New Editor

New year, new editorial team

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The New Year brings a change of editorship; after seven years of exceptional custodianship the journal says goodbye to Professor Chris Kennard. During his tenure he has maintained the key role of the journal as a premier European clinical neuroscience publication and witnessed an increase in submissions from about 1200 to over 2000 per annum. He has established online submissions via Bench>Press and established the website. He has overseen the introduction of *Neurology in Practice*, edited by Ian Bone and Geraint Fuller, which will continue in this series until 2005. A number of new features have been introduced, such as editorial commentaries. All of these provide added value to the quality of the submitted articles. It is this added value which is of such importance during the time of the information explosion and online publishing opportunities. These opportunities are indeed substantial, both to increase the amount of information available but also to distribute journals to a wider audience at ever lower marginal cost. The danger, however, is that as quantity increases quality falls. Chris Kennard has met these challenges and hands over the journal in excellent shape.

THE FUTURE

What of the future? *JNNP* was first published in 1938 (under the title of *Journal of Neurology and Psychiatry*) and the custodianship of such a journal is both an exciting challenge and a heavy responsibility. We reaffirm the aim of publishing the very best articles of clinical relevance in neurology, neurosurgery, and psychiatry. There are few clinical neuroscience journals that are as broadly based and it would be easy to focus just on neurology. However, we believe that this multidisciplinary nature is its strength, and indeed we hope to foster increased submissions in neurosurgery and psychiatry.

What then of the changes. ''If it ain't broke don't mend it''; and so with a successful journal, changes in response to changing demands should occur with minimal fuss. We hope to raise the international profile of the journal and to this end there will be changes in the balance of the editorial team and details of this will follow in future issues. As always, we depend very much on the generosity and support, not only of the editorial board, but also of the large number of referees who assist with maintaining the quality of the journal. With increasing pressure of time and the increasing submission rate, this becomes ever more onerous, but without such freely given scholarship the journal cannot survive.

There is one change that is already apparent, namely the cover. We felt it was time for a change and the new cover highlights the three clinical subjects of neurology, neurosurgery, and psychiatry. The picture will change each month but what has not changed is the colour; *JNNP* remains ''the green rag''.

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Alzheimer's disease

Contribution of cerebral amyloid angiopathy to Alzheimer's disease

S Love

Contribution of CAA to Alzheimer's disease

In patients with Alzheimer's disease (AD), focal and diffuse ischaemic abnormalities of the cerebral white matter can be demonstrated neuropathologically[1–3] and neuroradiologically.[4–8] The focal lesions have been shown to contribute to motor and neuropsychiatric manifestations of AD,[9–12] and the more widespread or diffuse abnormalities to impaired cognition.[13 14] In some series, ischaemic cerebral lesions in AD have been more frequent in patients homozygous or heterozygous for the epsilon 4 (e4) allele of the apolipoprotein E gene (*APOE*),[15–17] but other studies have found no such association,[18–21] Studies of the relation between white matter disease in patients with AD or probable AD, and the systemic manifestations of arteriosclerotic vascular disease, have yielded inconsistent findings.[1 11 21–24]

Several observations implicate cerebral amyloid angiopathy (CAA) as the probable cause of much of the white matter damage in AD. The vascular deposition of amyloid β protein (Aβ) is much more frequent and tends to be much more severe in patients with AD than in age-matched controls.[25–29] Furthermore, CAA is a well documented risk factor for cerebral infarction[16 30–32] and for focal and diffuse white matter ischaemic lesions.[33–36] The mechanisms whereby CAA may cause ischaemic damage to the white matter probably include a combination of luminal stenosis, endothelial damage, basement membrane thickening, thrombosis, loss of autoregulation, and vasospasm.[37–40] Because evidence of the involvement of CAA in AD is largely based on post-mortem studies, which are by their nature skewed towards end stage disease, it could be argued that any contribution of CAA may be confined to the terminal stages of disease. If this were true, it might be expected that an inverse relationship between the severity of CAA at autopsy and the duration of AD would be found. That this is not the case[28] suggests that CAA may exacerbate AD even at an early stage.

