: 5 hydroxyindoleacetic acid; 5 HT: 5 hydroxytryptamine; K: potassium; GABA: gamma aminobutyric acid; CCK: cholecystokinin; VIP: vasoactive inhibitory polypeptide; SLIR: somatostatin-like immunoreactivity; CRF: corticotrophin releasing factor.

number of neurotransmitters are used by cortical cells, and the major inhibitory system, gamma amino butyric acid (GABA), is involved in AD. Some GABA cells also contain neuropeptides (see Table III), which may explain the loss of somatostatin which is a consistent feature of AD. The excitatory amino acid glutamate is the presumed neurotransmitter of cortical pyramidal cells, and both concentrations and uptake by synaptosomes are reduced, providing a biochemical correlate of the pyramidal cell loss and associated neurofibrillary tangle formation.

Aetiology of AD

Molecular genetics

Despite the evidence for selective vulnerability in

Alzheimer's disease, there is no clear evidence to suggest why particular cell types are more vulnerable than others, or what makes a particular individual susceptible to the disease. A proportion of cases occur in families as an autosomal dominant disease, but the majority appear to be sporadic. The final common pathway of each of these diseases may be the same, and genetic factors might make potential sufferers more susceptible to environmental toxins.

In some families, AD appears to be transmitted over several generations as an autosomal dominant gene,³¹ whilst in other families the mode of transmission is unclear. Twin studies have been reported to show both concordance and discordance between sets of monozygotes where one or both twins had AD,³² but such studies are

hampered by the fact that the apparently unaffected twin may die or be lost to follow-up before the disease manifests itself. Apart from a slightly earlier age of onset, there is little to distinguish familial from sporadic cases, either clinically or in terms of cerebral metabolism.³³

The genetics of the disorder may be heterogeneous, i.e. in some cases due to mutation of a single gene, while late onset cases might be multifactorial. The frequent occurrence of Alzheimer type neuropathology in elderly patients with trisomy 21, and the increased incidence of Down's syndrome in other family members of patients with AD,³⁴ suggested that material encoded on this chromosome may play a crucial role in the pathogenesis of AD. The gene responsible for familial AD in four families was found to be closely linked to two DNA markers on the proximal part of the long arm of chromosome 21.³⁵ A complementary DNA (c-DNA) clone for amyloid A4 protein, which is derived from brain amyloid, has been characterized, and the gene coding for it is found to map on to chromosome 21³⁵⁻³⁹ close to the familial Alzheimer gene. However, there is a crossover between the familial Alzheimer's disease gene and the amyloid precursor gene in some families,⁴⁰ and it may be simply coincidence that they are so closely associated.

Environmental factors

Environmental neurotoxins have recently been implicated in the aetiology of a number of different neurodegenerative conditions, raising the possibility of their involvement in AD. Damage to the nigrostriatal pathway by MPTP⁴¹ can be shown to occur after doses too small to cause clinical symptoms;⁴² the amino acid MLA has been implicated in the pathogenesis of amyotrophic lateral sclerosis and Parkinsonian dementia complex of Guam.⁴³ In AD, aluminium has been considered a possible aetiological agent, in view of the dementia which can occur with long term dialysis, and which has been shown to be associated with NFTs at autopsy.⁴⁴ Although the NFTs do not share the PHF of AD, high aluminium levels are found in Alzheimer disease NFTs, and in the central region of the plaque cores in AD.⁴⁵ It is unknown whether the presence of high concentrations of aluminium are cause or effect. It would seem unlikely that high exposure itself would lead to AD, but rather that a breakdown in the mechanism for excluding aluminium from brain cells might occur. The transmissible spongiform encephalopathies, such as Creutzfeld-Jakob disease and kuru, resemble AD clinically and patho-

logically, but there is no evidence as yet for transmissibility in AD. Slow viruses, virinos and prions have been postulated as the infectious agent in these disorders.⁴⁶ Any aetiological theory must take into account the late age of onset of this disease; it is possible that damage from either genetic or environmental factors could interact with the features of normal ageing and so become clinically manifest.

Non-Alzheimer dementias

The term vascular dementia, the second most common cause, encompasses more than one disease process.

Strategic infarct In general, a single infarct would be expected to cause a discrete focal neuropsychological deficit rather than a dementia, but a strategically placed infarct may present clinically as dementia or as prominent memory disturbance.⁴⁷

Multiple small cortical infarctions constitute the typical picture of 'multi-infarct dementia', with a step-wise progression and associated signs such as brisk reflexes and extensor plantars.

