Alzheimer's disease

Alzheimer's disease robs millions of older people of their memories and independence. In the last few years, medicines have helped improve the lives of patients. Further advances could help keep patients out of nursing homes and make life easier for them and their families.

What is Alzheimer's?

Alzheimer's is the commonest cause of dementia, a group of progressive conditions which involve especially short-term memory loss, poor concentration, poor sense of time and space, difficulty in finding words or understanding other people, difficulty in perceiving and interpreting surroundings, mood changes and emotional upsets. As the condition worsens, the individual may get lost, become unable to carry out simple everyday tasks, or engage in inappropriate behaviour. Ultimately, personality is lost and dependency results. Alzheimer's disease accounts for 55 per cent of all cases of dementia.

Alzheimer's disease is caused by the synthesis and deposition of a naturally occurring peptide, beta-amyloid, which is produced from amyloid precursor protein (APP). If beta-amyloid is not cleared from the brain, it groups into larger molecules that are toxic to nerve cells. Eventually these macromolecules form fibrils and then the insoluble plaques that are characteristic of Alzheimer's.

Diagnosis of Alzheimer's is based on the exclusion of other causes of dementia and on medical history. Computed Tomography (CT) or Nuclear Magnetic Resonance (NMR) Imaging brain scans show tissue loss over time in specific areas, especially the hippocampus of the medial temporal lobe, and, in advanced cases, brain shrinkage. Conclusive diagnosis is only possible after death, when microscopic examination shows telltale protein deposits inside (neurofibrillary tangles) and outside (senile plaques) brain cells.

Who does Alzheimer's affect?

In Europe, dementia affects as many as five per cent of people over 65, rising to a third by people in their late 80s. The ageing of the population means that the number of people affected by Alzheimer's is likely to increase significantly, placing an increasing and costly burden on families and all parts of the health system. However, Alzheimer's is not merely a natural consequence of ageing. Apart from genetic predisposition, long-term risk factors for acquiring cardiovascular diseases are also considered to be risk factors for getting Alzheimer's.

A world-wide survey carried out in 2005 by Alzheimer's Disease International came to the conclusion that 24.3 million people had dementia, with 4.6 million new cases of dementia every year. The epidemiologists' forecast expected that the number of people affected would double every 20 years to some 81 million by 2040. The group noted that most people with dementia live in developing countries (60 per cent in 2001, rising to 71 per cent by 2040). Rates of increase are not uniform; numbers in developed countries are considered to increase by 100 per cent between 2001 and

2040, but by more than 300 per cent in India, China, and their south Asian and western Pacific neighbours.

Present treatments:

There is currently no cure for Alzheimer's, nor any medication that has been shown convincingly to halt the progress of the disease. However, it has been known for some time that levels of a chemical messenger in the brain called acetylcholine (ACh) are reduced by 20-40 per cent in Alzheimer's patients. Medicines that prevent the breakdown of ACh by inhibiting the enzyme acetylcholinesterase (AChE) have been introduced during the past five years.

