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Review

The Mechanical Cause of Age-Related Dementia (Alzheimer's Disease): The Brain is Destroyed by the Pulse

Jonathan Stone[a,b,*], Daniel M. Johnstone[a,b], John Mitrofanis[a,c] and Michael O'Rourke[d]
[a]*Bosch Institute, Sydney, Australia*
[b]*Discipline of Physiology, University of Sydney*
[c]*Discipline of Anatomy and Histology, University of Sydney*
[d]*Victor Chang Cardiac Research Institute, Sydney, Australia*

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Abstract. This review traces evidence that age-related dementia (Alzheimer's disease) results from the destructive impact of the pulse on cerebral vasculature. Evidence is reviewed that the neuropathology of the dementia is caused by the breakdown of small cerebral vessels (silent microbleeds), that the microbleeds result from pulse-induced damage to the cerebral vessels, and that pulse becomes increasingly destructive with age, because of the age-related stiffening of the aorta and great arteries, which causes an increase in the intensity of the pressure pulse. Implications for therapy are discussed, and evidence is reviewed that pulse-induced destruction of the brain, and of another highly vascular organ, the kidney, are becoming the default forms of death, the way we die if we survive the infections, cardiovascular disease, and malignancies, which still, for a decreasing minority, inflict the tragedy of early death.

Keywords: Alzheimer's disease, causes of death, dementia, pulse, vascular aging

The brain and its blood vessels are very different tissues. The nerve and glial cells of the brain (its processing machinery) develop from the ectoderm of the embryo; the brain's blood vessels (its system of oxygen supply and metabolite removal) develop from mesoderm, growing from the heart to surround and then penetrate the developing brain. By birth, vessels have branched through every millimeter of brain tissue, and they become involved in most, if not all, diseases or injuries of the brain.

Age-related dementia (ARD) has seemed, to Alois Alzheimer and to most observers since, to be a degeneration of the brain, of its nerve cells. This review brings together two bodies of evidence, from which we propose that the dementia is primarily vascular, caused by the destructive effect of the pulse on the cerebral blood vessels, with the loss of neurons occurring secondarily to vascular breakdown. We argue, further, that dementia is age-related because the pulse becomes more intense and destructive with age.

This idea is uncongenial and counterintuitive. It is uncongenial because it does not appear to offer a simple path to therapy, counter-intuitive because we are used to thinking of the brain as a dependent ward of the heart, not as a victim of its beat. The idea may be correct, however counter-intuitive, for its explanatory power is considerable. It links the pulse to hemorrhage, and to the neuropathology and arteriosclerosis that Alzheimer described; and it explains the link from age to dementia, in the stiffening of the walls of the great arteries, and the effect of that stiffening on the

*Correspondence to: Jonathan Stone, University of Sydney F13, NSW 2006, Australia. Tel.: +61 2 9351 4740; Fax: +61 2 93516470; E-mail: jonathan.stone@sydney.edu.au.

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intensity of the pulse. If this dementia is to be delayed in onset, slowed in progress (as achieved in other forms of neurodegeneration, for example [1]) and treated, it must be understood.

The first of these two bodies of evidence suggests that the neuropathology and cognitive decline of ARD are caused by clinically silent bleeding from small cerebral vessels. This evidence includes the analysis of genetic and non-genetic (lifestyle) risk factors, familial dementia, Down syndrome, the detail of plaques and neurofibrillary tangles, the relationship of plaques to capillaries, evidence that plaques co-localize with microhemorrhages, the relationship between ARD and vascular dementia, the role of neuroinflammation, and the significance of silent microbleeds.

The second line of evidence suggests that the hemorrhage from small vessels is induced by long exposure to the stress of the pulse; that the intensity of the pulse grows with age as the arterial tree stiffens; that vessels respond to this growing stress by maladaptive 'remodeling', followed by hemorrhage; and that the damaging impact of the pulse explains the links between age and dementia, between cognitive and kidney failure in the aged, and between stature and dementia.

Finally, we examine evidence that dementia and kidney failure are emerging as 'top-ten' causes of death as longevity increases, and may be 'default' forms of the death, the way we die, if we survive the old killers—heart disease, cancer, influenza, pneumonia—into the eighth, ninth, and tenth decades of life.

