The dementias

Dementia affects about 5% of the elderly population over age 65 years and has an unexplained predominance in women and a low rate in some cultures. Different forms of dementia are now distinguished—Alzheimer’s disease, dementia with Lewy bodies, frontotemporal dementia, and dementia secondary to disease, such as AIDS dementia. However, such nosological boundaries are being re-evaluated because different dementias are believed to have common underlying neuropathology. Neurochemical and neurobiological research has led to advances in understanding causes of dementia, and functional imaging has allowed identification of possible biomarkers; from these, a range of potential treatment approaches have arisen that focus on enhancement of neurotransmitter function, intervention at the level of amyloid production and deposition, and reduction of secondary risk factors such as hypertension, depression, and hypolipidaemia. Molecular diagnostic testing and genetic counselling for families with autosomal dominant early-onset dementia are new developments; however, this approach is not useful for late-onset dementia, in which the identified candidate susceptibility genes have a relatively small effect on risk. While fundamental research works towards new biological treatment strategies, much remains to be done in the area of disease management and the development of appropriate models of long-term care.

Dementia is a generic term that describes chronic or progressive dysfunction of cortical and subcortical function that results in complex cognitive decline. These cognitive changes are commonly accompanied by disturbances of mood, behaviour, and personality. A distinction is often made between primary degenerative dementias such as Alzheimer’s disease, dementia with Lewy bodies, frontotemporal dementia, and dementia secondary to another disease process, such as AIDS dementia. Since The Lancet International Conference on Dementias in 1996, such simplistic distinctions are being re-assessed as the complex interactive effects of genetic predisposition, neurochemical changes, and disease co-morbidity in the genesis of dementia syndromes are elucidated. Different forms of dementia are now known to have common underlying neuropathologies and histopathological studies have shown that mixed states (people presenting with features of more than one type of dementia) are probably more usual than pure dementia syndromes. These observations lead us towards a re-examination of nosological boundaries.

Epidemiology

The development of internationally recognised diagnostic algorithms for case identification in the 1980s prompted a proliferation of epidemiological studies, most of which are descriptive. Meta-analyses of studies done in developed countries have established dementia prevalence at around 1-5% at age 65 years, which doubles every 4 years to reach about 30% at 80 years. Overall incidence increases with age and is about 1% per year and is low in men and in people of African or Asian origin. In Europe and north America, Alzheimer’s disease is estimated to be more common than vascular dementia. On the other hand, vascular dementia has been reported to be more prevalent than Alzheimer’s disease in China, Japan, and the Russian Federation; although a study in Shanghai noted that Alzheimer’s disease accounted for 65% of all dementias. In developing countries, dementia of any type seems to be rare. Results from community surveys and autopsy reports suggest that Alzheimer’s disease does not occur in Nigerians. Differences in rates of dementia between developed and developed countries are difficult to explain, but might be attributable partly to difficulties in dementia diagnosis in areas with high rates of illiteracy, and survival bias due to high death rates at all ages. Dementia patients have a substantially shortened life expectancy; the average survival is 8 years from diagnosis. A longer survival time is reported for patients with Alzheimer’s disease than for those with vascular dementia and women have longer survival than men for both Alzheimer’s disease and vascular dementia, independent of sex differences in life expectancy.

Extensive exploration of possible risk factors, which has largely focused on Alzheimer’s disease, has been disappointing. Age, dementia in a close family member, and the E4 allele of the APOE gene are the only confirmed risk factors for the disease. Although early clinical studies in selected families showed that the APOE*E4 allele was specific for up to 90% of cases of dementia, subsequent population studies noted lower rates with decreased gene effects at higher ages. Female sex, herpes infection, low lipid concentrations, a history of head injury, and the protective effect of hormonal replacement therapy, are all factors that interact with APOE genotype to modify relative

Search strategy and selection criteria

This seminar is not an exhaustive review of all research in the area of dementia, but rather it presents an overview of some of the principal advances that have occurred based on the extensive and regularly updated literature databases that have been developed in the authors’ research institutes.
High education has been associated with low rates of Alzheimer’s disease, which could be at least partly attributable to compensatory strategies that delay detection of the disease. Several other possible risk factors for Alzheimer’s disease such as exposure to anaesthetic agents, diabetes, and the protective effects of non-steroidal anti-inflammatory drugs and alcohol are being re-evaluated with improved methodology.

