Science, medicine, and the future Alzheimer's disease

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There is a noticeable air of optimism in the research community studying Alzheimer's disease. This because the molecular basis of Alzheimer's disease and other neurodegenerative conditions, such as Parkinson's and Huntington's diseases, is rapidly being elucidated. From these molecular insights, it is likely that effective therapeutic strategies will be developed within the next 10 years. Future treatment will probably be based on combination therapies—such as neurotransmitter replacement combined with a drug to protect against the toxic effect of A β amyloid—tailored to the genetic profile of an individual. Assuming proved efficacy and safety, these forms of treatment are likely to be as widespread and acceptable as cholesterol lowering treatment is today.

In the past few years there has been an avalanche of knowledge surrounding the genesis of A β amyloid plaques, one of the principal pathological hallmarks of this disease (see fig 1). In the absence of a serious candidate for the pathway leading to the neurofibrillary tangle, the other major pathological lesion in Alzheimer's disease (fig 1), the focus will probably remain on amyloid plaques. Strong genetic risk factors have been identified for Alzheimer's disease, all of which interact directly or indirectly with the A β amyloid pathway. Undoubtedly, other genetic factors remain to be discovered, some of which might open the door to the neurofibrillary tangle. More importantly, the major environmental risk factors for Alzheimer's disease remain elusive. This is not surprising, given the relatively few analytical epidemiological studies that have been conducted and the difficulty of case ascertainment, particularly in the early stages of the disease.

We review briefly where the research is heading and give some predictions on where our concepts might lie a decade from now (for more details see recent reviews¹⁻³).

Central pathway of disease causation

Many lines of evidence confirm that the generation of A β amyloid from the amyloid precursor protein is the central pathway in Alzheimer's disease (see fig 2). The clinching evidence has come from the recognition that rare genetic mutations in the gene encoding amyloid precursor protein actually cause Alzheimer's disease at an early age (onset before 65 years).

Possible futures

Genotype screening, analysis, and counselling

Presymptomatic diagnosis

Rational preventive treatment—drug based or gene based

Advice on preventive measures—changes to lifestyle to avoid known environmental risk factor(s)

Drugs targeting the amyloidogenic pathway to modify the course of the disease

Amyloid precursor protein is a normal transmembrane glycoprotein that is widely expressed in the body, but particularly in brain and platelets. Its function remains uncertain: mice lacking the protein seem largely normal but have subtle defects in synaptic function. Expression of the gene for the protein is closely regulated and responds quickly to a wide variety of cellular stresses and exogenous factors (including trauma, oestrogens, and certain metal ions). Generated in the endoplasmic reticulum, amyloid precursor protein is sent to the Golgi apparatus for glycation before export to the cell surface.

At critical points of its biogenesis, amyloid precursor protein is subjected to enzymatic proteolytic cleavages, which in concert generate the A β peptides (fig 2). These enzymes, termed secretases, release the amyloid precursor protein from the cell membrane and thereby affect the proportion of the protein that remains on the cell surface or is released into the extracellular milieu. The A β peptides encompass part of the hydrophobic transmembrane domain. The exact cleavage sites of the γ -secretases are important, since the length of the hydrophobic tail of the A β peptide may be a crucial factor determining its aggregation and toxicity. Thus, the shorter A β_{40} is the species most often identified in non-neuronal cells and has less tendency to aggregate than the longer A β_{42} : it is this longer A β_{42} that is found at the centre of amyloid plaques. Neuronal cells have a propensity to make the longer forms, probably in a different cellular compartment

(the endoplasmic reticulum). How either form is released from the cell remains uncertain.

Once released from the cell, A β peptides aggregate into amyloid fibrils. The rates of deposition and clearance of A β from the brain may be critical determinants in establishing disease. The exact mechanisms by which A β exerts its toxicity or adverse "gain of function" is under intense scrutiny.

Other chronic degenerative diseases of aging nervous system

Recent elucidation of a variety of gene mutations causing diverse chronic neurodegenerative diseases point to a common mechanism—the toxic gain of function of small, relatively insoluble, protein polymers (see box). If further research confirms and extends this line of reasoning, Alzheimer's disease may eventually be seen as only one example of a process in which an abnormally shaped molecule accumulates in the brain and causes neuronal damage. In that case, a treatment developed for the toxic effect of the polyglutamine expression of the abnormal gene in Huntington's disease might be relevant for one or all of the other neurodegenerative diseases.

Genetic causes and risk factors

The discovery of the presenilin family of genes has been a major breakthrough for research.⁴ Together with mutations in amyloid precursor protein, mutations in these presenilin genes also cause early onset of Alzheimer's disease and probably act directly through the amyloidogenic pathway. We have now identified about half of all the causative genes (responsible for possibly 10-20% of all cases of Alzheimer's disease). Over the next decade, it is highly likely that the remaining genes will be discovered, particularly in view of the rapid progress in mapping and sequencing the human genome.

In contrast with the causative genetic mutations, genetic risk factors are emerging as important contributors to the occurrence of sporadic Alzheimer's disease (responsible for 80-90% of all cases). The first to be identified, the ApoE gene on chromosome 19, has provided clues to the likely size of effect of these "public" genetic polymorphisms in a complex disease. Thus, inheritance of the ApoE- ϵ 4 allele may increase the risk for Alzheimer's disease by up to eightfold. In the near future other genetic loci that act as susceptibility factors for Alzheimer's disease will undoubtedly be discovered. For example, there is much current interest in loci on chromosome 12. These discoveries will bring forward the emerging field of pharmacogenetics, in which treatments and preventive strategies will be tailored to an individual's genetic profile.

