

Alzheimer Disease

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Alzheimer disease is a major public health concern in the elderly. In the United States, it is the fourth leading cause of death and is the most common cause of dementia. Although some cases of Alzheimer disease are caused by genetic mutations, most cases are probably due to a number of genetic and environmental factors. There is currently no cure for this serious and debilitating disorder.

Introduction

As the population ages, Alzheimer disease is becoming more of a medical, social and public health concern. It is a dementing disorder that causes severe and permanent loss of intellectual function. Patients with Alzheimer disease begin having forgetfulness, then progress to having irreversible loss of memory (including the memory of their own families) and other previously well-learned skills. Within a few years, some patients may be totally incapable of even the most basic self-care, imposing a great burden on their families and communities.

Dementia: What Is It?

Dementia refers to a progressive deterioration of thinking abilities severe enough to interfere with social, occupational and intellectual functions. In the United States, dementia is a significant public health problem in the elderly. Dementia is caused by an underlying brain disease, and is not a normal consequence of ageing. Most people experience some mild memory loss associated with ageing which does not interfere with daily function and is not the same as dementia.

Physicians diagnose dementia by performing a careful medical, neurological and neuropsychological examination. They first exclude medical conditions that can cause delirium. Delirium is a state of confusion that often arises abruptly and may accompany such disorders as infections, impaired nutrition, head trauma or other potentially manageable medical or neurological diseases. Delirium is distinguished from dementia because delirious patients have impaired attention and alertness which contributes to the impaired thinking. Demented patients, by contrast, are alert and aware, except at the very late stages of the disease.

Dementia is typically documented by poorer than expected performance on neuropsychological tests which assess memory, general knowledge, language, abstract reasoning and the ability to perform certain tasks of

Introductory article

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minimal skill, including dressing and simple drawing tasks.

Figure 1 shows an example of a clock drawn by individuals with dementia who are given the following instructions: 'Please draw a clock. Put the hours on it and set the time at 2:45'.

Differential Diagnosis of Late-onset Dementia

The term late-onset dementia refers to intellectual deterioration which occurs after the age of 65 years. This chapter discusses Alzheimer disease, the most common cause of dementia, in detail. However, there are other diseases that cause dementia and most of these become more common as people age. Hypothyroidism and vitamin

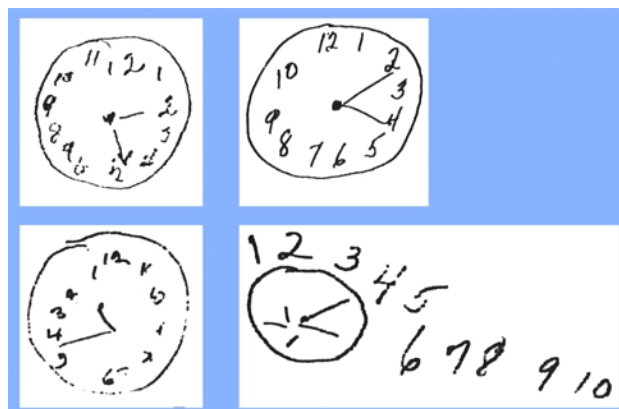


Figure 1 Clock drawings from four patients with varying severity of Alzheimer disease, who were asked as part of a neuropsychological test: 'Please draw a clock. Put the hours on it and set the time at 2:45'.

B₁₂ deficiency are two treatable medical conditions which may cause progressive memory impairment and, if untreated, dementia. Systemic diseases such as cancer may also cause symptoms of cognitive decline, mimicking dementia, or may, by metastatic spread to the brain, cause dementia. The elderly are at greater risk for a number of rare degenerative neurological disorders, which cause dementia and other progressive neurological symptoms; these diseases include Parkinson disease, Huntington disease and progressive supranuclear palsy. Certain conditions, for example brain tumours or repeated strokes, cause dementia by damaging the substance of the brain, and others such as hydrocephalus or subdural haematoma can do the same by causing increased pressure on the brain.

Many other conditions may be confused with dementia, and patients may fear that they have an incurable neurodegenerative disease, when they really may have a treatable condition associated with forgetfulness and inattention. As mentioned above, hypothyroidism and vitamin B₁₂ deficiency are two such readily treatable medical disorders. Depression and other psychiatric conditions can cause frequent forgetfulness and mimic dementia. Certain medications may exacerbate inattention and cause memory lapses. Finally, there is the very common age-associated memory impairment, which represents mild memory loss in an elderly person unassociated with other cognitive impairment or other diseases.