Studies of risk factors for vascular dementia, the second most frequent form of dementia, are fewer in number than those for Alzheimer’s disease, principally because of difficulties with the definition of research criteria for this group of disorders. Significant differences are seen in the number of vascular dementia cases identified according to whether or not cerebral imaging is used in the research criteria—studies using imaging tend to give low specificity, and those without have low sensitivity. Estimates of vascular dementia prevalence thus vary widely from 10–50% of all cases of dementia. Main risk factors identified for the disease are age, male sex, hypertension, myocardial infarction, coronary heart disease, diabetes, generalised atherosclerosis, smoking, high lipid concentrations, and a history of stroke. Although results from some studies suggest an association between vascular dementia and APOE *E4* this relation is not consistently noted, and might be attributable to difficulties in the differential diagnosis of Alzheimer’s disease and vascular dementia. Vascular pathology, notably atherosclerosis, white matter lesions, and mid-life arterial hypertension, have also been associated with Alzheimer’s disease and could enhance cognitive loss.

Thus, most cases of dementia have a common vascular pathology, which suggests that early diagnosis and treatment of vascular disorders could modulate the onset of dementia.

Results from descriptive studies have raised two important issues. First, dementia is no longer regarded as a single nosological entity and, even within its principal form, clinical subgroups of Alzheimer’s disease with their own risk factors and causes are likely to exist. Thus, epidemiological studies that group together all forms of dementia are likely to hide individual patterns of risk, clinical manifestation, and treatment success. Consensus criteria now exist to differentiate early-onset and late-onset Alzheimer’s disease and Vascular dementia, and diagnostic guidelines have also been suggested for dementia with Lewy bodies, frontotemporal dementia and progressive non-fluent aphasia. Second, although early studies calculated odds ratios for individual risk factors, it has become clear that the co-occurrence of multiple risk factors increases risk beyond the additive effect of each factor, and that some risk factors might only be activated in the presence of other factors. For example, signs of vascular disease detected in neuroimages and an APOE *E4* genotype combine to increase risk of Alzheimer’s disease in very elderly people. Analytical epidemiology has become increasingly important and allows testing of the predictive validity of complex models of disease causes that incorporate many interacting risk factors (figure 1). The challenge now is to calculate the relative importance of individual risk factors and their interactive effects, and to obtain maximum likelihood estimates for alternative models to assess their relative robustness in predicting transition to Alzheimer’s disease.

**Biology**

Increases in the understanding of the basic biology of Alzheimer’s disease and related dementias during the past 20–30 years have been substantial, and have led to potential treatment strategies that are just beginning to undergo clinical evaluation. Such advances have been made using three overlapping approaches: neuropathology, neurochemistry, and molecular biology.

**Neuropathological advances**

Alzheimer and his colleagues and contemporaries made an almost complete description of the core neuropathological lesions that occur in the dementias of young and middle-aged people. The first real advance in their work came with the realisation that the so-called senility that occurs in some, but not all, elderly people was accompanied by the exact same changes seen in dementias. This work had the important effect of reclassifying senile neurodegeneration as a set of disease entities that are suitable subjects for development of treatments.

