These results may explain the large number of Aβ deposits in Alzheimer's patients homozygous for *APOE-4*. Soluble Aβ is constitutively produced as part of normal APP metabolism, with $A\beta_{1-40}$ as a majority species and $A\beta_{1-42}$ as a minority species[22,23]. The mechanisms that lead from soluble Aβ in normal brain to amyloid fibrils in Alzheimer's disease brain are only poorly understood. An increased production of $A\beta_{1-42}$ is the net effect of several APP mutations linked to early-onset forms of Alzheimer's[24,25], suggesting that it may be one mechanism that leads to Aβ deposition.

Ma *et al.* show that proteins associated with amyloid deposits in the Alzheimer's brain promote Aβ fibril formation *in vitro*. They report a similar effect to apoE for α_1-antichymotrypsin, another protein associated with amyloid plaques. The relevance of apoE-induced stimulation of Aβ-fibril formation for understanding Alzheimer's disease depends on the part played by Aβ deposits in the characteristic nerve-cell degeneration that accounts for the disease symptoms. Amyloid-β protein can be toxic to cultured fetal or neonatal mammalian nerve cells[26], but the evidence for such an effect on adult nerve cells *in vivo* is scarce. Moreover, early neuropathological stages of Alzheimer's disease frequently show neurofibrillary lesions in the absence of Aβ deposits[27], suggesting that the deposits may not themselves trigger nerve-cell degeneration.

Pathological changes that are qualitatively indistinguishable from those in Alzheimer's disease are an almost invariable accompaniment of aging, but to a much lesser extent. From survival curves, it seems that, given a lifespan of 130–140 years, everybody would eventually develop the disease, whatever the *APOE* allele (see figure). The apoE-2 and apoE-3 isoforms may delay this process more than apoE-4 by prolonging the survival of affected nerve cells.

Although the experiments described here were carried out with Aβ, it should be noted that neurofibrillary lesions made of hyperphosphorylated tau protein correlate better with the disease symptoms than do amyloid plaques[28]. Here it may be significant that apoE-3 binds to the microtubule-binding domain of tau *in vitro*, whereas apoE-4 shows no significant binding[29]. Neither isoform binds to hyperphosphorylated tau. Light- and electronmicroscopic studies have shown apoE-like immunoreactivity in the cytoplasm of some human cortical neurons[30]. These observations have led to the proposal that interactions between apoE-3 and tau may protect tau from hyperphosphorylation, and account for the different ages of disease onset in individuals with *APOE3/3* and *APOE4/4* alleles[29]. ApoE is involved in peripheral nerve regeneration following lesioning[31]. Together with a lipid source, apoE-3 stimulates neurite outgrowth in cultured dorsal root ganglia, whereas apoE-4 has an inhibitory effect[32]. There may be similar differences at work in the aging human brain and these could differentially affect the ability of nerve cells to compensate for the progression of the underlying disease process.

Time will tell which, if any, of these mechanisms accounts for the striking effects of *APOE* genotype on the development of Alzheimer's disease. A great deal hangs on the outcome — a delay in the age of onset by 10–15 years, which might be induced by a drug acting like apoE-2, would result in a massive reduction in the number of disease cases. □

Michel Goedert is at the MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK. Warren J. Strittmatter and Allen D. Roses are in the Departments of Medicine (Neurology) and Neurobiology, Duke University Medical Centre, Box 2900, Durham, North Carolina 27710, USA.

1. Ma, J., Yee, A., Brewer, H. B. Jr, Das, S. & Potter, H. *Nature* **372**, 92–94 (1994).
2. Sanan, D. A. *et al. J. clin. Invest.* **94**, 860–869 (1994).
3. Glenner, G. G. & Wong, C. W. *Biochem. biophys. Res. Commun.* **120**, 885–890 (1984).
4. Masters, C. L. *et al. Proc. natn. Acad. Sci. U.S.A.* **82**, 4245–4249 (1985).
4. Goedert, M., Wischik, C. M., Crowther, R. A., Walker, J. E. & Klug, A. *Proc. natn. Acad. Sci. U.S.A.* **85**, 4051–4055 (1988).
6. Lee, V. M.-Y., Balin, B. J., Otvos, L. & Trojanowski, J. Q. *Science* **251**, 675–678 (1991).
7. Schellenberg, G. D. *et al. Science* **258**, 668–671 (1992).
8. Goate, A. *et al. Nature* **349**, 704–706 (1991).
9. Pericak-Vance, M. A. *et al. Am. J. hum. Genet.* **48**, 1034–1050 (1991).
10. Strittmatter, W. J. *et al. Proc. natn. Acad. Sci. U.S.A.* **90**, 1977–1981 (1993).
11. Saunders, A. M. *et al. Neurology* **43**, 1467–1472 (1993).
12. Corder, E. H. *et al. Science* **261**, 921–923 (1993).
13. Corder, E. H. *et al. Nature Genet.* **7**, 180–184 (1994).
14. Weisgraber, K. H. *Adv. Prot. Chem.* **45**, 249–302 (1993).
15. Boyles, J. K., Pitas, R. E., Wilson, E., Mahley, R. W. & Taylor, J. M. *J. clin. Invest.* **76**, 1501–1513 (1985).
16. Rebeck, G. W., Reiter, J. S., Strickland, D. K. & Hyman, B. T. *Neuron* **11**, 575–580 (1993).
17. Namba, Y., Tomonaga, M., Kawasaki, H., Otomo, E. & Ikeda, K. *Brain Res.* **541**, 163–166 (1991).
18. Han, S. H. *et al. Exp. Neurol.* **128**, 13–26 (1994).
19. Schmechel, D. *et al. Proc. natn. Acad. Sci. U.S.A.* **90**, 9649–9653 (1993).
20. Strittmatter, W. J. *et al. Proc. natn. Acad. Sci. U.S.A.* **90**, 8098–8102 (1993).
21. Iwatsubo, T. *et al. Neuron* **13**, 45–55 (1994).
22. Haass, C. *et al. Nature* **359**, 322–326 (1992).
23. Shoji, M. *et al. Science* **258**, 126–129 (1992).
24. Citron, M. *et al. Nature* **360**, 672–674 (1992).
25. Suzuki, N. *et al. Science* **264**, 1336–1340 (1994).
26. Kowall, N. W., Beal, M. F., Busciglio, J., Duffy, L. K. & Yankner, B. A. *Proc. natn. Acad. Sci. U.S.A.* **88**, 7247–7251 (1991).
27. Braak, H. & Braak, E. *Acta Neuropathol.* **82**, 239–259 (1991).
28. Arriagada, P. V., Growdon, J. H., Hedley-White, E. T. & Hyman, B. T. *Neurology* **42**, 631–639 (1992).
29. Strittmatter, W. J. *et al. Proc. natn. Acad. Sci. U.S.A.* (in the press).
30. Han, S. H. *et al. J. Neuropathol. exp. Neurol.* **53**, 535–544 (1994).
31. Ignatius, M. J. *et al. Proc. natn. Acad. Sci. U.S.A.* **83**, 1125–1129 (1986).
32. Nathan, B. P. *et al. Science* **264**, 850–852 (1994).
33. Roses, A. D. *et al. Lancet* **343**, 1564–1565 (1994).

DAEDALUS

Real recycling

AN Indian city recently acquired an expensive Western waste-utilization plant, a furnace intended to power generators. It never worked. The diligent rubbish-sorters of the city scoured the rubbish as it came in, removing everything of even trivial value. What they left behind, mainly rotting vegetable matter, would hardly burn. The costly, token, feel-good recycling of the West was neatly subverted by the genuine recycling of the Indian rubbish-sorters.

And yet the West does support a little real recycling. The car-boot sale, the bring-and-buy stall and the traditional English jumble sale all return unwanted material to the economy. Significantly, they operate on individual objects, not by clumsy bulk reprocessing. Daedalus wants to modernize them.

He points out how modern communications have transformed the financial markets, and are now transforming the industrial ones. So DREADCO programmers are writing the software for a continuous national jumble sale, to be maintained on the Internet. Each user will advertise any or all of his surplus possessions on the Net, while simultaneously appealing for anything he happens to want.

Daedalus expects a massive trade to develop. At first it will be dominated by fairly large and expensive consumer durables, laboratory and industrial equipment and so on. Those who throw such things out for trivial faults, or routinely replace them with the latest model, will be efficiently matched to the handymen who can repair them or work with older apparatus. But soon smaller objects will come crowding in. Books of all kinds will be sought and exchanged; then raw materials. The boilermaker's useless offcut is valuable raw material to the toolroom engineer, and his scrap would be snapped up by the model maker. A surplus load of an industrial chemical would be cornucopia to the laboratory chemist. Such materials will repeatedly re-enter the economy in ever increasing subdivision, until they reach the point where the cost of moving them further outweighs the value of the trade.

Each user of the service will release his own 'gopher' programs into the Net to seek out and strike bargains with other users and their gophers. The automated haggling of thousands of individual trades will establish 'going rates' for the most surprising objects: half-used tins of paint in all shades, nuts and bolts of every size, lengths of cable, pipe and string and bin-ends of cement. This truly efficient market will be far more economical than the token recycling of a few raw materials.

David Jones