The occurrence of CAA in AD is strongly associated with possession of the e4 allele of *APOE*.[17 28 32 41] Indeed, possession of the e4 allele of *APOE* is much more strongly correlated with vascular than parenchymal deposition

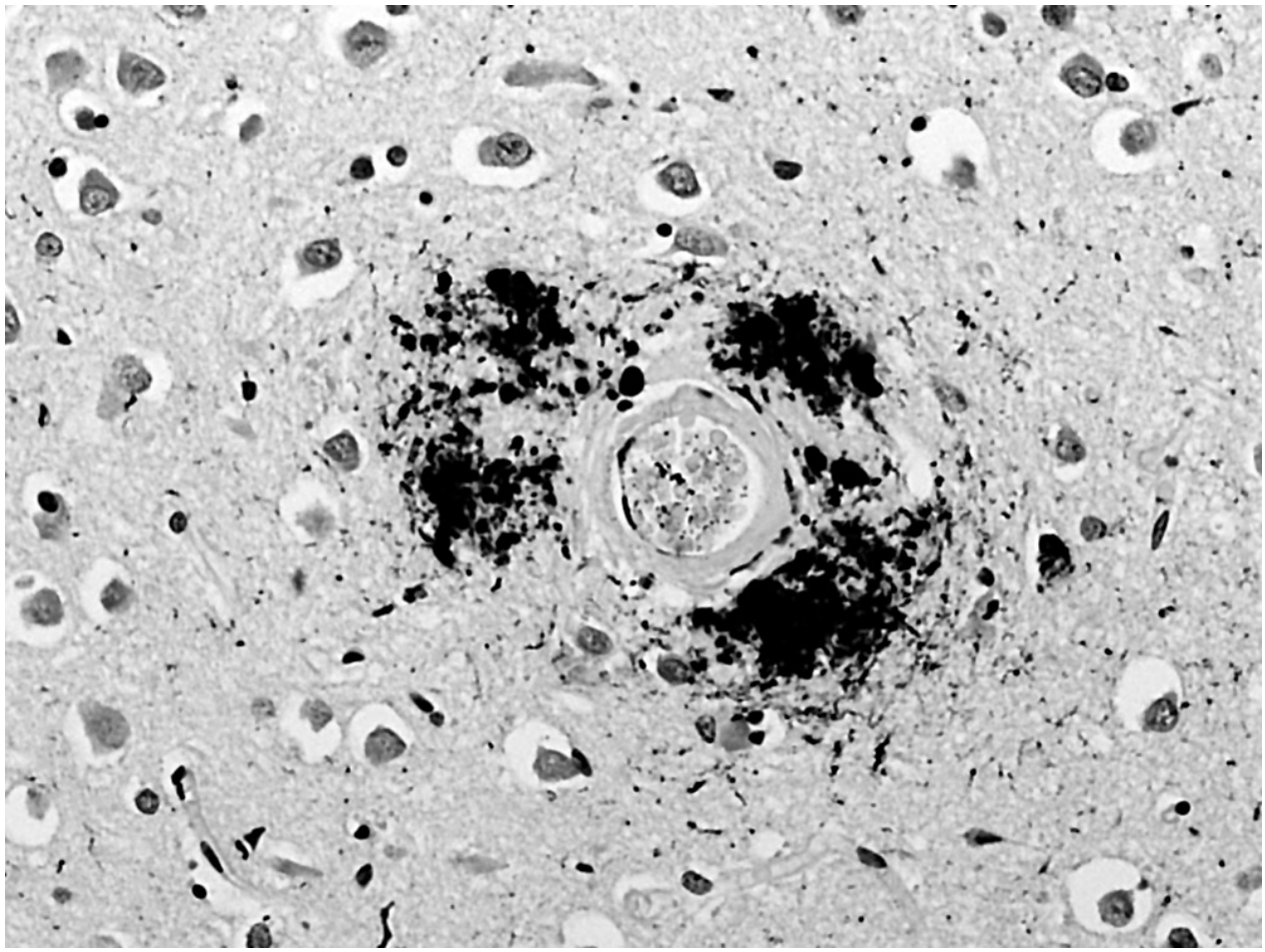

Figure 1 Tau immunopositive neurites clustered around a cortical artery with dyshoric amyloid angiopathy.