Neuropathological studies have begun to redefine our nosological understanding of these conditions. For example, immunohistological techniques were used to identify Lewy bodies in the cortex. A co-worker of Alzheimer first described these intraneuronal inclusion bodies in the substantia nigra of patients with Parkinson’s disease, and they are now known to accompany a distinct dementia syndrome—dementia with Lewy bodies—characterised by parkinsonism, visual hallucinations, and fluctuating confusion. Lewy bodies are composed of aggregated synuclein and, in very rare instances,
mutations in the \textit{SNCA} gene can cause autosomal dominant familial Parkinson’s disease.\textsuperscript{34} The same pattern of rare variants of disease being associated with mutations in a gene that codes for a protein that is abnormally aggregated in both rare and common forms of the disease is found repeatedly. Thus, mutations in the \textit{MAPT} (tau) gene can be a cause of frontal lobe dementia and aggregations of tau protein in neurons and glia are seen in both frontal lobe dementia and Alzheimer’s disease.\textsuperscript{35} All this work has begun to lead to a redefinition of the dementias—ie, one grouped by pathogenesis and pathological changes rather than by clinical symptoms. Thus, the synucleinopathies include Parkinson’s disease, dementia with Lewy bodies, and multisystem atrophy. Tauopathies include frontal lobe dementia and progressive supranuclear palsy. Alzheimer’s disease is both an amyloidopathy (as are the transmissible encephalopathies to some extent) and a tauopathy. This regrouping of disease entities is not entirely academic because an intervention to prevent synucleinopathy might be effective against all synucleinopathies but not tauopathies, and vice versa, leading to the somewhat unexpected conclusions that therapies for frontal lobe dementias might also be useful in progressive supranuclear palsy. Likewise, if therapies for Alzheimer’s disease target amyloid, they might have some relevance for other amyloidopathies, but not for frontotemporal degeneration even though these two disorders have many of the same clinical characteristics.

\textbf{Neurochemical advances}

Studies of the neurochemistry of Alzheimer’s disease have resulted in tangible benefits in treatment of symptoms. The finding that markers of cholinergic function are lost first and most in Alzheimer’s disease led to the cholinergic hypothesis that postulates that this disease is mainly a cholinergic disorder. Post-mortem examination of brain tissue from patients with Alzheimer’s disease shows a loss of cholinergic markers and pronounced attrition of neurons in the locus coeruleus, the region where cholinergic fibres originate. Evidence from work in animals suggests that lesions of cholinergic tracts induce severe cognitive deficits. Such combined evidence prompted investigators to develop strategies to rectify cholinergic loss,\textsuperscript{37} which resulted in development of cholinesterase inhibitors. Subsequent work has shown other neuronal markers are also lost, and some evidence suggests that the diversity of clinical symptoms results from relative loss of serotonergic or noradrenergic function in addition to cholinergic function.\textsuperscript{37} The loss of these other neurotransmitter systems probably also sets the limits of potential benefits of the cholinergic, symptomatic approach.

\textbf{Advances in molecular biology}

Although research into the neurochemistry and neuropathology of dementia has produced practical outcomes, the real hope of advances in treatment comes from studies in molecular biology, which could advance our knowledge of the pathogenesis of neurodegeneration. Studies in molecular biology and genetics have led to an almost complete understanding of the process of formation of the two key pathological lesions of Alzheimer’s disease—ie, the plaque and tangle. Animal models of both processes have been developed and compounds that affect both, at least in the laboratory setting, have been discovered. We do not yet understand how these lesions relate to each other, why some neurons are more vulnerable than others, and which factors determine individual susceptibility to neuronal lesions.

The plaque is an extracellular lesion composed of a core of an amyloid peptide of 40–42 aminoacids designated $\text{A}_\beta$.\textsuperscript{38} This peptide is in turn derived from amyloid precursor protein (APP), the gene for which is on...
chromosome 21. Mutations in the gene occasionally cause familial Alzheimer’s disease, and these mutations cluster around the three sites where APP is known to be cleaved in vivo (figure 2). Cleavage at two of these sites—at the β-amyloid cleaving enzyme (BACE) and the γ-secretase sites—liberates the Aβ peptide, whereas cleavage at α-secretase is non-amyloidogenic. BACE has been cloned and characterized, and potentially therapeutic inhibitors have been developed.49 In fact, γ-secretase has been shown to be very closely associated with (and perhaps even is) the product of genes that are also mutated in some families with the rare autosomal dominant form of Alzheimer’s disease. These genes are known as the presenilins—PS-1 on chromosome 14 and PS-2 on chromosome 1.46 Inhibition of γ-secretase activity might also be effective in the treatment of Alzheimer’s disease. However, loss of the γ-secretase function in transgenic mice is lethal, whereas loss of the BACE gene in mice causes no apparent deficits.