Environmental causes and risk factors

Environmental factors might be expected to have a role in causing Alzheimer's disease, in common with all multifactorial complex diseases, but, surprisingly, none has yet been convincingly identified. Estimates of relative risk indicate that factors such as low education, head trauma, smoking, concomitant vascular disease, diabetes, and the menopause have modest or inconsequential effects. Is there a major environmental risk

Neurodegenerative diseases associated with abnormal protein conformations (toxic gain of function)

Disease	Gene product
• Alzheimer's disease	Amyloid precursor protein and A β amyloid
• Creutzfeldt-Jakob disease	Prion protein
• Amyotrophic lateral sclerosis	Superoxide dismutase
• Parkinson's disease	α -synuclein
• Huntington's disease	Huntingtin
• Machado-Joseph disease	Ataxin-3

factor still waiting to be discovered by some enterprising epidemiologist? Could some subtle factor in the Western diet or lifestyle be uncovered through a more thorough understanding of the amyloidogenic pathway? For example, we know that metal ions (such as copper and zinc) interact adversely with amyloid precursor protein and A β , and evidence is emerging that oxidative stress mediated by hydroxyl radicals could underlie the basis of A β toxicity. These clues may provide the impetus for future epidemiological studies.

Experimental models

A major impediment to the development of rational treatments has been the lack of an authentic and practical small animal model of Alzheimer's disease. Fortunately, this seems to have been solved by the development of various transgenic mouse models, which are progressively looking more like the human disease. The latest are based on the overexpression of amyloid precursor protein combined with the effects of the causative human mutations.⁵ The next step may be to modulate the strain background of the mice or to

Fig 1 The central pathway leading to Alzheimer's disease involves the processing of amyloid precursor protein into A β amyloid, which accumulates as amyloid plaques or perivascular amyloid. Concomitantly, degeneration occurs in neurons and their processes, leading to neurofibrillary tangles. (Images are from Spielmeier's *Histopathology of the Nervous System*, 1922.) Mutations in the gene encoding amyloid precursor protein can cause Alzheimer's disease, as do mutations in the presenilin genes. Inheritance of particular polymorphisms in genes such as ApoE also can increase susceptibility for Alzheimer's disease. Major environmental risk factors for Alzheimer's disease remain to be determined

Fig 2 (a) Cleavage of amyloid precursor protein (APP) by enzymes (secretases) release the Aβ amyloidogenic fragment. (b) The critical region of amyloid precursor protein shown schematically in the one letter amino acid code. The secretases act at three principal sites (α, β, and γ). Mutations in the gene for amyloid precursor protein at these sites can adversely affect the action of secretases: mutations towards the NH₂ terminus increase the absolute rate of β-secretion, while mutations near the COOH terminus affect the ratio of Aβ₄₂ to Aβ₄₀. The Aβ₄₂ forms are more damaging for nerve cells

introduce another transgene to replicate the full human phenotype. Progress in this area has been so rapid that there is every reason to believe that an effective mouse model will soon be available.

Clinical trials and future therapeutics

In the past decade, much has been learned about the conduct of clinical trials by which the efficacy of any proposed treatment for Alzheimer's disease can be assessed. The licensing of compounds such as tacrine, donepezil, and rivastigmin have set standards by which all future drugs will be judged. There are currently four drugs awaiting approval and more than 16 drugs undergoing phase III clinical evaluation. Most are directed at the cholinergic system. Drugs specifically

Therapeutic targets in the amyloidogenic pathway

- Inhibit Aβ forming enzymes
- Redirect processing of amyloid precursor protein away from Aβ₄₂
- Inhibit aggregation or promote dissolution of Aβ
- Ameliorate toxicity of Aβ
- Suppress reactive responses to Aβ toxicity

targeting the amyloidogenic pathway (see box) are only now beginning to emerge in a preclinical setting.

Looking ahead to the next decade, it is likely that a comprehensive package of genotypic analysis, presymptomatic diagnosis, and advice on preventive measures will be advocated (see box), with the use of a combination of drugs that effectively modify the course of the disease. Perhaps it is too much to expect any form of curative treatment by the year 2008, but the underlying concepts and principles for preventing the amyloidogenic processes from damaging neurons is straightforward and eminently amenable to intervention. Current estimates of the economic and social costs of Alzheimer's disease vary widely within and between countries, but all agree on the immense size of the problem and that it will increase dramatically over the next decade. The cost effectiveness of any preventive treatment is potentially enormous. In contrast with the small effect of today's symptomatic treatments,⁶ future strategies may alleviate a burden that threatens most families; up to 25% of a family's annual income is required to care for a member with Alzheimer's disease.⁷ As the average duration of the illness is 10 years, it is relatively easy to derive a rough estimate of the economic impact of the disease. Since a large proportion of the population is at risk of developing Alzheimer's disease (possibly over half), an effective drug based preventive treatment would justify universal screening (probably beginning at ages 40-50 years, when amyloid plaques are starting to appear in the temporal cortex).

Managing Alzheimer's disease in the year 2008

- Genotype screening, analysis, and counselling
- Presymptomatic diagnosis
- Rational preventive treatment—drug based or gene based
- Changes to lifestyle—avoiding the environmental risk factor(s)

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One hundred years ago

The doctor as a journalistic attraction

The "medical column" is put forward as an attraction by various newspapers in this country, but not even the most enterprising of our journalistic impresarios has yet as far as we know offered the services of a real live doctor to his subscribers. It is announced that a well-known Paris newspaper has adopted this means of extending its circulation. It has engaged a doctor of medicine at a

salary of £480 a year to give gratuitous advice at the office of the paper to all the purchasers of an illustrated weekly supplement which it publishes. Many years ago a firm of cheap tailors in London used to boast that they kept a poet; is the time coming when daily newspapers will advertise the fact that "we keep a doctor?" (*BMJ* 1898;i:1283)