Although the list of diseases that cause or mimic dementia is long, by far the most common cause of dementia is Alzheimer disease. The typical patient with Alzheimer disease may otherwise be in good health, but presents with decline in memory, especially for recent events, that progresses through subsequent years to include loss of recall of much past and recent history. Early on, there may be language difficulties, such as impaired naming and word-finding, which later progress to incomprehensible though fluent-sounding speech. Later, spontaneous speech is lost and patients become mute. Likewise, the ability to perform other skilled activities deteriorates until the patient requires help to perform normal daily tasks such as bathing, dressing and using the bathroom.

Alzheimer disease itself can be definitively diagnosed only by examining the brain for the characteristic pathology. However, the clinical diagnosis can be made highly accurate if the following criteria are observed:

1. Documentation of dementia by clinical examination, the use of standard dementia screening tools, and neuropsychological testing.
2. Deficits in two or more areas of cognition.
3. Progressive worsening of memory and other cognitive functions.
4. No disturbance of consciousness.
5. Onset between 40–90 years of age.

6. Absence of systemic disorders or other brain diseases that by themselves could account for the progressive deficits in memory and cognition.

Types of Alzheimer Disease: Early-onset Familial and Late-onset Sporadic

Alzheimer disease is generally diagnosed after the age of 65 years, when it is referred to as late-onset Alzheimer disease. The condition affects 5% of the population aged over 65 years and more than 20% of the population over 85 years.

Only 10% of all persons diagnosed with Alzheimer disease develop symptoms before the age of 65 years. They are said to have early-onset Alzheimer disease, and approximately 10% of these early-onset cases have a familial form of the condition, which is transmitted as an autosomal dominant trait. Mutations in three genes – amyloid precursor protein, presenilin-1 and presenilin-2 – cause the majority of cases of familial Alzheimer disease. However, the vast majority of cases are not clearly transmitted as inherited traits. Most early- and late-onset cases generally occur sporadically or with familial clustering that has no clear mendelian inheritance pattern.

Other than the difference in the age of onset, early-onset familial Alzheimer disease and the late-onset sporadic type are difficult to distinguish clinically and pathologically. Therefore, the appearance of Alzheimer disease may represent a common pathway of neurodegeneration, which can be initiated by one of several distinct factors, including single gene mutations or a combination of genetic and environmental effects.

Pathophysiology: Senile Plaques and Neurofibrillary Tangles

A definite diagnosis of Alzheimer disease can be made only by autopsy examination of a patient's brain. This neuropathological evaluation reveals gross cerebral atrophy, signifying loss of neurons. The diagnostic lesions are found on microscopic evaluation of the most affected areas of the brain, which reveal the presence of large numbers of extracellular neuritic plaques and intracellular neurofibrillary tangles, which are shown in **Figure 2**. Plaques and tangles are found predominantly in the frontal and temporal lobes, including the hippocampus. In more advanced cases, the pathology extends to other regions of the cortex, including the parietal and occipital lobes.

Plaques are insoluble extracellular deposits composed mainly of a 40–43 amino acid peptide called β -amyloid. β -Amyloid derives from a larger protein, β -amyloid

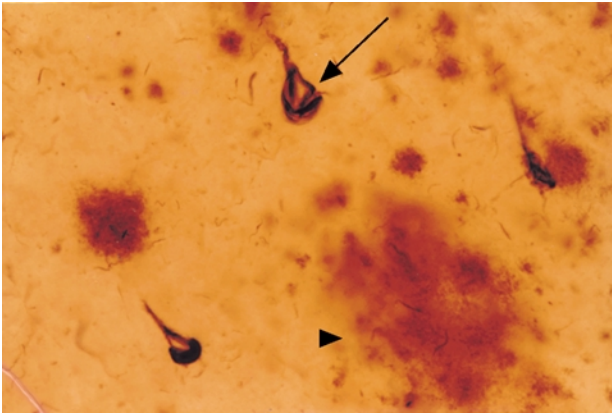


Figure 2 Light micrograph of Alzheimer disease neuropathology. Section from the cortex of a patient with Alzheimer disease showing tangles and plaques. The intraneuronal tangle (arrow) is stained dark brown with an antibody that specifically targets paired helical filaments. These filaments are also seen as the dense brown material (dystrophic processes) embedded in the extracellular plaque (arrowhead). The lighter reddish staining of the plaque is from another antibody directed specifically against β -amyloid.

precursor protein (APP) by proteolytic processing. Plaques can be described as diffuse or classical. Diffuse plaques are amorphous aggregates of β -amyloid which are typically not associated with dystrophic neurons and abnormal neurites. Classical neuritic plaques contain densely aggregated β -amyloid and are generally associated with degeneration and neuronal cell loss. Because soluble β -amyloid aggregates spontaneously into fibrils that are indistinguishable from those found *in vivo*, it is thought that plaques result from raised β -amyloid levels. Patients with Alzheimer disease also have an increased coincidence of cerebrovascular disease, possibly related to deposition of amyloid within the cerebral vasculature, which occurs in most cases.