AGE-RELATED (ALZHEIMER'S) DEMENTIA IS A SMALL-VESSEL VASCULAR DEMENTIA

The suggestion that Alzheimer's disease (AD) is a vascular dementia is often refuted on the grounds that 'if it's vascular, it's not Alzheimer's'. The authority for this response can be traced to Alois Alzheimer's description [2, 3] of the dementia whose pathology he described, as a 'distinctive disease of the cerebral cortex'. The dementia seemed distinctive because of its neuropathology, and because two things were absent: there was no co-morbidity (such as syphilis or stroke, the most common causes of dementia then known), and no evidence of focal bleeding at postmortem, such as occurs in stroke. In the concluding paragraph of his 1907 paper, Alzheimer urged that 'we must not be satisfied to force (this distinctive disease) into the well-known disease groups'. Most subsequent investigators have preserved Alzheimer's distinction, classifying dementia following stroke as vascular; and the insidious (co-morbidity-free) onset of dementia has been established as a criterion for a diagnosis of AD (for example in [4]).

In science, authority can be challenged by evidence, and the evidence that ARD is nevertheless vascular in cause can also be traced to Alzheimer's work. In his 1907 report, Alzheimer noted the presence at postmortem of arteriosclerosis of larger vessels, 'focal lesions in the endothelium' and some evidence of neovascularization. Alzheimer's influential mentor, Emil Kraepelin [5], supported Alzheimer's assessment that he had observed a distinctive disease, but Kraepelin also noted 'in senile dementia – alterations that do not differ from arteriosclerotic alterations. A peculiarity of senile arteriosclerosis (is) that the small vessels entering from the surface of the cortex are attacked' (translation from [6]). In recent decades, several lines of evidence have been reported, which suggest that vascular dysfunction is always present in ARD, and may be causal.

'Alzheimer' pathology and vascular pathology co-occur

Examination of the dementia-affected brain postmortem has provided evidence of 'co-occurrence', i.e., of the plaques, neuritic tangles, and neuroinflammation that Alzheimer described occurring together with macroscopic evidence of hemorrhage, in cases with a diagnosis of stroke and vascular dementia; and of larger vessel involvement in cases with a diagnosis of AD (i.e., of insidious-onset dementia). Whole volumes of journals have been committed to consideration of this co-occurrence [7–9]. One commonly adopted response to the co-occurrence, for example in [10, 11], is to refer to the dementia in a brain with both plaques and stroke pathology as 'mixed'.

The 'mixed' notation implies that plaques, tangles, and inflammation are not vascular pathologies, but distinctive 'Alzheimer' pathologies. Other authors make the point, in several ways, that involvement of vasculature in dementia is not surprising; vessels infiltrate the brain at the sub-millimeter level, and any degeneration must involve the vasculature. The question is not whether two disease processes co-exist (the mixed dementia hypothesis) but, as Hachinski [12] noted, whether the vessel damage is causal or consequential to degeneration of neural tissue. A number of authors [13–19] have opted for the view that cerebrovascular damage is causal; that the plaques, neurofibrillary tangles, and inflammation that Alzheimer observed occur

downstream from cerebrovascular pathology, so that vascular and 'Alzheimer's' dementia differ only in the involvement (or not) of larger vessels.

Non-genetic risk factors for dementia, hemorrhagic stroke, and cardiovascular disease overlap

The overlap of lifestyle (modifiable) risk factors between dementia, stroke, and cardiovascular disease has been reviewed extensively [20–25]. Though these reviews develop different emphases, they identify high blood pressure, uncontrolled diabetes, cholesterolemia, arteriosclerosis, and atherosclerosis as significant factors predisposing to cognitive loss. A more skeptical view can be found in Daviglus and colleagues [26], based on their assessment of the quality of preceding studies. Among most investigators, however, there is consensus that dementia is delayed by factors that improve cardiovascular health. Exercise and weight control are also identified as preventative against dementia (for example [27]), presumably because they also optimize cardiovascular health. Risk factors for hemorrhagic stroke and vascular dementia include, in addition to age, hypertension and vessel-related factors such as amyloid angiopathy [24, 25]. This overlap of risk factors suggests that cardiovascular disease, stroke and ARD have a cause in common. We suggest, following [15, 18], that the common mechanism is damage to the vasculature. The suggestion of vascular damage as a cause is not, of course, controversial for cardiovascular disease or stroke; for ARD, it is central to this review.

The genetic risk factors for dementia, hemorrhagic stroke and vascular disease overlap

The genetic risk factors for dementia come in (at least) three forms. In each form the genetic variance that predisposes to/regulates dementia also regulates vascular dysfunction.

High penetrance (familial AD) mutations damage vessels

Several genetic mutations cause high penetrance, early-onset dementia, often called familial AD. These mutations occur [28] in *AβPP*, the gene for amyloid-β protein precursor (AβPP); or in *PSEN1* or *PSEN2*, genes for proteins which regulate the enzyme γ-secretase, which is important in the cleavage of AβPP, to produce the peptide amyloid-β (Aβ). The genome of the first case described by Alzheimer has recently [28] been shown to contain a single base substitution in *PSEN1*. This clustering of dementia-causing mutations in relation to Aβ production has led to the conclusion that ARD, whether in these severely affected families or in the more common 'sporadic' cases, is a disease of Aβ, independently of the vasculature.

