

NEUROLOGICAL AGEING FACTORS: NEUROBIOLOGY OF AGEING AND PREVENTION OF DEMENTIA

In a world of ageing populations, an understanding of the neurological factors affecting ageing is important.



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By the year 2000 the total human population passed the 6 billion mark. It is estimated to peak at 9 billion around 2070 before declining to 8.4 billion at the end of the century. The decline will largely be due to reduced fertility rates, improved health care and quality of life. However, currently the proportion of elderly (i.e. over 60 years of age) is 10%; this is expected to reach 34% by 2100.

Life expectancy in the USA has reached 78 and 80 years for white men and women, respectively – figures barely achieved by those South Africans who manage to reach the age of 60. Non-communicable diseases that cause premature death are cardiovascular disease, cancer, respiratory disease and the dementias. These diseases in turn are greatly influenced by our state of nutrition (under-nutrition, malnutrition, obesity), physical activity and substance abuse (alcohol, cigarettes, drugs).

Longstanding disability before death has become an increasingly important social and national health problem and we thus distinguish between life expectancy (longevity) and healthy life expectancy (number of years that we live without disability). The two are inter-related. In general, years of healthy life lost because of disability amount to 8% in Western countries as opposed to 18% in developing countries. Interestingly, increased health expenditure per capita increases healthy life expectancy more than total life expectancy.

Disability and ageing in turn have an impact on each other and it is increasingly clear that the two previously opposing sets of hypotheses on the cause of ageing, namely the 'genetic' theories and the 'environmental' theories, are interconnected and may be regarded as comprising different aspects of the same phenomenon.

GENETIC THEORIES

Most ageing research is conducted in rodents

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because methodological obstacles limit the study of DNA and RNA obtained from human brain tissue. Therefore the role of genetic regulation on human brain ageing and the effect of ageing on genetic function are not clear. The genetic theories hypothesise ageing as the consequence of somatic mutations, multiple genetic errors and programmed cell death.

Programmed cell death (apoptosis) states that a cell can only divide a limited number of times before death. Cells that regenerate and then die are similarly restricted. In 1961 Hayflick and Moorhead discovered that human fetal fibroblasts will double about 50 times before dying.² Further, this is species specific and correlates with the longevity of the animal. For example, fibroblasts from a mouse embryo (life span 3 years) divide about 15 times and those from the Galapagos tortoise (life span 175 years) about 90 times.³

Genetic studies of the nematode worm *Caenorhabditis elegans* have provided key insights. This small, soil-dwelling worm consists of a fixed number of cells (959 in the hermaphrodite and 1 031 in the male form) and has recently had its entire genome sequenced.^{3,4} About 15% of its identified cells, most of them neurons, undergo programmed cell death and about a dozen cell death genes are known to control apoptosis.⁴ Several groups of workers have bred long-lived strains with mean increases in life span of up to 70%.² This type of apoptosis underlies the death of all cells.⁴

At the other end of the spectrum, accelerated ageing featuring in all organ systems is found in Hutchinson-Gilford progeria and Werner's syndrome. Progeria is a rare syndrome occurring in 1 in 8 million individuals. Affected patients survive until around the age of 12 years. Most victims (80%) die of myocardial infarctions caused by disseminated atherosclerosis. While normal intellect is retained, these children commonly manifest cataracts,⁵ balding, osteoporosis and neoplasms.⁵ The retention of intellect suggests that

dementia may not be a necessary consequence of ageing or that a more prolonged time period is required for dementia to express itself. Cell lines from patients suffering from either syndrome have diminished replicative life spans. Both diseases implicate a loss-of-function mutation in a gene that encodes a DNA helicase and both conditions produce excessive concentrations of hyaluronic acid.^{2,4,5}

ENVIRONMENTAL THEORIES

Life-span studies suggest that heritability accounts for less than 35% of variance in longevity, while human twin studies show that non-shared environmental factors account for over 65% of variance.⁵

Studies on rodents show that a 40% reduction in caloric intake will extend life span by 40 - 50%. Diminished feeding of rodents not only slows ageing but prolongs the reproductive life span. Such dietary restrictions are thought to lower oxidative stress by slowing metabolism.⁵

Oxidative damage is produced by extrametabolic insults (e.g. smoking, pollution and radiation) or intrinsic metabolic sources. Approximately 2 - 3% of oxygen consumed by cells results in oxygen-free radicals.^{5,6} Free radicals form part of reactive oxygen species (ROS), a collective group of oxygen compounds. Among these the hydroxyl radical initiates a detrimental chain reaction in membranes, called lipid peroxidation. The hydroxyl radical may also react with protein molecules in the cell membrane causing fragmentation, increased susceptibility to proteolysis and crosslinking.⁶ Nuclear DNA and mitochondrial DNA are also susceptible and the net result is that oxidative stress may contribute to ageing and neurodegenerative disease.^{5,6}

Efficient antioxidant defence systems mop up the harmful chemicals in order to achieve some balance and to protect at least partially against ROS damage. These defences include metal chelators

(e.g. transferrin and melatonin), enzymes (e.g. superoxide dismutase and catalase) and antioxidant nutrients (e.g. vitamins A, C, E and beta-carotene).⁶

Healthy ageing may therefore require a proper balance of free radical production and detoxification. Oxidative stress may result from increased sensitivity to free radical damage, decreased antioxidant protection, altered calcium homeostasis or an impaired ability to repair the damage.⁵