of Aβ.[28] This may reflect on the pathogenesis of neurodegeneration in AD in patients with e4. AD patients with severe CAA, almost all of whom possess at least one e4 allele, have significantly less parenchymal Aβ than do patients with lesser degrees of CAA.[28 42 43] This is further evidence against the argument that CAA is simply a late manifestation of AD, and raises the possibility that CAA and parenchymal Aβ have additive effects on the progression of clinical disease. Although the Aβ within vessel walls could, in theory, also cause local neurotoxicity in the cerebral cortex, we have found no evidence of any associated reduction in the density of immunostaining of synaptophysin,[44] a sensitive marker of presynaptic integrity.

Observations of Weller and colleagues suggest that the involvement of CAA in AD may go beyond a contribution of ischaemia to the clinical and pathological manifestations of the disease, and that CAA may be involved in the development of plaques and tangles, the histological hallmarks of AD. Weller *et al*[45 46] propose that soluble Aβ is normally eliminated from the brain within interstitial fluid pathways that reach the cerebrospinal fluid in the subarachnoid space by passing along perivascular spaces in the cerebral cortex. If this model is correct, the obstruction to drainage of interstitial fluid caused by perivascular accumulation of amyloid could contribute to the accumulation of Aβ within the parenchyma and the development of the plaques and tangles. Support for this comes from the occasional finding of tau immunopositive neurites clustered around larger arteries with dyshoric amyloid angiopathy (angiopathy in which amyloid extends from the affected blood vessels into the surrounding brain parenchyma) (fig 1). Although the flow of interstitial fluid within the perivascular space occurs in the opposite direction to that of the arterial blood flow, it may be enhanced by the pulsatile arterial distension. A failure of this propulsive mechanism has been proposed to explain the association of capillary CAA with thrombosis of overlying cortical arteries.[47]

However, several other observations indicate that the relationship between CAA, plaques, and tangles is more complicated than would be predicted by a simple model of obstruction to drainage. These include the mutually exclusive topographical relationship between capillary CAA and extensive diffuse plaques,[47] and the inverse correlation between overall severity of amyloid angiopathy and parenchymal amyloid load in patients with moderate to severe CAA.[28 43 45] Further evidence suggests that soluble Aβ within the brain is largely cleared by lipoprotein receptor related protein-1 mediated transcytosis across the endothelial cells of the blood–brain barrier.[48] Impaired clearance of Aβ across the blood–brain barrier is probably central to the development of CAA in hereditary cerebrovascular amyloidosis with Dutch type haemorrhage[49] caused by a G→C transition at codon 693 of the β amyloid precursor protein gene.

Studies by Wyss-Coray *et al*[43 50 51] identify transforming growth factor β (TGFβ) as a key influence on the relationship between parenchymal and vascular Aβ in AD. TGFβ1 levels are significantly increased in patients with

AD, not only in the cerebral cortex,[52] but also in the serum and CSF.[53 54] Chao *et al*[53] observed a significant *in vivo* correlation between the level of TGFβ1 in the serum and the severity of dementia. On the face of it, this might seem paradoxical, as TGFβ1 has been shown to promote the clearance of Aβ from the parenchyma of transgenic mice expressing human β amyloid precursor protein.[43] However, in contrast to the beneficial effects of TGFβ1 on clearance of parenchymal amyloid, expression of TGFβ1 by astrocytes in transgenic mice actually induces deposition of amyloid in cerebral blood vessels, this being accelerated by co-expression of human β amyloid precursor protein.[50 51] A parallel can be drawn between the latter finding and the detection of severe CAA in regions of brain with markedly reduced parenchymal Aβ in a patient with AD who was immunized with Aβ (peptide fragment AN-1792).[55] The relevance of the observations of Wyss-Coray *et al* to AD was strengthened by the authors' demonstration of a strong correlation between TGFβ1 mRNA levels and the severity of CAA in post-mortem brain tissue from 15 patients with AD and 7 controls.[51] However, while these post-mortem findings are of interest, it should be noted that the number of cases studied was small.