In several forms of 'familial AD', however, there is evidence that the cerebral vasculature is damaged (reviewed in [29]); these include a Dutch form [30] in which amyloidosis of vessels is associated with intracerebral hemorrhage; a Flemish familial dementia in which stroke is also common and plaques form around damaged capillaries [31]; a familial dementia in an Iowa family, in which an AβPP mutation is also associated with severe amyloid angiopathy [32]; and a Belgian family in which an AβPP mutation is associated with both early onset dementia and cerebral hemorrhage [33].

Overall, seven *AβPP* mutations have been identified in patients with cerebral amyloid angiopathy [34], the deposition of amyloid (usually Aβ) in the wall of cerebral vessels, predisposing them to hemorrhage. Of these seven, three have also been classified as familial dementia mutations or have been identified in patients with an autopsy diagnosis of AD (A692Q, E693 G, A713T) [35–39], indicating overlap in the genetic etiology, clinical signs, and neuropathology of ARD and amyloid-induced hemorrhage. Other genes linked to familial dementia, *PSEN1* and *PSEN2*, have also been shown to harbor pathogenic mutations causing cerebral amyloid angiopathy or intracerebral hemorrhage [40–43]. The ties between presenilin and vascular health are also highlighted by the observation that $Psen1^{-/-}$ mice that survive until birth exhibit cerebral hemorrhages, among other central nervous system abnormalities [44].

In summary, in families afflicted with early-onset dementia related to a specific mutation, vessel damage is consistently involved. As with non-familial dementia, it can still be debated whether vascular damage induces the formation of plaques and neurofibrillary tangles, or vice-versa. But it remains possible that the primary damage in familial dementias is vascular; that these dementias too are forms of vascular dementia.

Lower penetrance regulation of non-familial dementia

At least 10 genes have now been identified, of which widely occurring variations (alleles) modulate the risk of non-familial ARD ('sporadic' AD). Of these genes, *APOE* (apolipoprotein E) is the most powerful modulator; for individuals with two copies of the *APOE-ε4*

allele, the chance of suffering dementia is increased by as much as ten-fold [45]. Two lines of evidence suggest that the damaging *APOE-ε4* allele predisposes to dementia by damaging the cerebral vasculature. First, *APOE-ε4* also predisposes to stroke and vascular dementia [46, 47], to dementia pugilistica [48] (which has a strong vascular/hemorrhage component), and to cardiac/coronary disease [49, 50]. The factor common to these conditions is, we argue, loss of integrity of blood vessels. Second, evidence has emerged in animal models that *APOE* plays a significant role in spontaneous hemorrhage from cerebral vessels in a mouse model of cerebral amyloid angiopathy [51], and that *APOE-ε4* damages the integrity of cerebral vessels and of the blood-brain barrier, by inducing a pro-inflammatory action in pericytes [52–54], via the cyclophilin A pathway. This is argued to be a direct effect of *APOE-ε4* on cerebral vessels and, as these authors note, is a strong indication of the involvement of vascular damage in dementia.

In addition, genome-wide association studies have identified other genetic modulators of AD risk. While variations in these genes confer only a small (<20%) increase in risk of dementia when considered in isolation, the genes involved cluster into common molecular pathways. Collectively [55], the current 'top 10' genes which contain polymorphisms that influence non-familial (sporadic) dementia play roles in pathways relating to lipid metabolism, and to innate and adaptive immunity [56]. Lipid metabolism is strongly associated with cardiovascular health, and the immune system may regulate the extent of damage to local nervous tissue following hemorrhage. For example, two of the top 10 dementia-risk genes (clusterin and complement receptor 1) are involved in complement activation, and inhibition of the complement cascade has been shown to attenuate brain injury resulting from intracerebral hemorrhage [57, 58]. Finally, a recent meta-analysis of three large genome-wide association studies (over 14,000 participants) specifically identified cardiovascular disease-related pathways as being enriched for genetic risk variants for AD [59].

Down syndrome

Down syndrome is a trisomy of chromosome 21. Those affected often show an early-onset dementia comparable in its neuropathology to ARD, particularly in the occurrence of Aβ+ plaques and neurofibrillary tangles. One of the 200–300 genes on chromosome 21 is *AβPP*.

