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AMYLOID- β JUNKIES

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Evidence indicates that, in the very near future, by either snorting or injecting amyloid- β , it will be possible to remove amyloid- β -laden senile plaques from the brains of individuals with Alzheimer disease.¹ Given the wealth of in-vitro, genetic, and pathological criteria, it is generally thought that removal of senile plaques will have a beneficial effect and may arrest or reverse Alzheimer's disease.² However, before we all rush to become amyloid- β junkies, there are several biological issues that indicate that such a regimen may ultimately be detrimental.

First, analysis of many aged and even middle-aged individuals shows that amyloid- β deposits are often extensive in cognitively intact people. Amyloid- β deposition is clearly insufficient to develop frank Alzheimer's disease and, in fact, there is only a weak correlation between amyloid- β burden, neuronal cell loss, and cognitive status.³ Second, animals with amyloid- β even more extensive than that found in Alzheimer's disease do not replicate the full range of Alzheimer's disease pathology nor the dementia associated with Alzheimer's disease.

Furthermore, the net result of neurotoxic and neurotrophic effects of amyloid- β in in-vitro experiments and their relationship to in-vivo conditions remains unresolved. Third, amyloid- β is produced in response to injury to the nervous system in various diseases and experimental paradigms and its precursor, β -PP, is one of the best markers of neurological injury and is used as such in pathological diagnosis in a clinical setting.⁴ Indeed, amyloid- β may, in fact, rather than being detrimental, play a part in the defence of the aged brain.⁵ Amyloid- β , like ubiquitin, heat-shock protein, or antioxidant proteins, is increased as a consequence of the aetiological process. It would be preposterous to suggest these responses to the primary aetiological event actually mediate pathogenesis, and to invoke amyloid- β as the primary agent is equally so.

Given this uncertainty, we are playing a dangerous game in focusing efforts on the removal of amyloid- β , which could quite likely have the opposite effect to that promised: of a return to cognition.

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2 Selkoe DJ. Translating cell biology into therapeutic advances in Alzheimer's disease. *Nature* 1999; **399** (suppl II): A23-31.

3 Davies L, Wolska B, Hilbich C, et al. A4 amyloid protein deposition and the diagnosis of Alzheimer's disease: prevalence in aged brains determined by immunocytochemistry compared with conventional neuropathologic techniques. *Neurology* 1988; **38**: 1688-93.

4 Roberts GW, Gentleman SM, Lynch A. β -A4 amyloid protein deposition in brain after head trauma. *Lancet* 1991; **338**: 1422-23.