THE DEMENTIAS

The presence of dementia predicts poor 7-year survival after age 85. The neuropathological distinctions between 'normal' ageing and disease are frequently obscure, and some neuropathologists have proposed a continuum from normal ageing through pathological ageing to disease states.⁵ For example, neurofibrillary tangles, senile plaques, amyloid deposits, and cholinergic deficits were considered disease markers until studies demonstrated similar alterations in some cognitively intact elderly humans.⁵

In the USA Alzheimer's disease (AD) ranks as the fourth leading cause of death in adults, after heart disease, cancer and stroke. The risk for dementia increases dramatically with age. Over half of the dementias in elderly Western populations are attributable to AD with a prevalence of approximately 6.2% over age 65, 20% over 80, and 45% over 95 years of age. Monozygotic twin studies show that when one twin develops AD, approximately 40% of the co-twins also develop the disorder. Often, however, there is a long delay before the second twin is affected, suggesting both environmental and genetic contributions to the disorder.⁷

AD, AD with cerebrovascular disease and vascular dementia (VaD) account for over 90% of the dementias. We also know that there is a strong association between the risk factors for cardiovascular disease and the above-

Table I. Control of cardiovascular risk factors

- Hypertension – note age-acceptable blood pressure
- Diabetes mellitus – note age-acceptable blood glucose levels
- Platelet aggregation – aspirin 80 - 150 mg a day
- Hyperlipidaemia – dietary modifications and lipid-lowering agents, e.g. statins^{12,13}
- Smoking – should be stopped
- Alcohol – reduce to an equivalent maximum of three tots of spirits a day
- Body mass index – dietary modification and regular exercise
- Endothelial stress and inflammation – thiamine¹⁰
- Hyperhomocysteinaemia – folic acid, vitamins B6 and B12¹²

mentioned dementias. The cardiovascular risk factors, in turn, include hypertension, diabetes, hyperlipidaemia and smoking (Table I). Atherosclerosis, common to both AD and VaD, should be regarded as an inflammatory systemic disease with many different manifestations, e.g. claudication, ischaemic heart disease or cognitive impairment, and should therefore be treated vigorously.⁸ Systemic atherosclerosis begins in the second decade of life (5% of the population affected) and accelerates after the third decade. Less than 4% of 90-year-olds escape atherosclerotic change in their cardiovascular system.⁹ Atherosclerosis predisposes to AD and the prevalence of AD rises with the degree of atherosclerosis. There is also an interaction between atherosclerosis and apo E-4 in the development of AD.⁸

In the penetrating vessels of the brain the vascular endothelial lining is affected and in turn responsible for free radical production, perivascular inflammation, disrupted nutrient supply and selective neuronal (i.e. cholinergic, because of greater vulnerability than other neurons) death with resultant cog-

nitive decline, a situation aggravated by low thiamine levels.¹⁰ This subcortical microvascular pathology not only provides a common substrate for AD, AD and cerebrovascular disease, and VaD, but also clinically manifests mild degrees of AD pathology which, on its own, would have remained asymptomatic.^{11,12}

Since atherosclerosis has a complex pathogenesis which includes, among others hyperlipidaemia, diabetes, hypertension and elevated platelet numbers, lipid-lowering agents play a major role at this level. Apart from their lipid-lowering effect, statins reduce membrane lipid peroxidation by decreasing free radical production and vascular inflammation. The overall net effect of lipid-lowering agents is the reduction of cholesterol, atherosclerotic plaques and plaque rupture, and improved endothelial function and blood flow. The Canadian Study of Health and Ageing (CSHA) showed that the clinical use of lipid-lowering agents was associated with a lower risk of dementia, specifically AD.¹³

Other measures delaying the onset of AD or slowing down its course include:

- low-dose anti-inflammatories, e.g. ibuprofen 200 mg several times a week¹⁴
- red wine (approximately 250 - 500 ml per day, most likely because of ingredients such as resveratrol)¹⁵
- intellectual stimulation and higher education – thought to improve the number of synapses, thus creating greater reserves¹⁴
- hormone replacement therapy (initiated perimenopausally where indicated and restricted to oestrogen)¹⁴
- vitamin E (more than 400 IU) in combination with vitamin C (500 mg or more) daily, – associated with a reduced prevalence and incidence of AD.¹⁶

While the effect of chronic physical and emotional stress on ageing is unclear, elevated glucocorticoids are toxic to rodent hippocampal neurons⁵ and oxidative stress is increasingly

being linked to ageing of the brain and neuropathogenesis.^{6,16}

General lifestyle measures associated with healthy ageing therefore include:^{1,5}

- good sleep
- regular physical activity (enhances brain vascularity)
- cessation of smoking
- reduced salt intake
- ingestion of seafood
- olive oil/Mediterranean diet
- diet rich in vegetables and fruit and low in animal proteins and fats.

References available on request.

IN A NUTSHELL

Our current population of elderly is steadily increasing as is the population's life expectancy (longevity), although not necessarily the healthy life expectancy (years lived without disability).

Life-span studies suggest that heritability accounts for less than 35% of variance in human survival duration.

Therefore 'genetic' theories and 'environmental' theories of ageing are interlinked and may be regarded as comprising different aspects of the same phenomenon.

The genetic theories hypothesise ageing as the consequence of somatic mutations, multiple genetic errors and programmed cell death, while environmental theories focus on oxidative stress resulting from microvascular pathology (especially in the brain) and lifestyle.

Cardiovascular risk factors are paramount in the production of atherosclerosis which determines the degree of disability and the expression of dementia.

Lifestyle changes concentrating on cardiovascular risk factors are recognised as delaying the onset and severity of dementias such as Alzheimer's disease as well as reducing disability.