More generally, however, Down syndrome has many pathologies, including abnormalities of the heart and vasculature. Some of the vascular abnormalities are morphological, including septal defects of the heart [60], malformation of the large cerebral arteries [61], anomalies of the portal vein system [62], and abnormally high numbers of retinal vessels at the optic disc [63]. At the cellular level, Costa and colleagues [64] have reported a reduction in the number of circulating endothelial precursor cells, and an increase in their fragility. Some of the outcomes are benign, such a reduction in Down syndrome sufferers in the neovascularizing complications of diabetes, and in the occurrence solid tumors, effects attributed the anti-angiogenic factor endostatin, the gene for which is also located on chromosome 21 [63]. As previously [18], we suggest that the early-onset dementia and Alzheimer-like pathology seen in Down syndrome result from a fragility of cerebral vessels caused by the trisomy.

Plaques form at the site of microhemorrhages

Plaques and microhemorrhages occur in similar sizes and numbers

Hemorrhage in the brain can be detected postmortem with a chemical test for iron, the Prussian blue or Perls reaction. The reaction identifies the ferric (Fe^{3+}) ion and can detect iron moieties at the sites of cerebral hemorrhage, long after other blood-derived elements (red cells, white cells, clotting factors) have disappeared. Cullen and colleagues [16] developed the Perls reaction to detect Fe^{3+} with high sensitivity in the postmortem human brain, showing small haem-rich [18] deposits in cerebral cortex, increasing in number with age and dementia. They further showed [15] that haem-rich deposits match $A\beta^{+}$ plaques in size, numbers, and distribution, implying that hemorrhage and the deposition of insoluble Aβ occur at the same site, the senile plaque. Taken alone, this colocalization does not indicate whether a bleed causes the plaque, or vice-versa. Other evidence suggests that the primary lesion is vascular.

Microhemorrhages and plaques form in relation to capillaries

Miyakawa [65] used electron microscopy to show that many plaques surround capillaries. Kumar-Singh and colleagues [17, 31] reported, using light microscopy in both human material and a transgenic mouse model, that 'dense-core' plaques form around capillaries. Cullen and colleagues [15, 16] reported that haem-rich deposits and $A\beta^{+}$ plaques form in statistically close relationship to capillaries, often

surrounding them. Purushothuman and colleagues [66] used thin-section light microscopy and immunohistochemistry to confirm these relationships.

Blood derived proteins are found in neuropil of end-stage brain

If the aging brain suffers continual small-vessel hemorrhages then, at postmortem, there should be evidence of blood in the neuropil. Cullen and colleagues [15, 16] tested this point, reporting that red cells, fibrinogen, and von Willebrandt's factor are present in the neuropil of the end-stage dementia brain, in relation to a minority of plaques. Because most of the cells and proteins released into the neuropil by a hemorrhage are removed within 7d of the bleed, they interpreted these blood-specific cells and proteins as evidence of recent bleeds.

Hemorrhage can cause the formation of plaques, neuritic tangles, and inflammation

The idea that microhemorrhages (bleeds from capillaries) cause the formation of plaques at the sites of the bleeds was proposed by Cullen and colleagues [15]. The demonstration [67] that hemoglobin induces the oligomerization of Aβ *in vitro* led to the suggestion [18] that this induction causes the deposition of insoluble forms of Aβ in human senile plaques. This role of hemoglobin in the formation of plaques has been confirmed by two experimental tests. Chuang and colleagues [68] reported that human hemoglobin injected into the hippocampal cortex of AβPP/PS1 transgenic mice causes the deposition of Aβ along the track of the injection; and Purushothuman and colleagues [66] made small, hemorrhagic (needlestick) lesions in the cerebral cortex of the young, healthy rat, reporting that plaques, neurofibrillary tangles of hyperphosphorylated tau, and macro- and microgliosis occur at the site of hemorrhage. These observations confirm that the pathology that Alzheimer described a century ago can result from hemorrhage. Chuang and colleagues suggested that the binding of hemoglobin to Aβ has the protective role of reducing the toxicity of hemoglobin, confirming earlier suggestions (e.g., [69]) that Aβ may be protective *in vivo*.

Three Corollaries

Simplifying hypotheses (in the present case that plaques form at the sites of small-vessel hemorrhage) often raise questions that probe the explanatory value of the hypothesis. Here are three such examples.

Does dementia predispose to stroke?

If ARD is caused by small-vessel fragility progressing to hemorrhage, a correlation might be expected between the dysfunction of large vessels (as in stroke) and the breakdown of smaller vessels (as proposed for ARD). Clinically, stroke and insidious-onset dementia co-occur extensively (see above). When they occur separately, stroke predisposes to dementia, and vice-versa. That is, patients who have suffered a stroke, but are cognitively unimpaired, have a higher risk than age-matched controls of developing dementia [70]; and patients with cognitive impairment suggesting ARD (AD) have an increased risk of stroke [71, 72].