A very unexpected advance in treatment came about when researchers showed that immunological treatment could reduce plaque formation in transgenic mice.49 Subsequently this result was repeated with both active and passive immunisation, and workers showed that such treatment had positive effects on the cognition of the transgenic animals.49,50 Phase 2 trials of vaccination with amyloid (AN-1792) began in 2001, on 375 patients with mild to moderate disease. These trials were the first product of research into the molecular biology of Alzheimer’s disease to reach the stage of clinical assessment, but were halted in March, 2002, because of signs of nervous system inflammation and worsening of Alzheimer’s disease symptoms in 5% of patients. The exact cause of these deleterious side-effects remains uncertain, although it has been speculated that activated T cells might have entered the brain, or that specific tissue types could have overstimulated the immune system. Research on mice with two Alzheimer’s-disease-linked transgenes has shown that immunisation upregulates a membrane protein in immune-system cells in the hippocampus, which causes microglial activation, which in turn is a sign of inflammation.44 However, this study was done on young mice and, furthermore, was unable to establish a direct link between microglial activation and autotoxic inflammation.

The other lesion of Alzheimer’s disease is the neurofibrillary tangle—an intraneuronal lesion of highly phosphorylated and aggregated tau (figure 3). Tau protein is a normal and essential component of neurons where it stabilises the microtubule cytoskeleton that is essential for axonal transport.46 In Alzheimer’s disease this cytoskeleton is lost and the aggregation of tau is an early event in pathogenesis that correlates well with cognitive loss.48 We do not know why tau aggregates, but it might be due to the loss of normal tau function that accompanies some tau mutations in frontotemporal dementia, the altered isoform expression caused by other tau mutations, or the increase of phosphorylation that occurs in Alzheimer’s disease.47 Tau phosphorylation is regulated in neurons, in part, by an enzyme, glycogen synthase kinase-3 (GSK-3), and inhibition of this enzyme is another potential treatment strategy, especially since the neurotoxic effects of Aβ are reduced by GSK-3 inhibition.46,49 This reduction might be the answer to one of the most enduring and frustrating puzzles in our understanding of Alzheimer’s disease—ie, the link between plaques and tangles. Such a link must exist, but proof that amyloid production leads to tau aggregation has remained elusive.50

Apart from the mutations associated with early-onset familial Alzheimer’s disease, polymorphic variation in genes affect personal susceptibility to late-onset disease. Only one gene is known thus far to affect risk—APOE. The E4 allele increases risk, or reduces age of disease onset (three to four-fold for the heterozygous form of disease, and up to ten-fold for the rare homozygous condition), but the E2 allele decreases risk.51 Other genes are almost certainly associated with Alzheimer’s disease, and linkage suggests that there are regions of interest on chromosomes 10, 12, and 9.52–54

**Practical consequences of advances in biology**

Acetylcholinesterase inhibitors55–57 are modestly efficacious in treating the symptoms of cognitive deficits, and there is some evidence for an effect on behaviour and function. Results from early trial data suggest that for every three to seven patients treated with acetylcholinesterase inhibitors, only one will have improvement in symptoms, or a delay in clinical deterioration.56 Trials that led to the licensing of these compounds were done almost exclusively in people with mild to moderate Alzheimer’s disease, but some evidence shows that the cholinergic loss in early stages of this disorder is mild,57 suggesting that effectiveness might not be lost entirely in those with severe disease. Evidence about long-term use of acetylcholinesterase inhibitors, their use in severe dementia, use in vascular dementia, and head-to-head comparisons between different compounds is being gathered and should help to inform evidence-based practice. Early signs are that the cholinesterase inhibitors might be especially useful in dementia with Lewy bodies.58 Other approaches in development of treatment for dementia seek to modulate different neurotransmitter systems to those affected by acetylcholinesterase inhibitors, suggesting the possibility of combination therapies.

Genetic advances have led to molecular diagnostic testing, and predictive testing is now a reality for those few families with clear-cut autosomal dominant early-onset dementia. Such people should be referred to clinical geneticists for counselling. The molecular biology of late-onset Alzheimer’s disease is more complicated than early-onset disease, since the APOE susceptibility gene alters
MRI alone (90%). Functional imaging without the radioactive isotopes, yet it provides superior spatial metabolism with the advantage of not requiring dynamic susceptibility contrast provides information on reducing tau phosphorylation. Such compounds include; that show promise in reducing amyloid formation or treatment, are identification of hundreds of compounds likelihood, and few feel it has any use in diagnosis at testing should not be used for prediction of disease APOE genetic testing for late-onset Alzheimer’s disease—APOE risk only slightly. There are no discernible clinical uses of genetic testing for late-onset Alzheimer’s disease—APOE testing should not be used for prediction of disease likelihood, and few feel it has any use in diagnosis at present.

