Letters to the Editor

George C Cathcart

Editor—I am collecting material preparatory to writing a biography of my great uncle, Dr George C Cathcart. He was born in Edinburgh in 1860, moved to London in 1891 and died in 1951.

I have contacted the relevant medical institutions, all of whom have been very helpful and I have copies of various obituaries and other published material, both by and about him. I have also spoken to several retired doctors.

I now wish to obtain further material of both a professional and personal nature and should be grateful if any of your readers can help.

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Catastrophe and Alzheimer's disease

Editor—In his F E Williams Lecture (September/October 1995, pages 412–8), Dr Martin Rossor advances a pathogenetic model for familial Alzheimer's disease (AD) in which there is a non-linear accumulation of soluble amyloid β peptides (sAβ), themselves derived from the amyloid precursor protein (APP), a process triggered by the increased production of the longer 1–42 sAβ peptide. This metabolic change then leads in some unspecified way to the abrupt onset of cognitive decline. As he points out, the physiological roles of sAβ and soluble APP (APP_s) have yet to be fully delineated, and thus changes in their metabolism may result in loss of biological functions, gain in toxicity, or both. Plausible though his hypothesis is, other mechanisms of disordered APP_s/sAβ metabolism may be relevant to the pathogenesis of some cases of AD, the more so in view of the clinical and genetic heterogeneity of the condition.

Other hypotheses may be formulated in which a small change in APP_s/sAβ metabolism may lead to non-linear, catastrophic change [1]. For instance, APP_s and sAβ may be envisaged as physiological ligands with opposing paracrine effects on neuronal survival and neurite outgrowth, APP_s being trophic, sAβ being inhibitory; there is *in vitro* evidence to support both these suggestions. Neuronal health may thus be a function of the differential effects of APP_s and sAβ acting at the cell surface. Furthermore, the synthesis of these ligands from a common precursor, APP, may be reciprocally controlled through negative feedback loops, with sAβ synthesis predominating when the APP gene is overexpressed [1]. Increased intraneuronal APP gene expression, secondary to a variety of neuronal insults, would therefore result in a reduction in the APP_s:sAβ ratio in the extracellular space, a situation predicted to be detrimental for neuronal growth and survival due to both loss of biological function (reduced APP_s) and gain of toxicity (increased sAβ), as well as promoting extracellular accumulation of sAβ and hence its precipitation as β-amyloid as a by-product. Reductions in the APP_s:sAβ ratio in CSF, consequent upon reduced APP_s [2] or increased sAβ levels [3] have been reported, and correlate with the presence of dementia in monozygotic twin pairs concordant and discordant for AD [2].

This mechanism may be applicable not only to familial AD but also to late-onset sporadic AD, Down's syndrome, and dementia pugilistica [1]. If so, manipulation of the APP_s:sAβ ratio may provide a further therapeutic target, proximate to the post-translational structural change of sAβ to β-amyloid, at which to arrest development of the neuropathological and cognitive changes of AD.

References

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2 Wagner SL, Peskind ER, Nochlin D, Provow S, *et al.* Decreased levels of soluble amyloid β-protein precursor are associated with Alzheimer's disease in concordant and discordant monozygotic twin pairs. *Ann Neurol* 1994; **36**:215–20.
3 Nakamura T, Shoji M, Harigaya Y, Watanabe M, *et al.* Amyloid β protein levels in cerebrospinal fluid are elevated in early-onset Alzheimer's disease. *Ann Neurol* 1994;**36**:903–11.

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Brain stem death

Editor—I was disappointed that the recent review by the working group on the criteria for the diagnosis of brain stem death (September/October 1995, pages 381–2) failed to give guidance as to the interval between the two examinations. The fact that the clinical criteria seem to have served us well for the last 17 years should not be used as an excuse for complacency. The diagnosis of brain stem death is usually a self-fulfilling prophecy. Clinicians involved in confirming brain stem death are often placed under severe pressure to make the diagnosis quickly. There is an understandable desire by the transplant team to obtain organs while they are in a usable condition and the shortage of intensive care (ITU) beds means that delay in the diagnosis may deprive others of life saving treatment. In addition, in the brave new NHS time spent in an ITU bed has cost implications. The consequences of a single

publicised error made in the diagnosis of brain stem death for the transplant programme would be horrendous. It would be helpful for those actually diagnosing brain stem death if the time between neurological examinations was stipulated. I would suggest 12 hours where raised intracranial pressure from subarachnoid or intraparenchymal haemorrhage is the mechanism and 24 hours for other diagnoses. Particular care has to be exercised where brain stem demyelination may be a factor as it can contribute to loss of brain stem reflexes [1].

References

1 Ringel RA, Riggs JE, Brick JF. Reversible coma with prolonged absence of pupillary and brainstem reflexes: an unusual response to a hypoxic-ischemic event in MS. *Neurology* 1988;**38**:1275–8.

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An appropriate admission depends on your viewpoint

Editor—Whether admission is appropriate or not (July/August 1995, pages 311–4) depends on your standpoint. An admission deemed inappropriate by clinicians may be deemed essential by frightened patients or their anxious, hard pressed carers.

With the growing emphasis on consumer issues, complaints, rights and charters within the health service, the views of patients and their relatives are increasingly influential. They will frequently feel that admission to hospital is required in situations where doctors may not. I suspect that this is more fully appreciated by general practitioners than by hospital-based physicians. As a GP trainee I have learnt the importance of negotiating an agreed plan of action with patients and carers. Day hospitals, urgent domiciliary visits and GP units are all valuable options when agreeing a management plan to maintain an individual in the community. There are, however, occasions when patients or their relatives/ carers are obviously not happy with a situation and press for admission to hospital. On purely clinical grounds the admission is inappropriate but taking a wider view one could argue that in such situations admission is entirely appropriate and unavoidable. It is not easy at a patient's home to explain on the telephone to junior doctors that one is well aware that there are scant clinical grounds for admission but that the home situation and patient's carer's expectations are such that there is no feasible alternative. In such circumstances admission is appropriate.

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Why do research ethics committees disagree?

Editor—Claire Foster (July/August 1995, pages 315–8) explains the inconsistent performance of ethical committees [1] by describing three moral outlooks which may be represented to a greater or lesser extent in any committee. She suggests an 'ideal' committee would balance these outlooks. If one committee is ideal, it follows that less balanced ones are less than ideal. If committees do not give reliable answers, it is reasonable to question the validity of their answers. Providing an explanation for a flawed system does not make the flaws go away.

Quite apart from the ethical debate, the present system is costly: I have recently been obliged to send the same proposal on a multicentre randomised controlled trial to 18 committees. In addition to the obvious drain on research and secretarial time this involved for the project, there are considerable costs to the NHS. Assuming each committee had six health service employees (say two consultants, a general practitioner, a senior nurse, another health care worker, and an administrator) and the proposal took each person one hour to digest (ie reading, discussing, reaching conclusion, reviewing revisions and deciding to accept or reject) in all, 108 hours (ie two and a half weeks) of senior staff time were used to process this project. Multicentre studies are not uncommon so this sort of waste is being multiplied many times. There is a valid utilitarian argument that such waste is unethical, and staff could be more usefully employed elsewhere.

We are paying through the nose for an inefficient system. The most ethical and cost effective system must surely be a properly funded national committee for multicentre research.

Reference

1 Hotopf MH, Wessely S, Noah N. Are ethical committees reliable? *J R Soc Med* 1995;**88**:31–3.

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