Why is neuroinflammation prominent in ARD?

In the 1990 s, Rogers, McGreer, and colleagues [73–76] drew attention to the prominence of inflammation in the end-stage ARD brain. They noted that elements of Alzheimer's original description, particularly of cellular proliferation around plaques, would in modern terms be identified as inflammation; and their surveys showed intense expression of a range inflammation-related proteins and cytokines at postmortem.

Their observations complemented evidence that non-steroidal anti-inflammatory drugs are protective against dementia. These studies began with an observation [77, 78] that dementia is uncommon in arthritis patients. After a series of more systematic studies, meta-reviews concluded [18] that the use of non-steroidal anti-inflammatory drugs (in arthritis) is associated with a delay in the onset of dementia.

Intervention studies followed, but were disappointing [79, 80], suggesting that, despite the prominence of inflammation in the degenerating brain, inflammation is not the major cause of continuing degeneration. Inflammation is reliably prominent, however, presumably because it is an outcome of intracerebral hemorrhage [81].

The silence of microbleeds

The evidence summarized above implies that ARD is insidious because the vessels that are damaged supply too small a volume of brain tissue for their failure to generate acute symptoms; and that clinically silent hemorrhages occur before dementia can be detected. On the latter point, several studies have suggested that clinically silent cerebrovascular incidents outnumber those that give rise to symptoms, and therefore a diagnosis of stroke, by several-fold [82].

Evidence that microhemorrhages occur before dementia is detectable is nevertheless limited, because

plaques are too small (typically 100 μm) to be observed *in vivo*. Two lines of evidence are available, however, on this point. Cullen and colleagues [15, 16] detected haem-rich deposits and plaques in brains with no clinical history of stroke, and as young as 29 years. Both were very sparse in the younger brains, and their frequency increased with age and with a diagnosis of ARD. 'Senile' plaques are thus not unique to old age and dementia; they occur in youth and in health and accumulate with age. Their cumulative effect, beyond some presumed threshold, can be detected, in later life, as cognitive loss.

Second, recent advances in the resolution of cerebral imaging have enabled the detection in cognitively normal humans of cerebral hemorrhages as small as 5-10 mm. Termed silent microbleeds, these small hemorrhages resemble the haem-rich deposits reported by Cullen and colleagues in being clinically silent (by definition) and in the increase of their occurrence in association with age [83], with memory loss, mild cognitive impairment, and a diagnosis of AD [84, 85]; and with the deposition of amyloid [86]. They also resemble plaques in the increase of their occurrence in relation to high blood pressure and APOE-ε4 [83]. Microbleeds are too big to be the haem-rich deposits described by Cullen and colleagues [16] or plaques, both typically <100 μm in diameter, and their frequency is much lower overall than that of plaques or deposits. It seems possible that, at this improved level of resolution, the scanners are detecting just the largest of a cohort of clinically silent microbleeds. Previous workers (for example [87]) have suggested that clinically evident stroke is the 'tip of an iceberg' of clinically silent bleeds which do most of the damage in vascular dementia. We suggest, following [15], that most of the damage done in ARD is caused by small-vessel (capillary) bleeds.

The Exception and summary

Proof, philosophers of science have long concluded, is just not available in science. Whatever evidence suggests, in the present debate for example, that small-vessel hemorrhage causes plaque and tangle formation, it remains just possible that plaques and tangles cause the hemorrhage. In the course of such debates, each scientist makes a judgment, or withholds judgment and waits for more evidence. In 2004, de la Torre [13], summarizing many years' consideration, made a call, and proposed that ARD be termed a vasocognopathy. The present review supports his suggestion, though our hypothesis places emphasis on hemorrhage, rather than the structural blockage of capillaries, as the key vessel pathology.

A judgment like this, after a long debate, is often the beginning of another quest—if microhemorrhages cause plaques and tangles, what next? In attempting that quest, it is sometimes the observation that does not fit the idea that can be informative. There is one risk factor for ARD that is not a risk factor for cardiovascular disease, trauma to the head. Could this exception, we asked, give a clue to the next challenge, which is to understand why cerebral vessels bleed in an age-related pattern?

In the next sections, we trace ideas that arose from this exception, and led us in an unexpected direction.