Tangles are intracellular deposits of the microtubule-associated protein tau (τ) found within dystrophic neurons. Tau is normally found in great abundance in neurons, where it binds tubulin monomers together to form stable polymers that are presumed to be essential in cellular transport and axonal growth. In Alzheimer disease tangles, the tau becomes hyperphosphorylated and this leads to less efficient binding to microtubules. The unbound tau then spontaneously aggregates into insoluble paired-helical filaments, which are seen as deposits in the neurons.

While plaques and tangles do occur in normal ageing brains, they are more numerous and more widely distributed in brains of patients with Alzheimer disease. The determination of whether plaques and tangles cause neuronal degeneration or are simply markers of it is essential for designing effective treatment strategies.

Cortical and Hippocampal Cell and Afferent Loss

Although the role of plaques and tangles in Alzheimer disease is still not known precisely, they are found in greatest abundance in the areas of the brain most affected in Alzheimer disease, namely the hippocampus, parieto-occipital cortex, temporal cortex and frontal cortex. The hippocampi are small sea-horse-shaped structures nestled in the temporal lobes, which play a central role in establishing and maintaining memory. The hippocampi show the earliest changes in Alzheimer disease and have the greatest concentration of plaques and tangles. This finding corresponds to the early and progressive symptoms of memory loss in patients with Alzheimer disease. The development of plaques and tangles in cortical areas correspond to the other clinical findings seen in Alzheimer disease, including abnormal visuospatial orientation, difficulty with skilled tasks and language abnormalities.

The progressive loss of neurons and neuronal interconnections, known as synapses, is associated with decreased concentrations of neurotransmitters, the chemical signals that are sent between neurons. One such neurotransmitter is acetylcholine, the decline of which is hypothesized to be one of the factors responsible for the intellectual deterioration seen in both normal ageing and in Alzheimer disease. There is a dramatic decrease in the levels of choline acetyltransferase, the enzyme needed for the synthesis of acetylcholine, in Alzheimer disease brains as compared with controls. For this reason, there has been much interest in developing drugs that increase the level of acetylcholine in the brain as a treatment for Alzheimer disease.

Genetics of Alzheimer Disease

There are three genes known to be important in the aetiology of the early-onset familial condition: the *APP* on chromosome 21, the presenilin-1 (*PS1*) gene on chromosome 14, and the presenilin-2 (*PS2*) gene on chromosome 1. Apolipoprotein E on chromosome 19 is an important risk factor for sporadic Alzheimer disease.

APP mutations

As noted above, the main protein component of the extracellular plaque is β -amyloid. Soluble β -amyloid is a normal constituent of human brain generated by cleavage of the larger APP by two enzymes called β -secretase and γ -secretase (**Figure 3**). An alternative proteolytic pathway involving α -secretase prevents A β formation. β -Amyloid in the brain is heterogeneous, consisting of a series of peptides varying in length from 39 to 43 amino acids. β -Amyloid of size 40 amino acids is referred to as A β_{40} , and is

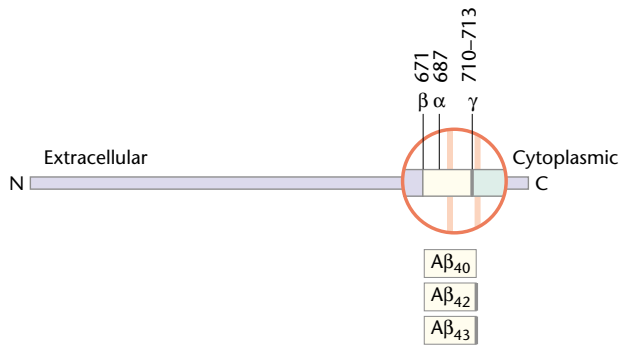


Figure 3 Schematic diagram of β -amyloid precursor protein (APP). The secretase cleavage sites are shown. Cleavages by β - and γ -secretases release $A\beta$ peptides. $A\beta_{42-43}$ are the major constituents in amyloid plaques.

normally the most abundant form. $A\beta_{42}$ and $A\beta_{43}$ refer to the 42 and 43 amino acid forms, and the proportions of these two forms increase in the amyloid plaques of Alzheimer disease brains. Mutations in the *APP* that are known to cause some forms of autosomal dominant Alzheimer disease appear to alter normal APP processing by causing increased production of $A\beta_{42}$ and $A\beta_{43}$.

