A century of cognitive decline

If we live long enough, will we all become demented?

Bruce A. Yankner

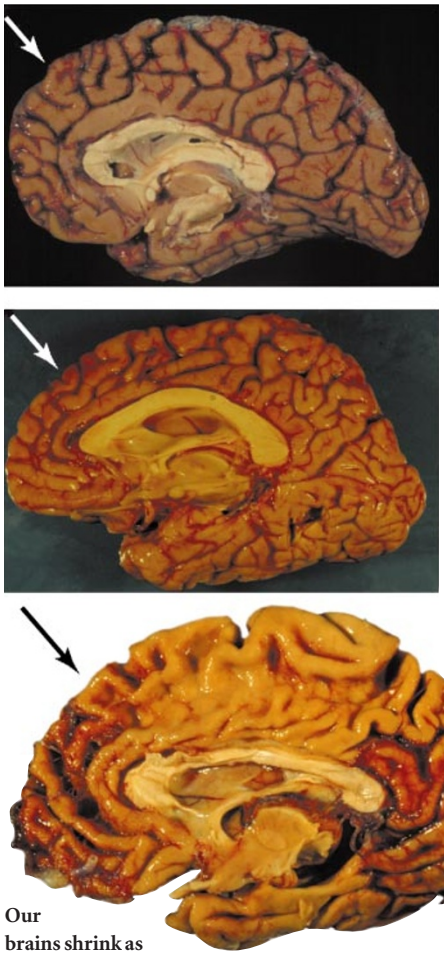
The relationship of longevity to cognitive decline was a major medical issue of the twentieth century. Several evolutionary arguments have been advanced to account for either the preservation or loss of cognitive function with ageing. For example, it has been argued that dementing illness occurs at an age that was rarely achieved during much of man's evolution, and therefore could not have been subject to selective pressure. It has also been suggested that the preservation of function in old age conferred a selective advantage by creating a class of older individuals who could care for children, freeing the mother for other activities such as foraging or food preparation.

However, an equally plausible argument is that the burden of an ageing population would have selected for rapid cognitive and physical decline after the age of maximal reproductive fitness. These arguments are all based on the idea that cognitive decline is linked in some way to the ageing process — a concept that has undergone major upheaval in the past century.

The description by Alois Alzheimer in 1907 of a distinct pathology associated with dementia laid the foundation for the modern study of neurodegenerative diseases. However, it was not until late in the century that the molecular components of amyloid plaques and neurofibrillary tangles — the hallmark lesions of Alzheimer's disease — were elucidated. An intense debate emerged as to which of these two lesions, or some other process, is the cause of dementia.

Proponents of the so-called amyloid hypothesis argue that all genetic mutations that give rise to Alzheimer's disease also predispose to amyloid deposition, and that amyloid is neurotoxic. Sceptics note that amyloid plaques correlate poorly with the degree of dementia, and that animal models of amyloid-plaque deposition do not replicate the neurodegenerative changes in an Alzheimer brain. The debate rages on, and will probably not be settled until drugs are available that block plaque formation.

The focus on plaques and tangles has obscured a potentially more fundamental issue — the relationship of dementia to the ageing process. Although there are rare examples of early-onset dementia due to genetic mutations, the vast majority of dementing illness occurs after the age of 65. For much of the century, Alzheimer's disease was thought of as senility, an inevitable decline in the cognitive ability of aged individuals.



Our brains shrink as we age: the brains of normal 60- and 98-year-olds (top and middle, respectively), and a 76-year-old with Alzheimer's disease (bottom; not to scale). There is age-related atrophy of the frontal lobe in the 98-year-old (arrows), and extreme atrophy in Alzheimer's disease. Photo courtesy of Neil Kowall.

It took the ground-breaking studies of Robert Terry, Henry Wisniewski and their colleagues in the 1970s to show that dementia of the Alzheimer type is a disease, rather than an inevitable consequence of ageing. Plaques and tangles can appear in the brains of many cognitively normal aged individuals, but the degree of pathology is usually much greater in Alzheimer's disease. This watershed concept argued against the idea that senility is normal, and gave rise to the hope that Alzheimer's disease could be prevented or reversed.

Although Alzheimer's disease is not a consequence of normal ageing, it is likely to be related in some way to the ageing process. Most people over the age of 70 exhibit some degree of cognitive decline, particularly for short-term memory, and this accelerates with age. Furthermore, a new clinical entity, called mild cognitive impairment, has been increasingly recognized in the elderly.

This syndrome usually consists of an isolated memory deficit which is not severe enough to fulfil the criteria for Alzheimer's disease, but is greater than average for age. Some, but not all individuals with mild cognitive impairment will progress to Alzheimer's disease. Even asymptomatic individuals who carry the apolipoprotein E4 allele, a genetic risk factor for Alzheimer's disease, can show reduced brain activity in PET scans many years before the onset of cognitive decline. Thus, Alzheimer's disease may be preceded by a long, clinically silent prodrome.

The continuum between normal ageing, mild cognitive impairment and Alzheimer's disease provides support for an old idea, namely, that Alzheimer's disease may be an accelerated form of brain ageing, and raises an old conundrum: if we live long enough, will we all become demented? Aside from the philosophical issues, this concept has important implications for understanding the mechanisms of neurodegenerative diseases. If these diseases represent pathological variants of the ageing process, then understanding mechanisms of normal brain ageing may lead to fundamental insights into the disease mechanisms.

For example, Alzheimer's disease, Parkinson's disease and frontotemporal dementia are all characterized by abnormal accumulations of aggregated proteins. Are these disorders extreme manifestations of the impaired protein folding that occurs to a lesser extent in normal brain ageing? If so, would therapeutic interventions for these disorders also retard normal age-related cognitive decline? Conversely, would therapeutic interventions designed to ameliorate age-related protein misfolding in the brain be effective in a variety of neurodegenerative disorders? The twentieth century has witnessed a dramatic prolongation of lifespan, but little progress in preventing age-related cognitive decline. The anticipated further prolongation of human lifespan in the twenty-first century will be a hollow victory unless cognitive function can also be preserved. ■

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