WHAT CAUSES THE CEREBRAL CAPILLARY BED TO BLEED? THE CONCEPT OF PULSE-INDUCED ENCEPHALOPATHY

Bateman [88] and Henry-Feugeas [87, 89] proposed that the pulse damages the brain, by damaging its blood vessels, causing 'encephalopathies'. Both included 'AD' in the spectrum of encephalopathies that might be pulse-induced; they also considered vascular dementia and normal pressure hydrocephalus. These authors did not speculate on the precise pathology of pulse-induced trauma, but both were influenced by the early work of Byrom [90], describing microvascular damage to the brain in a hypertensive rat model. What is the evidence for pulse-induced damage to cerebral vessels?

Why the brain is vulnerable to the pulse

Three features of the evolved human brain make it vulnerable to the pulse. All relate to the power of the brain.

Processing power, high metabolism, just-in-time supply

One source of vulnerability is well understood, and widely known. The metabolism of the brain (its consumption of energy) is high. The brain's demand for oxygen is met by a large flow of blood, volume/weight (∼500 ml/kg/min, about 20% of resting cardiac output); the blood is required to provide oxygen, to fuel oxidative phosphorylation in its nerve cells. The supply of oxygen to the brain is constantly within 10 seconds of failure, and within 2 minutes of irreversible damage. The heart can recover from 10 minutes of ventricular fibrillation; the brain cannot.

Low vascular impedance, high pulse penetrance

The need for a high-volume flow of blood creates a second and opposite vulnerability; it makes the brain vulnerable to the long-term beat of the heart. To enable high flow, the resistance of the brain's vessels is low. Its capillary bed is profuse, its arterioles are kept dilated by autoregulatory mechanisms and the pulse penetrates into the capillaries, and can be detected in the cerebral veins [91]. The finest vessels of the brain (its capillaries) are thus exposed to every beat of pulse, throughout life. It was this exposure that led Bateman and Henry-Feugeas [87–89] to the idea that, with long exposure, the cerebral vessels are damaged by the pulse.

The desire—and the potential—for longevity

The processing power of the brain gives us consciousness and, with that, hope, determination and intellectual power: hope for a long life, determination to achieve it and the intellectual power to understand and counter whatever shortens life. The human brain makes decisions for longevity, with success. That success is a third factor in the vulnerability of the brain; by extending life, the human brain exposes itself to the pulse for longer periods.

In this context, an evolutionary biologist might argue that the human brain has evolved to function to the age required to generate and raise children. Beyond, say, the fifth decade of life, the aging of the brain has, by this argument, not been subject to evolutionary pressure. Furthermore, the pace at which we have increased longevity (doubling average lifespan since the 19th century), has outstripped the pace of which evolution is capable. We cannot adapt in an evolutionary way to the pace of this major change in human life.

What happens to an organism that survives the lifetime for which it has evolved? Death in mammals—if not from disease or predation or starvation—is typically from failure of an organ, or of several. We argue below that, for humans, the organs that fail in extreme longevity are the brain and kidney, both high-blood flow organs, both damaged by long exposure to a pulse of increasing intensity.

External trauma damages cerebral vessels

The concept of trauma to blood vessels arising from the pulse can be seen as novel, and some discussion of familiar forms of brain trauma is warranted.

The idea that boxing could cause dementia was controversial in its time, resisted by the enthusiasts of the sport. Most boxers are cognitively normal when they retire from the ring, and most remain so, but, in subsequent decades, boxers as a group suffer dementia at rates above the general population [18]. Dementia pugilistica shares several features of ARD. The cognitive decline is slow and age-related, and increases in frequency and severity as the ex-fighters age [92, 93]; onset and progress are regulated in the same way by alleles of APOE [48, 94]; and, at postmortem, the brain shows atrophy, plaques, and tangles [95–98] and loss of cholinergic neurons from the basal forebrain [99].

A key step in the overcoming of skepticism about boxing-induced dementia was Martland's [100] demonstration of the neuropathology of head trauma. He showed that 'closed-head' trauma (including boxing) causes multiple small hemorrhages, with the released blood forming a collar around the ruptured vessels, and suggested that trauma-induced hemorrhages may be too small to cause acute, stroke-like symptoms, but sufficient to induce major, irreversible cognitive changes. Martland's interpretation of vascular damage in brain trauma was confirmed by experimental work. In a baboon model of cerebral cortex [101], trauma was reported to induce petechial (small, punctate) bleeding and morphological changes in the endothelium of capillaries. In a pig model [102], the cerebral cortex 10 hours after a brief (<1 second) compression showed 'edema, infiltration of inflammatory cells, pericapillary hemorrhage, and petechial hemorrhages in the white matter'. Evidence that, within a few days of head trauma, AβPP is upregulated in human brains [103] and that amyloid deposition occurs rapidly, within days [104] or hours [105], provides a link to the amyloid deposition seen in ARD, familial dementia, and Down syndrome.