The most promising practical advances in research for treatment, are identification of hundreds of compounds that show promise in reducing amyloid formation or reducing tau phosphorylation. Such compounds include; inhibitors of β-secretase or γ-secretase, either of which should reduce production of amyloid; agents to reduce fibrillogenesis of the amyloid peptide, which might reduce its toxicity; and inhibitors of glycogen synthase kinase-3 (GSK-3), which might reduce tau aggregation and tangle formation. Other approaches based on epidemiological findings include NSAIDs, vitamin E or vitamin B12 supplementation, and hormone replacement therapies. All methods hold some promise, but none have been adequately tested.

Structural and functional neuroimaging
Neuroimaging is becoming increasingly important as a means to identify potential biomarkers in dementia. CT and MRI are now often used in research, and to a lesser extent in clinical settings, to identify rare forms of dementia and to add specificity to the differential diagnosis of Alzheimer’s disease, dementia with Lewy bodies, and vascular dementia. These imaging techniques have also been used to show the extensive overlap in the underlying pathologies of dementias; Alzheimer’s disease, for example, is often associated with white-matter lesions on MRI and vascular dementia with temporal lobe atrophy on both CT and MRI. Functional MRI with dynamic susceptibility contrast provides information on blood flow, and is an indirect indicator of brain metabolism with the advantage of not requiring radioactive isotopes, yet it provides superior spatial resolution and better rates of dementia identification than MRI alone (90%). Functional imaging without the injection of paramagnetic contrast agents is also now possible, but requires considerable cooperation from the patient. Neuropsychological research has consistently shown that tests of delayed free recall, verbal fluency, and spatial organisation are sensitive to early neuropsychological degeneration. In combination with neuroimaging, these tests can be used to chart the precise locations of functions within the brain, monitor compensatory processes, and observe treatment effects. Presently however, functional imaging is largely confined to research studies and has not been integrated into standard clinical practice.

Another procedure that could advance diagnosis of dementias is serial registration (the mathematical comparison of images taken at different points in time), which might detect progressive preclinical hippocampal atrophy even before cognitive decline is detected by clinical examination. Presently, the principal use of this method is for the estimation of power calculations to detect drug effects in clinical trials.

Biochemical changes in the brain that are associated with dementia can now be detected by magnetic resonance spectroscopy. By contrast with post-mortem studies, this imaging technique offers a non-invasive method to follow disease progression. Detection of biochemical changes that occur before cognitive and behavioural changes, could eventually provide a method of screening for dementia before the onset of clinical signs.

Neuropsychiatric disorders in dementia
In terms of patients’ management, one of the most important developments in recent years has been the recognition of the role of psychiatric and behavioural disorders in dementia syndromes. Such disorders include affective disorder (depression, anxiety, euphoria), personality change, behavioural difficulties (agitation, apathy, irritability, disinhibition, aberrant motor behaviour), hallucinations, delusions, and eating disorders. Neuropsychiatric disorders, which occur in up to 90% of dementia patients, are one of the main causes of care-giver stress and patients’ admission to institutions. However, they provide important clues to the underlying pathophysiological processes of dementia, and are key determinants of differential diagnosis and prognosis. Depression is perhaps the most widely studied of these disorders, because of the difficulties of differential diagnosis between early dementia and depressive syndromes. It is now recognised that depression and dementia are not mutually exclusive; on the contrary, depression occurs in about 40–50% of cases. Some evidence suggests that depressive symptoms change in the course of the disease from a reactive syndrome, to loss of competence, and increasing psychomotor and vegetative signs attributable to deterioration of limbic-system structures. Apart from the distress caused by depressive symptoms, the co-occurrence of depression in dementia accelerates loss of autonomy, and treatment with antidepressants is now widely advocated. Preference is given to therapy by selective serotonin reuptake inhibitors (SSRIs) and related drugs that do not have a significant anticholinergic effect, which could accelerate cognitive loss. Similarly, in the treatment of psychotic symptoms in dementia some of the older antipsychotic medications have a substantial anticholinergic effect and should be avoided. For both depression and psychosis, however, non-pharmacological strategies, such as elimination of physical causes including pain and infection, environmental and behavioural management, and professional and non-professional carer training should be attempted first—if only because the risk
of harm to patients is lower than that associated with medication. The management of what has become known as the behavioural and psychological symptoms of dementia is receiving much-needed attention, and randomised controlled trials of pharmacological and non-pharmacological treatments are being done.