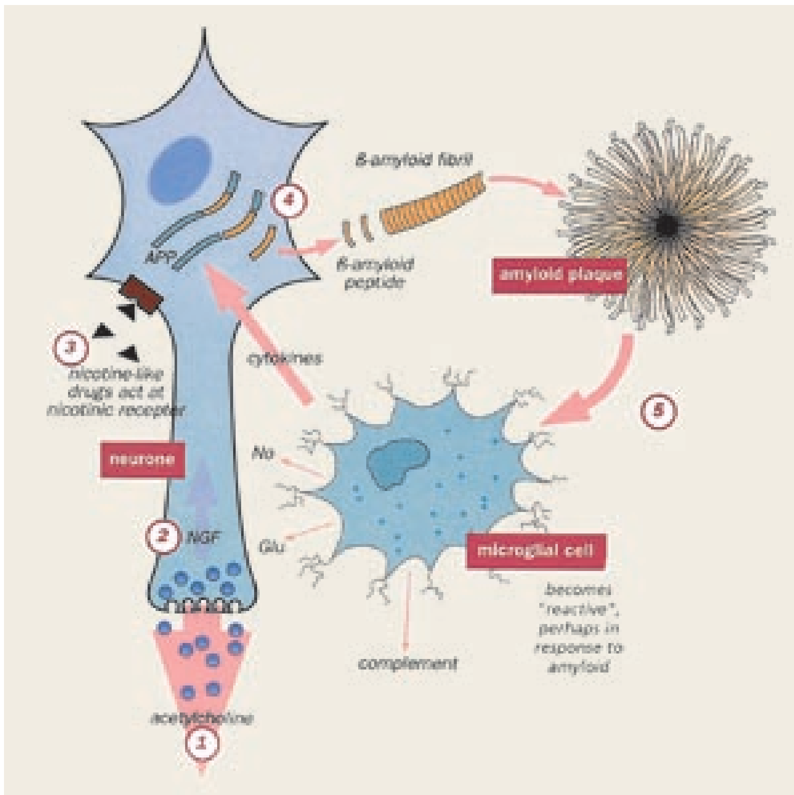

FIGURE 1: Some sites at which Alzheimer's medicines may act

Several AChE inhibitors are available in European countries. Clinical trials have shown that about 10-30 per cent of patients experience an improvement in one or more of cognition, global functioning and activities of daily living with these medications. However, long-term data on effectiveness are limited.

The blocking of NMDA receptors in the brain is an approach which attacks the disease from another front as it inhibits a substance that damages nerve cells. Glutamate is a potentially damaging substance when present in excess, and an inhibitor of the NMDA receptor which responds to glutamate has been shown to produce cognitive and behavioural improvement even in the more advanced stages of Alzheimer's, where AChE inhibitors are less effective.-

An NMDA receptor antagonist is available for the treatment of patients with mild to moderate Alzheimer's disease. The combination therapy of an AChE inhibitor and a NMDA receptor antagonist has been shown to produce sustained improvement in patients, maintaining higher levels of cognition and daily living function.

What's in the development pipeline?

Further AChE inhibitors are under development. This class of molecules is of undoubted value, helping to prolong independent living and reduce the burden on carers, but they are only a first step towards the development of effective medication for Alzheimer's. Muscarinic and nicotinic receptors in the brain are found in parts rich in acetylcholine and compounds that stimulate these receptors are of therapeutic interest. Medicines interacting with nicotinic receptors are also being developed.

The eventual goal must be to develop medicines that modify the course of the disease. Therapeutic principles which may do this can be grouped according to the sites at which they act. One approach would be to develop molecules which mimic nerve growth factor (NGF) and are taken up at nerve endings, where they promote repair. Another possibility could be compounds that prevent plaque formation by inhibiting the enzymes involved in its production, while others may act to damp down the secretion of nerve-damaging compounds by glial cells.

Medicines that act in a nerve growth factor-like manner, mimic NGF, or which stimulate production of NGF are already in clinical trials. It has been shown that they can improve memory and behaviour in patients with mild to moderate disease. Further research is concentrating on compounds which can be given orally once a day and which act in a NGF-like manner. Among the other neurotransmitter substances found in the brain, serotonin (5-HT) is thought to play a role in cognition. Thus, antagonists which bind to 5-HT_6 receptors could be of interest in order to affect the cognitive impairment seen in Alzheimer's.

The longer-term future:

Interest in developing new treatments for Alzheimer's remains intense. Targeting the build up of beta-amyloid in the brain remains the major avenue in treating Alzheimer's. New therapeutic principles include molecules that bind to soluble beta-amyloid, preventing it from forming amyloid fibrils. Such compounds have been shown to help to clear soluble beta-amyloid from the brain and to inhibit the inflammatory response associated with amyloid build up.

Another method of preventing the build up of beta-amyloid is to inhibit the enzymes that separate APP into beta-amyloid. The first to be targeted was gamma-secretase, but this has similar actions elsewhere in the body, some of which are part of important pathways. Probably a better target is beta-secretase, which works on fewer substances in the human body, so inhibiting it is not expected to cause adverse events. Several companies are developing gamma- and beta-secretase inhibitors.

Preventing the copper-mediated oxidation of beta-amyloid may also lower its level in the brain. Therefore, metal-attenuating molecules are being sought. Finally, raising antibodies against beta-amyloid has been proposed to help treat Alzheimer's disease. Further research is underway on 'anti-plaque agents', on an muscarinic-2 receptor antagonist, on the promotion of combined noradrenaline and dopamine reuptake, and on neuroimmunophilins that may help nerves regenerate.

Another avenue could be gene therapy. The therapy is produced by taking the patient's skin cells and genetically modifying them in culture to produce NGF. These cells are surgically implanted into the brain region that is important in memory and cognitive function, and where cell degeneration occurs in Alzheimer's.

It is also of interest to note that even established medicines from other disease areas may have applications in Alzheimer's. Recently, studies demonstrated that the risk of having dementia was 70 per cent lower in patients receiving lipid-lowering statins. The reason for their protective effect is not known. However, the prospect that they might be able to prevent or slow down Alzheimer's will surely stimulate further research, since a delay of only five years in its onset would cut the number of people with Alzheimer's by 50 per cent.

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