In recent reviews, given urgency by the recognition of cumulative brain damage (chronic traumatic encephalopathy) in those who play hard-contact sports, head trauma is confirmed as a major 'environmental' cause of dementia [106], with many forms of pathology associated. These reports include hemorrhage as one of the sequelae of head trauma [107], but give more emphasis to 'Alzheimer'-like pathologies, such as amyloid deposition and the hyperphosphorylation of tau [106, 108]. The degree to which hemorrhage generates these latter pathologies remains undefined in the literature on trauma-induced dementia.

Vascular aging: Internal trauma to cerebral vessels

The strongest risk factor for dementia is age, and the concept of vascular aging has been the subject of recent reviews [109–112]. The idea that vascular

aging is a key determinant of longevity is not new. The renowned Canadian physician, William Osler, wrote in 1906 ([113] at p. 848):

> *"As an involution process, arteriosclerosis is an accompaniment of old age, and is the expression of the natural wear and tear to which the tubes are subjected. Longevity is a vascular question which has been well expressed in the axiom that "a man is only as old as his arteries". To a majority of men, death comes primarily or secondarily through this portal. The onset of what may be called physiological arteriosclerosis depends in the first place on the quality of arterial tissue (vital rubber) which the individual has inherited, and secondarily upon the amount of wear and tear to which he has subjected it"*

Loss of elasticity: Its effect on flow and pressure

The aging of the vasculature has many features, important among them the loss of elasticity in the walls of the aorta and great arteries [110]. Comparing the aortic wall of a twenty-year-old with that of an eighty-year-old, O'Rourke and Hashimoto [109, 110] noted that the elastic modulus of the wall, which is frequency-dependent, is higher in the older tissue, at all frequencies tested. At age 80, the modulus is four to nine-fold higher than at age 20. A comparable stiffening has been reported in other large, predominantly elastic arteries [110].

The loss of elasticity occurs because of cyclic stretching and relaxation of the elastic component of the aortic and arterial walls, with each pulse (30 million times a year). As argued previously [110], the non-cellular, elastic components of the arterial wall are subject to a 'stress/number' relationship, such that fracture becomes more likely as the number of cycles of stretch and relaxation increases. The thoracic aorta is most vulnerable, since its wall stretches more (10-15% of diameter in the young) than the wall of any other artery. Breakdown of the elasticity of the wall with age is correspondingly greater in the aorta, the elastic modulus of the wall increasing 4–9 fold between 20 and 80 years of age. From being the most distensible artery, the aorta becomes the least distensible. As a result, the velocity of at which the pulse propagates along the aorta (the pulse wave velocity or PWV) increases 2–3 fold from age 15 to 75, from ~5 to 10–20 m/s; in muscular arteries such as carotid, cerebral, brachial, radial, and femoral, PWV increases from 8 to 10 m/s.

The effects of loss of elasticity can be described in many ways. Two are of particular significance here.

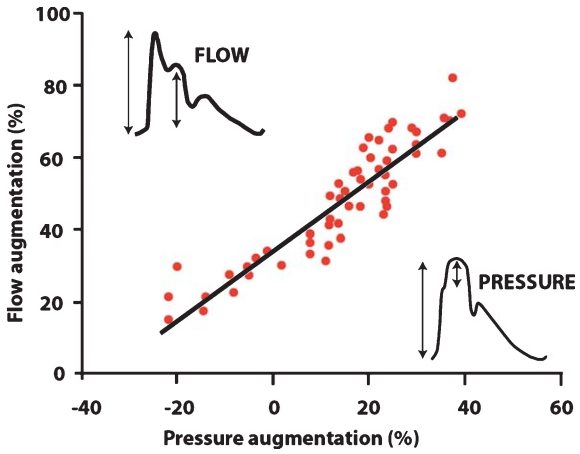

Fig. 1. The relationship between augmentation and simultaneously recorded flow and pressure in the carotid artery of 56 normal subjects aged 20–72 years ($R = 0.913$, $p < 0.0001$). Lowest values of augmentation were seen in younger and highest values in older individuals. Insets show the parameters used for calculating flow and pressure augmentation, as late systolic augmentation/pulse height. Redrawn from Fig. 10 in [110].

First, the pressure pulse generated by the left ventricle is increased directly by stiffening of the proximal aorta. Second, the initial pulse in early systole is further increased or "augmented" by a wave reflected from the trunk and lower limbs; the increased aortic PWV causes this wave to travel faster so that it returns earlier, in mid-systole, augmenting pressure and flow in the carotid arteries which supply the brain. Pressure and flow augmentation are tightly correlated (Fig. 1); both increase with age and both can induce maladaptive response in cerebral arteries.