Patterns of neuropsychiatric disorder vary with the type of dementia syndrome (panel) Several scales developed for use in clinical research and drug trials, might also be useful in clinical practice. Most often used are the BEHAVE-AD, the Neuropsychiatric Inventory, the MOUSEPAD, and the CERAD behaviour rating scale for dementia. A detailed review of these scales has been published elsewhere.

**Care and caregivers**

Care strategies have developed in parallel with research into causes and management of Alzheimer’s disease. Perhaps the most important advance in this area is the recognition that caregiving can cause pathology; professional and lay carers of dementia patients have high rates of physical and mental disorder. Caregivers who live with the person they care for are more reluctant to admit the person into an institution, and more likely to be depressed than carers who live apart from their patient. Results from community studies have also shown high rates of abuse both of and by the dementia patient. These observations have not only led to the development of preventive health-care strategies for carers and availability of respite care, but also to a questioning of the long-held assumption that all elderly people with dementia are better off in the community. On the other hand, institutionalisation is not always the perfect solution to caregiver stress, often creating other difficulties such as guilt, exclusion from decision making and care, a financial burden, and difficulties in maintaining relationships.

An alternative approach has been to develop models of care that bring the institution closer to the community, involving family care-givers within the professional care setting, and to adapt the architecture of institutions to the needs of dementia patients—eg, the elimination of corridors. The move from community to institutional care is still, in most cases, poorly planned and often a response to a crisis rather than an organised transition. Behavioural disorder and functional loss, notably aggression and delirium, are more likely to occur in holiday periods than at other times of the year, and if the carer is a husband rather than a wife, and a child rather than a spouse. Lay and professional care givers should work as a team, allocate responsibilities for medical care and psychosocial intervention, and plan institutionalisation as a response to a predicted stage of the disorder rather than a reaction to a family crisis or caregiver burn-out.

**Conclusions**

Overall rates of dementia are much the same in developed countries, and incidence rises exponentially until the eighth decade of life. Advances in medical technology have prolonged survival at high ages, but have had little effect on disease incidence. Because dementia prevalence increases with age, this situation has led to a rapid increase in the proportion of dementia sufferers within the population. The causes of these disorders are complex. Workers in epidemiology have had to develop risk models in parallel with changing knowledge of biological risk factors. Dementias are now thought to be the end result of a complex interaction of genetic risks, biological changes attributable to several underlying associated and non-associated pathologies (including disorders which may have occurred in young adulthood), environmental trauma, hormonal changes, and effects of medication.

Potential targets for treatment include neurotransmitter function, Aβ production and deposition, and reduction of secondary risk factors such as arterial hypertension and hyponatraemia. Although there is no definitive effective treatment in view, cholinergic therapies have had mild short-term success in stabilising cognitive loss and, along with psychotropic drugs, reducing associated behavioural disorders. Treatment of depression also reduces the rate of loss of ability to do daily activities. Although such contributions are modest at the individual level, clinical intervention to prolong patients’ autonomy, even if only for a few months, will have a substantial effect on the public health burden of Alzheimer’s disease. High rates of morbidity in professional and family care-givers have led to the development of respite services, and better adaptations of institutional care to the needs of dementia patients and their families.

Many promising research avenues are yet to be explored: properly powered genetic studies, neuroimaging and other biomarker techniques for diagnosis and disease monitoring, targeting of other non-cholinergic neurotransmitters, and wider assessment of treatments for behavioural and psychological symptoms of dementia, and strategies to support carers. Improved diagnosis, wider recognition, and the prospects for disease modification make the future management of Alzheimer’s disease an exciting specialty.

**Conflict of interest statement**

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