Another type of APP abnormality occurs in patients with Down syndrome, a condition caused by an extra copy of part or all of chromosome 21. Patients with Down syndrome are intellectually impaired and have a number of developmental abnormalities noted early in life. In mid-adulthood, many go on to develop dementia with widespread deposition of β -amyloid in plaques and tangles similar to those seen in Alzheimer disease.

Presenilin mutations

The most common known cause of familial Alzheimer disease is mutations in the presenilin genes. The presenilin proteins are transmembrane proteins that are localized primarily in the endoplasmic reticulum and the Golgi apparatus. They are widely expressed but their functions are unknown. A gene similar to the presenilins has been isolated in the nematode *Caenorhabditis elegans*. Mutations in this gene cause a phenotype, linked to defects in the Notch signalling pathway, which is important for cell-fate decisions during development. Mice lacking PS1 also show severe defects that resemble a phenotype in which Notch is missing, supporting the role of PS1 in this signalling pathway. So far, most of the mutations found to cause familial Alzheimer disease have been in *PS1*, with only two mutations found in *PS2*, which is 67% homologous to *PS1*. Through an unknown mechanism, all the mutations increase the amount of $A\beta_{42}$ and $A\beta_{43}$ produced, which accelerates β -amyloid aggregation and amyloid plaque formation.

Apolipoprotein E $\epsilon 4$ allele polymorphism

The genes whose mutations cause familial Alzheimer disease are among the few known 'causes' of Alzheimer disease, but they are responsible for less than 1% of the total number of cases. Of greater public health significance has been the finding that the $\epsilon 4$ allele of the apolipoprotein E gene (ApoE- $\epsilon 4$) occurs in sporadic cases of Alzheimer disease with increased frequency compared with controls. Apo E is a major serum lipoprotein involved in cholesterol metabolism. There are three naturally occurring alleles of the ApoE gene, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, which differ from one another by a single codon. While the $\epsilon 4$ allele is overrepresented among patients with Alzheimer disease compared with control populations, the $\epsilon 2$ allele frequency is lower in patients with Alzheimer disease than in controls, implying that this allele may be protective against developing the condition. The ApoE- $\epsilon 4$ allele shows a dose-dependent increase in risk for Alzheimer disease, apparently mediated through a decrease in the age of onset, such that individuals with two copies of the $\epsilon 4$ allele have an earlier onset than those with one copy, who have an earlier onset than individuals with no $\epsilon 4$ allele. The molecular mechanism by which the ApoE genotype is involved in Alzheimer disease pathogenesis is unclear, but patients with ApoE- $\epsilon 4$ show a significant, dose-dependent increase in the density of β -amyloid deposits.

Aetiology of Alzheimer Disease

For the majority of patients with Alzheimer disease the aetiology is unknown, but is likely to represent a combination of genetic and environmental factors. Certainly a major risk factor is age, with the prevalence approximately doubling every 5 years between the ages of 65 and 85 years. Other risk factors, which have been described above, include Down syndrome (trisomy 21), inheriting the $\epsilon 4$ allele of the ApoE, or having a first-degree relative with Alzheimer disease. The inheritance of ApoE- $\epsilon 4$ seems to promote earlier onset of the disease. It also may modify nongenetic risk factors, such as head injury, which becomes a risk factor for Alzheimer disease only in people with the $\epsilon 4$ genotype. The ApoE- $\epsilon 4$ allele cannot account for all sporadic cases of Alzheimer disease, about 50% of patients with Alzheimer disease develop the disease in the absence of this allele.

It is likely that other genes will be identified that modify the development of Alzheimer disease, and that an individual's likelihood of developing the condition will depend on the interaction between inheritance of specific alleles of particular genes and nongenetic exposures.

