dying for reasons other than head trauma or dementia.

While we are prepared to believe that severely head-injured individuals with an ε4 allele have acutely increased amyloid deposition with head injury, extrapolation for these data to mechanisms of AD pathogenesis cannot be accepted without appropriate age-matched controls. Twenty-eight-year-old (+-18 years) people do not get Alzheimer's disease. Other investigators have found that nondemented controls of 60 years older have a significant amyloid deposition, and the effect of head injury acutely increasing amyloid deposition may be enhanced in the ε4 group[5–7].

The data presented by Nicoll *et al.* have little to say about the pathogenesis of AD, only the pathobiology of amyloid deposition and the possible importance of apoE isoforms in recovery from head injury. Head injury as a risk factor for Alzheimer's disease may reflect altered metabolism in ε4 carriers leading to decreased recovery from stress with coincidental increased Aβ deposition. Aβ deposition in brains of normal older individuals as well as Alzheimer's patients may be particularly obvious when ε4 is present. The relevant genetic factor for increased Aβ deposition and Alzheimer's disease is the ε4 allele, but there is no evidence from this report to support the hypothesis that Aβ deposition "may be followed by the development of the full spectrum of Alzheimer's disease."

ALLEN D. ROSES & ANN SAUNDERS
Joseph and Kathleen Bryan Alzheimer's Disease Research Center
Departments of Medicine (Neurology) and Neurobiology
Duke University Medical Center
Durham, North Carolina 27710-2900, USA

Nicoll et al. reply — Head injury is the major environmental risk factor for Alzheimer's disease[8]. Our recent paper in *Nature Medicine* is the latest in a series of studies we have undertaken to explore the mechanisms which may underlie this association between head injury and AD. AD is widely, although not universally, regarded as an "amyloidopathy" with accumulation of Aβ as a key initiating event[9]. It is with this background we suggest that head injury may act as a risk factor for AD by causing acute deposition of Aβ. A greater number of patients over the age of 60 years who died from a head injury have plaques of Aβ than patients of similar age who died from other causes[8]. As we discussed, a proportion of the head-injured patients are likely to have "age-related" Aβ deposition and, as yet, we have no way to distinguish these from the trauma-related deposits. However, Aβ plaques are present in head-injured patients at younger ages, when they are not seen in non-head injury controls. The implication from this finding is that the head injury in some way "triggers" deposition of Aβ.

Roses and Saunders raise the interesting suggestion that patients who have a head injury and do not develop Aβ deposits may be more likely to survive, and that this may a possible source of bias in our study. Without the ability to image Aβ in living patients it is difficult to test this hypothesis directly, however even if this were the case it would not influence our finding of an association between Aβ and apoE-ε4. Age-stratification of our data showed ε4 is significantly associated with Aβ deposition in patients under the age of 50, under the age of 60 and in the total group (Table 3).

ApoE-ε4 has been identified as a major risk factor for AD and several lines of evidence suggest that it acts by increasing Aβ deposition. We provided further evidence to support the association between apoE-ε4 and Aβ deposition. Of likely relevance to the acute deposition of Aβ is the demonstration of increased immunostaining for β-amyloid precursor protein[8] and apoE (unpublished observations) following head injury. Taken together our data indicate that the major known environmental and genetic risk factors for AD can operate together. This observation is supported by the elegant epidemiological studies of Mayeux and colleagues who have shown that a history of a previous head injury and ε4 interact synergistically: "a 10-fold increase in the risk of AD was associated with both apolipoprotein-ε4 and a history of traumatic head injury, compared with a two-fold increase in risk with apolipoprotein-ε4 alone"[10].

Despite the evidence outlined above we are aware that the "amyloid hypothesis" for AD is not proven and that others hold alternative views. In our paper we referred to work by Roses, Saunders and others[11] which argues that ε4 is a risk factor for AD because it may interact with tau and increase the likelihood of tangle formation. Our work does not rule out the possibility that other mechanisms relevant to AD, in addition to Aβ deposition, may also be activated in head trauma. Recent evidence associating ε4 with impaired outgrowth of neurites and impaired synaptogenesis provide additional mechanisms which may be equally important in recovery from trauma. This provides further support for our suggestion that there is a genetic susceptibility to the effects of a head injury determined by apoE genotype.

1. Saunders, A.M. *et al.* Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43(8)**, 1467–1472 (1993).
2. Roses, A.D. Apolipoprotein E affects the rate of Alzheimer disease expression: Beta-amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. *J. Neuro. exp. Neurol.* **53(5)**, 429–437 (1994).
3. Schmechel, D.E. *et al.* Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late onset Alzheimer disease. *Proc. natn. Acad. Sci. U.S.A.* **90(20)**, 9649–9653 (1993).
4. Nicoll, J.A.R, Roberts, G.W. & Graham, D.I. Apolipoprotein E ε4 allele is associated with deposition of amyloid b-protein following head injury. *Nature Med.* **1**, 135–137 (1995).
5. Berr, C. Hauw, J.J., Delaere, P. Duyckaerts, C. & Amouyel, P. Apolipoprotein E allele epsilon 4 is linked to increased deposition of the amyloid beta-peptide (A-beta) in cases with or without Alzheimer's disease. *Neurosci. Lett.* **178(2)**, 221–224 (1994).
6. Arriagada, P.V., Marzloff, K. & Hyman, B.T. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the patter in Alzheimer's disease (see comments). *Neurology* **42(9)**, 1681–1688 (1992).
7. Mayeau, R. *et al.* Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease. *Neurology* **45(3)**, 555–557 (1995).
8. Roberts, G. W. *et al.* β-amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *J. Neurol. Neurosurg. & Psychiatr.* **57**, 419–425 (1994).
9. Selkoe, D.J. Alzheimer's disease: a central role for amyloid. *J. Neuropath. exp. Neurobiol.* **53**, 438–447 (1994).
10. Mayeux, R. et al. Synergistic effects of traumatic head injury and apolipoprotein-ε4 in patients with Alzheimer's disease. *Neurology* **45**, 555–557 (1995).
11. Strittmatter, W.J., *et al.* Hypothesis: microtubule instability and paired helical filament formation in Alzheimer's disease brain are related to apolipoprotein E genotype. *Exp. Neurol.* **125**, 163–171 (1994).

JAMES A.R. NICOLL & DAVID I. GRAHAM
Department of Neuropathology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, G51 4TF, UK

GARETH W. ROBERTS
Molecular Neuropathology Department, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK