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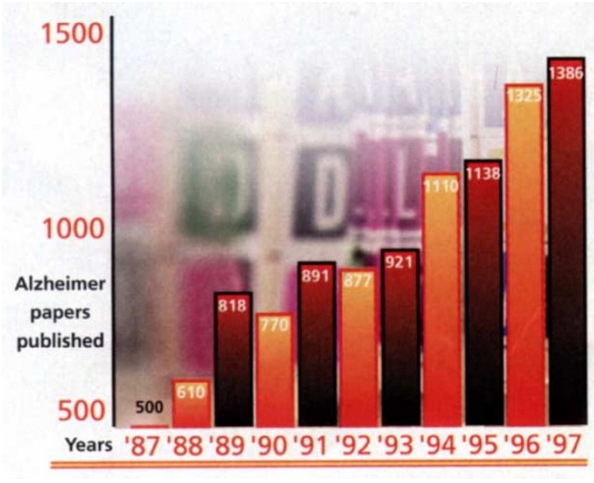
Amyloid and Alzheimer disease

Ectopic protein inclusions are found in AD and other progressive, neurodegenerative diseases such as multiple system atrophy, amyotrophic lateral sclerosis and Parkinson disease. In a Commentary article on page 755 Michael Brownstein and colleagues postulate a central role for alpha synuclein in these disorders. The suggestion stems from the discovery of alpha synuclein gene mutations in Parkinson disease and although any extrapolation to AD is premature—the authors have found alpha synuclein in AD hippocampal neuritic tangles but have not yet looked for it in Aβ fibrils—there is a seductive attraction to the idea of mutant synuclein acting as a common trigger for the development of protein inclusions in a number of disorders.

Over the last decade or so, the number of papers listed by the US National Library of Medicine with the word Alzheimer in their title has grown steadily—in all, some twelve thousand are listed. Yet despite this level of activity and the fact that this disease, thought to represent the most common cause of dementia, has received the attention of many outstanding research groups around the world, Alzheimer disease (AD) refuses to give up some very basic secrets. For example, it is still next to impossible to definitively diagnose AD until it is too late (post mortem examination offers the only certain diagnostic opportunity) and in all but a very few cases the underlying genetic predisposition is unclear. Foremost among the mysteries of AD is the part that amyloid protein plays in the disease. Yet progress, however slow, is being made and on the eve of the 6th *International Conference on AD and Related Disorders* it is fitting that this issue of *Nature Medicine* includes a number of papers that contribute to that progress by clarifying the role that amyloid β-protein (Aβ) has in AD.

On page 827, Bruce Yankner and colleagues address the question of why rodent models of the disease do not show the same neuronal loss seen in patients. Although there is no question that the inappropriate accumulation of cerebral amyloid is a hallmark of this disease, the importance of this accumulation for the onset and progression of AD is less clear. Based on pathology and many *in vitro* experiments, the theory that Aβ deposits were causal became popular. But this idea was dealt a near-fatal blow when it was shown that rodents made transgenic for human Aβ developed amyloid deposits but not the neuronal loss central to AD. Working with rhesus monkeys, Yankner *et al.* now show that the neuronal toxicity of Aβ is not only species-specific but also age-dependent. Microinjection of Aβ into the cerebral cortex of older rhesus monkeys resulted in neuronal loss, whereas the same treatment of either younger rhesus monkeys or marmosets produced far less damage. Not only does this explain the rodent results, it also provides the community with a good model of AD.



Pitschke *et al.* (page 832) have exploited the telltale biochemistry that leads Aβ to form fibrillar aggregates as the basis for a diagnostic test. By examining the polymerizing potential of single Aβ aggregates in cerebrospinal fluid from patients, their novel assay was able to distinguish all 15 affected (based on medical, neurological and psychiatric histories) patients from 19 patients with other neurological conditions. Promising as these results are, it is still unclear whether this test will be able to differentiate AD from similar conditions such as cerebral amyloid angiopathy, and whether the assay will be able to detect early stage disease.

If amyloid deposition is a key event in the AD pathogenesis, argue Claudio Soto and colleagues (page 822), then inhibiting the deposition of amyloid should prevent disease. The idea of preventing amyloidosis by using small molecules to interfere with the development of beta sheet structures has been discussed for a number of years. Here, Soto *et al.* describe a five-residue peptide with partial homology to the Aβ protein that is not only capable of preventing Aβ fibrillogenesis *in vivo*, but also able to dissolve existing fibrils *in vitro*. Their 'β-sheet breaker' approach is promising not just for AD but for other amyloidoses and conformational disorders.

As Robert Kisilevsky remarks in an accompanying News & Views (page 772), the evidence in favor of a central role for Aβ in AD is quite compelling but still incomplete. These three studies strengthen that evidence.