Many questions remain as to the relation between CAA and AD. Apart from e4, the putative genetic risk factors for CAA show relatively little overlap with those for AD,[56 57] and despite the fact that e4 is a major risk factor for CAA in AD and in patients presenting with cerebral haemorrhage, CAA is probably not associated with the *APOE* genotype if these conditions are excluded.[29] Although CAA is present in over 90% of patients with AD, it is not present in all cases and is therefore clearly not necessary for the development of the disease. Indeed, it is becoming increasingly clear that what we refer to as AD is really a spectrum of disorders with different genetic (and probably environmental) risk factors but having overlapping pathological and clinical phenotypes. For example, e4 associated AD tends to be a disease with moderate to severe CAA, AD caused by some presenilin mutations is characterized by cotton wool plaques and pyramidal tract degeneration,[58–63] and AD in patients with an e2 *APOE* allele and CAA carries an increased risk of parenchymal brain haemorrhage.[64 65]

The accurate diagnosis of CAA is likely to become increasingly important as we evaluate and implement treatments such as immunization, which are aimed at clearing parenchymal Aβ in AD, particularly if these carry a risk of promoting vascular deposition of Aβ.[55] However, the ante-mortem diagnosis of CAA in AD remains a challenge. Measurement of plasma levels of Aβ and TGFβ was found to be unhelpful in predicting CAA.[66] For the time being, except in the relatively few patients who manifest with lobar cerebral haemorrhage[67] or have a brain biopsy,[68 69] we will have to continue to rely on examination of the brain at autopsy to make a confident diagnosis of CAA.

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Alzheimer's disease

Cognitive profiles in Alzheimer's disease

N A Johnson

Diagnosing vascular dementia

In the paper by Graham *et al* (see pp 61–71, this issue)[1] the authors provide a useful foundation for delineating the neuropsychological profile of a well defined group of subjects with vascular dementia and for differentiating this profile from that typically associated with Alzheimer's disease. One of the main weaknesses in previous studies that attempted to characterise the neuropsychological profile of subjects with vascular dementia has been the within group heterogeneity. Unlike Alzheimer's disease, in which well established, validated diagnostic criteria exist, multiple clinical criteria for the diagnosis of vascular dementia have been proposed.[2] Acceptable sensitivity and specificity for the detection of vascular dementia in clinical practice have yet to be established for any of the proposed clinical criteria,[3] and application of different criteria has resulted in wide variations in the prevalence of vascular dementia.[4] The primary focus in establishing clinical criteria for vascular dementia has been the identification of vascular factors; relevant neuroimaging findings, focal neurological signs, and establishing a temporal relationship between symptoms and cerebrovascular events, although minimal attention has been paid to defining the dementia in vascular dementia. Similar to clinical features used to define Alzheimer's disease dementia, the clinical symptoms required for the identification of dementia in vascular dementia frequently emphasise memory impairment as the primary criterion. However, despite the limitations of previous research due to the lack of uniform diagnostic criteria, as well as the individual variability associated with cerebrovascular disease, the most consistent finding that has emerged regarding the neuropsychological profile in vascular dementia has been the relative preservation of memory functioning as compared with subjects with Alzheimer's disease.[5] This finding, as well as other characteristic neuropsychological impairments as described in the current study, may eventually lead to an improvement in the ability to accurately diagnose vascular dementia in the clinical setting. Continued research is needed in this area, including clinicopathological studies, to further refine the clinical