Alzheimer's disease and amyloid

Two well publicized papers reporting transgenic mouse models for Alzheimer's disease have been retracted. But this setback may not be quite so serious as press reports have suggested.

THE amyloid precursor protein (APP) is a transmembrane glycoprotein of unknown function that is produced in most tissues, including the neurons and blood vessels of the central nervous system. An insoluble C-terminal degradation product, beta amyloid, accumulates in the ageing brains of humans and some other mammals and forms extracellular plaques. Dense amyloid plaques in aged brains may sometimes be associated with intracellular fibrils of different composition known as neurofibrillary tangles, accompanied by some neural degeneration. In Alzheimer's disease, which affects about 10 per cent of people in their seventies and 30 per cent in their eighties, very pronounced plaques, tangles and neuronal degeneration are accompanied by dementia. These observations have led to the hypothesis that the accumulation of beta amyloid itself is responsible for the progressive neuropathology and ultimately loss of cognitive function.

If this is the case, then a transgenic mouse expressing an extra amyloid gene in its brain might develop the same pathology, thus both establishing the role of amyloid deposits in the aetiology of the disease and providing a model on which to test potential therapeutic drugs. Three such transgenic animals have been reported, two of them showing what appear to be amyloid deposits[1,2] and the third, published by Kawabata *et al.* in *Nature*[3] apparently also showing intracellular neurofibrillary tangles and neuronal degeneration. Kawabata *et al.* have now retracted their paper on the grounds that they cannot repeat the neuropathological observations[4], originally made by Higgins, who is the subject of an NIH investigation[5]; Wirak *et al.*[1] will also shortly retract their paper because it has turned out that the abnormalities they saw are characteristic of the strain of mouse they used; the amyloid staining was probably an artefact. The remaining paper, by Quon *et al.*[2], still stands; but although their transgenic mice show amyloid deposits in cortex and hippocampus, they show no other pathology and so at this stage neither establish the role of amyloid in Alzheimer's aetiology nor provide a model for testing drugs.

The two retractions have inevitably raised questions about the conduct of research and publication practices. The best time to take up these questions is when the NIH enquiry on Kawabata *et al.* is complete, although it is important that in both cases the problem was brought to light by the vigilance of others in the field and that retraction followed promptly. In the meantime perhaps more important is the question of how this dual disappointment affects the understanding of Alzheimer's neuropathology and the hope of progress.

There is in fact remarkably little understanding of the mechanism of Alzheimer's neuropathology, leaving room for several different theories about the role of amyloid in its aetiology. It is possible for example that amyloid deposits in the blood vessels rather than in the neurons do the damage; and although there is some evidence that beta amyloid is directly toxic to neurons *in vitro*[6], there is controversy over its effects *in vivo* and some believe the release and accumulation of beta amyloid is the consequence and not the cause of neural death. The transgenic mice of Quon *et al.* were designed to test yet another hypothesis — that Alzheimer's disease might result from an abnormal balance of the three normal isoforms of APP. They therefore used a transgene encoding one isoform, beta APP751, high relative levels of which have been reported by some in Alzheimer's disease. This is distinct from the other principal isoform, beta APP695, in containing an N-terminal serine protease inhibitor domain. The function of this domain and its contribution, if any, to the neuropathology of Alzheimer's disease, again, are unknown.

The special significance of the Kawabata *et al.* transgenic mouse was that it seemed to show characteristic Alzheimer's pathology and thus to be the best model of the three. Yet even had it held up (the suggestion is that the slide showing the neuropathology was in fact from human Alzheimer's brain), its credentials as a model were not perfect. As Dennis Selkoe pointed out in an editorial accompanying the publication of the paper in *Nature*[7], the transgene they used encodes a C-terminal amyloid fragment that is never made physiologically. The mouse was therefore at best imperfectly mimicking the process that produces amyloid plaques in man. Selkoe also points out that, unlike normal APP genes, their transgene was under the control of a promoter that allows its expression only in neurons, at levels that might be toxic for reasons other than those operating in Alzheimer's. It is unclear however whether the neurones are affected by the excess amyloid at all — always assuming that the protein itself is actually made: Kawabata *et al.* have shown expression only at the RNA level.

The best evidence implicating the amyloid protein in neuropathology probably now lies with recent studies in human genetics. In a small minority[8] of families with an hereditary predisposition to Alzheimer's diease, a missense mutation close to the C-terminal end of beta amyloid segregates with the disease phenotype[9–12]. Alzheimer's disease in these families follows an autosomal dominant pattern, which means only one mutant copy of the gene should be needed to produce the abnormality and a mouse model could thus be made by the introduction of a mutant transgene without the need to eliminate the normal gene.

Although such a mouse might provide a better test of the role of amyloid than one carrying an extra copy of a normal gene, as in the Quon *et al.* mouse, dosage effects are in fact also implicated by human genetics. Trisomy 21 in Down's syndrome confers an extra copy of the normal APP gene and presumably as a consequence, amyloid plaques accumulate, with full Alzheimer's neuropathology by the 5th decade. It may be that an animal with a lifespan as short as a mouses's can never develop a pathology that in man takes decades.

In the meantime almost everything remains to be learned about the processing of APP at the cellular level and its function at any level; and in the circumstances, the collapse of a possible partial Alzheimer's model may seem to leave us little further back than we were.

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