Lacunes are small ischaemic infarcts found in the deeper parts of the brain, principally in basal ganglia and pons. They are associated with hypertension, and when present in large numbers ('état lacunaire') may be associated with dementia and pseudobulbar palsy.⁴⁸

Binswanger's disease (subcortical arteriosclerotic encephalopathy) usually presents with strokes, dementia, incontinence and upper motor neurone signs. It is associated with microinfarction and demyelination in white matter, with associated gliosis,⁴⁹ and areas of diffuse low attenuation in cerebral white matter on CT.

Features of the other common dementias are shown in Table IV.

Prospects for the future

Dementia is often referred to as a global impairment of cognitive function, but such a definition does not recognize the clinical heterogeneity of the many causes. AD itself may also vary in its presentation. Most patients present with memory loss, but the first signs in others may be of personality change, dyspraxia or speech disturbance, and some patients may develop motor

Table IV Features of other common dementias

Disorder	Clinical features	Histopathology	Neurochemistry (reference no.)
Pick's disease	Clinically similar to AD but with more pronounced frontal lobe features	Argentophilic Pick bodies ⁵⁰ cell loss + + especially nucleus basalis ⁵¹	52
Down's dementia	Difficult to demonstrate superimposed on mental retardation	Amyloid plaques and NFTs in cerebral cortex	53
Parkinson's disease	Frontal lobe deficits. ⁵⁴ Some patients have more widespread cognitive deficit ⁵⁵	Lewy bodies ⁵⁶ especially in brain stem projection system	57
Progressive supra nuclear palsy	Prominent frontal lobe deficits ⁵⁸	Degeneration of ascending projection from brain stem nuclei ⁵⁹	
Huntington's disease	Variable severity of dementia with chorea and psychiatric disturbance	Atrophy of corpus striatum and cerebral cortex	60
Alcoholic dementia	Widespread memory loss ⁶¹	Cortical atrophy (cf. Wernicke-Korsakoff) ⁶¹	

signs. Both neurochemical changes and neuropathology vary according to age. It has been suggested that AD may thus represent more than one disease, similar to the older distinction between senile and presenile cases or it might be seen as a spectrum of disorder. Careful definition of clinical subgroups, with post-mortem correlation, will be necessary to clarify the nosology of the disorder.

Biochemical studies on post-mortem tissue have provided valuable information on the nature of neurotransmitter deficits. However, there are clear disadvantages to post-mortem biochemistry, as the studies are usually of end stage disease. Biopsy studies allow analysis of fresh material earlier in the disease process, but there are considerable practical and ethical difficulties in obtaining cortical biopsies from demented patients. *In vivo* studies of biochemical markers are now possible using positron emission tomography, allowing visualization of at least some neurotransmitter systems non-invasively. Correlation of clinical features with *in vivo* biochemistry should give some insight into the biochemical nature of clinical subgroups, and thus direct possible future therapies. Attempts have been made to treat AD on the basis of the neurochemical deficits described, but treatment with precursor substrate loading with choline has been largely unsuccessful.⁶³ One study showed some improvement in a subgroup of patients who had

inhibition of cerebrospinal fluid cholinesterase while on treatment.⁶⁴ A recent study using tetrahydroaminoacridine (THA),⁶⁵ a centrally acting cholinesterase inhibitor, demonstrated significant improvements in some patients, although this is currently being assessed in a larger study. However, in view of the complexity of neurotransmitter abnormalities in AD, it would appear unlikely that simple cholinergic replacement would be of value, except perhaps in a subgroup of patients with a primarily cholinergic deficit. Neurotransmitter replacement would be most likely to be of value in those conditions such as the subcortical dementias, where a specific pathway is damaged. It is less likely to be of value in situations of massive neuronal loss.

In summary, the dementias are an ill understood group of disorders of differing aetiology and pathogenesis. Whilst rare disorders may be due to a single enzyme defect (e.g. metachromatic leucodystrophy), the aetiology of the commonest disorder, Alzheimer's disease, is unknown and probably multi-factorial. The final common pathway is disruption of neuronal connections in the cerebral cortex; some dementias are reversible, implying disruption at a metabolic level, while neuronal loss or damage to neuronal processes is largely irreversible. It is hoped that improved understanding of the pathophysiology will identify patients at the early, reversible stage.

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