In a small minority of cases in which the disease is familial and inherited as an autosomal dominant trait, a gene defect has been identified as the cause of the disease

(see Genetics of Alzheimer Disease, above). All gene defects identified so far lead to enhanced production, increased aggregation or perhaps decreased clearance of β -amyloid peptides; this also seems to be true for patients with Alzheimer disease who have inherited the ApoE- ϵ 4 genotype. The gradual buildup of β -amyloid in brain tissue leads to local microglial and astrocytic activation, and to inflammatory neuronal–neuritic changes that characterize Alzheimer disease brain tissue.

There appears to be a connection between cerebrovascular disease and Alzheimer disease. Affected patients often also have cerebral amyloid angiopathy (CAA), which is characterized by deposits of β -amyloid in and around cerebral and meningeal blood vessels. These patients have increased risk of spontaneous cerebral haemorrhage, as well as haemorrhage resulting from trauma and brain surgery. Mutations of *APP* can lead to CAA or Alzheimer disease, or a mixed phenotype.

Further support for a connection between cardiovascular health and Alzheimer disease comes from studies of the ApoE gene. ApoE- ϵ 4 is not only a risk factor for Alzheimer disease, CAA and dementia following stroke, but is also associated with high levels of total serum cholesterol, myocardial infarction and atherosclerosis.

The lack of a small animal model has hindered the development of treatments or preventive strategies for Alzheimer disease. Advances in genetic studies have led to the development of transgenic mice which express mutant forms of human *APP* and presenilin. These mice develop age-dependent β -amyloid deposition, but do not show neuronal loss or tangles. When transgenic mice that overexpress *APP* are crossed with mice that lack ApoE, their offspring show far less β -amyloid deposition than when ApoE is present, suggesting that ApoE may influence aggregation and/or clearance of β -amyloid peptides.

The data from mouse models would indicate that, in addition to abnormal metabolism of β -amyloid, other factors are necessary for the development of Alzheimer disease. The pathology of Alzheimer disease includes inflammatory changes (not seen in the mouse transgenic models) and reactive gliosis by microglia. One hypothesis is that the plaque secretes factors or signals that induce the normally quiescent microglia to interact with the plaque. The activated microglia then produce a variety of neurotoxic substances, which lead to neuronal injury and death.

Treatment and Prevention

The most important class of drugs used in the specific treatment of Alzheimer disease was developed for the ability to increase acetylcholine levels in the central nervous system. Not only are acetylcholine levels reduced in Alzheimer disease brains, but memory and cognitive

impairment can be induced in healthy young persons and animals whose cholinergic transmission systems are pharmacologically blocked. There are now two classes of compounds that can increase brain acetylcholine levels: (1) acetylcholinesterase inhibitors (ACEIs), which increase synaptic concentrations of acetylcholine; and (2) muscarinic agonists, which mimic acetylcholine by directly stimulating the muscarinic acetylcholine receptor.

ACEIs have been shown to be of modest clinical benefit in Alzheimer disease, and some ACEIs have been commercially available to treat the condition for several years. Since acetylcholinesterase breaks down acetylcholine, ACEIs act to increase the concentration of acetylcholine in the synapse. This provides more acetylcholine to interact with the brain's cholinergic receptors, the most important of which are thought to be the muscarinic cholinergic receptors. These receptors, when activated, have effects on learning, memory and behaviour; they may also be involved in the processing of *APP*. While ACEIs do modestly decrease the rate of cognitive decline in patients with Alzheimer disease, the dementia remains progressive and the benefits of these medications, while measurable, are small.

The muscarinic agonists currently being developed are specific for the muscarinic M1 receptor subtype. The M1 receptors are localized in the cortex and hippocampus, whereas other muscarinic receptors are also found in smooth muscle and glandular tissue. The latter may be responsible for the uncomfortable side effects – namely, salivation, sweating, nausea and vomiting – seen when trying to manipulate the cholinergic system pharmacologically. The research has been promising, but so far, no M1 receptor agonist is available commercially.

Epidemiological studies have found a decreased risk for Alzheimer disease in women who have taken oestrogen replacement therapy. Oestrogen has a number of well documented effects on the cardiovascular system, including protection against atherosclerosis and vascular injury. Oestrogen may also interact with ApoE to reduce the development of atherosclerotic lesions in the cerebral blood vessels, and it may be this effect that lowers the risk of Alzheimer disease. Oestrogen has other beneficial effects, which include increasing levels of choline acetyltransferase, the enzyme needed to synthesize acetylcholine, in the basal forebrain, and promoting the growth of axons and dendrites, the projections that nerve cells send out to communicate with one another, in injured neurons.

Several epidemiological studies have demonstrated that chronic use of nonsteroidal antiinflammatory drugs (NSAIDs) reduces the risk of Alzheimer disease, supporting the hypothesis that development of the condition involves inflammation. Use of NSAIDs could delay the onset of Alzheimer disease by 5–7 years. Studies also indicate that patients with Alzheimer disease taking these drugs for other purposes have slower progression of the dementia.

Other studies have been done using vitamin E or other antioxidants, which can protect the neurons against free radical damage. Experiments in cell culture have shown that β -amyloid neurotoxicity may be due to its ability to increase production of hydrogen peroxide in nerve cells. Hydrogen peroxide is a chemical that releases hydroxyl radicals, which can in turn damage cell membrane lipids and other cell components.

Other treatment avenues that are being explored include:

1. reducing calcium toxicity with calcium channel blockers, which protect neurons from calcium ion-induced injury by limiting calcium ion entry;
2. using cholesterol-lowering drugs to lower the brain concentrations of ApoE- ϵ 4;
3. reducing the chemical changes in the tau protein;
4. preventing the development of plaques, neuritic dystrophy and gliosis by early immunization with A β ₄₂; and
5. preventing the formation of β -amyloid by inhibiting the secretases that release it from APP or by preventing β -amyloid from aggregating into its toxic form.

Although some of the proposed treatments described above, such as oestrogen replacement and chronic NSAID use, do seem to lower the risk for developing Alzheimer disease in certain populations, it is unclear how effective they might be at preventing the condition. Prevention is an effective strategy in diseases where the risk factors or aetiology are understood and modifiable (e.g. cessation of smoking to prevent lung cancer or vaccines to prevent childhood illness). Unfortunately, the best known aetiologies or risk factors for Alzheimer disease are genetic mutations, in the case of the familial condition, or the ApoE- ϵ 4 allele in the case of sporadic Alzheimer disease. While these are not readily modifiable, they may suggest certain populations at highest risk for Alzheimer disease in whom more aggressive intervention may be worthwhile.

Summary

Alzheimer disease is the single most common cause of late-life dementia in the industrialized world. The prevalence of the disorder rises with age after the age of 65 years. While some genetic mutations are known to cause a few cases of Alzheimer disease, the aetiology for the vast majority of

cases is unknown. It is likely that Alzheimer disease represents the final degenerative pathway initiated by a number of genetic and environmental factors. So far, the most important risk factor seems to be the ApoE- ϵ 4 allele, which occurs disproportionately in patients with Alzheimer disease compared with the healthy elderly population. Treatment of Alzheimer disease slows the cognitive decline to a modest degree, but severe dementia eventually occurs. As yet, there is no treatment that can reverse the effects of Alzheimer disease, and there is no effective prevention.

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Further Reading

- Hutton M and Hardy J (1997) The presenilins and Alzheimer's disease. *Human Molecular Genetics* **6**: 1639–1646
- Lendon CL, Ashall F and Goate AM (1997) Exploring the etiology of Alzheimer disease using molecular genetics. *Journal of the American Medical Association* **277**: 825–831.
- Ray JW, Ashall F and Goate AM (1998) Molecular pathogenesis of sporadic and familial forms of Alzheimer's disease. *Molecular Medicine Today* **April**: 151–157.
- Selkoe DJ (1998) The cell biology of β -amyloid precursor protein and presenilin in Alzheimer's disease. *Trends in Cell Biology* **8**: 447–453.
- Morrison-Bogorad M, Weiner FM, Rosenberg RN, Bigio E and White CL III (1997) Alzheimer's disease. In: Rosenberg RN, Prusiner SB, DiMauro S and Barchi RL (eds) *The Molecular and Genetic Basis of Neurological Disease*, pp. 581–600. Boston: Butterworth–Heinemann.
- Roses AD (1997) Apolipoprotein E and Alzheimer's disease. In: Rosenberg RN, Prusiner SB, DiMauro, S and Barchi RL (eds) *The Molecular and Genetic Basis of Neurological Disease*, pp. 1019–1035. Boston: Butterworth–Heinemann.
- Levy-Lahad E, Tsuang D and Bird TD (1998) Recent advances in the genetics of Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology* **11**: 42–54.
- Anderton BH (1999) Alzheimer's disease: clues from flies and worms. *Current Biology* **9**: 106–109.
- Marx J (1996) Searching for drugs that combat Alzheimer's. *Science* **273**: 50–53.