Direct measurement of cerebral blood flow became available late last decade, using magnetic resonance and trans-cranial Doppler ultrasound techniques. These measurements (for example [114], reviewed in [115]) showed that mean cerebral blood flow in the basilar and internal carotid arteries declines with age, but that arterial flow becomes concentrated in systole, and falls to near-zero during diastole. As a consequence, the volume of blood entering the brain within each systole increased with normal aging (between 25 years and 70 years mean ages) by about 50% (Bateman and colleagues [114]).

This link from age to loss of elasticity to the augmentation of pulse intensity is, we argue below, the link from age to dementia.

The response of arteries to mechanical stress

The tissues of arterial walls respond actively to mechanical stress [11, 116], in ways that have been described at molecular and cellular levels.

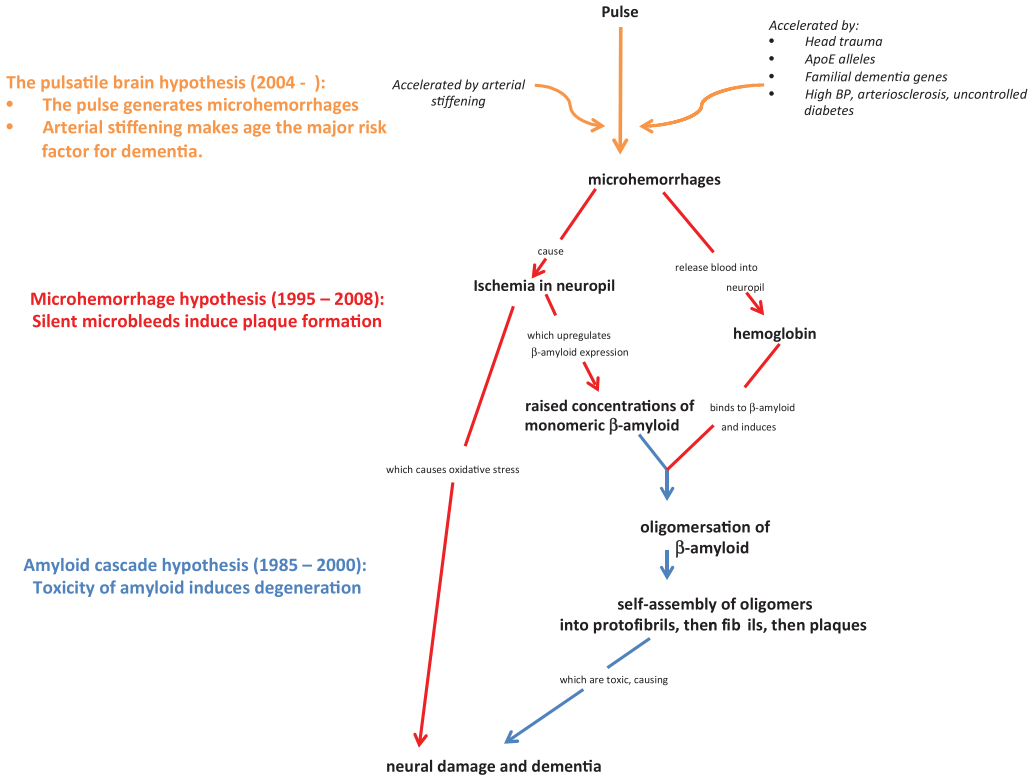

Fig. 2. Relationship of the 'pulsatile brain' hypothesis to the microhemorrhage and amyloid cascade hypotheses. The pulse damages cerebral vessels, inducing the hemorrhages that create the proteinopathies; neuronal death results from the hemorrhages and perhaps also from the toxicity of abnormal proteins. Genetic and environmental regulators of dementia may act predominantly at the initial pulse-causes-hemorrhage step, by regulating vessel fragility. Age-related stiffening of the arterial tree makes age a major factor in the cascade of events.

Cellular response: Vascular remodeling

The idea that adult vessels can respond to their local environment in well-adaptive ways goes back at least to the 18th century, when the English surgeon John Hunter experimented on the artery that supplies the antlers of deer, kept in his private menagerie in London. The antler artery, an extension of the superior temporal branch of the external carotid, grows and shrinks as the antlers form in spring and are shed in autumn. Hunter's experiment was to ligate the artery supplying an antler during the rapid phase of antler growth. Although initially the antler cooled noticeably, it eventually survived and grew; and Hunter showed by dissection that small arteries near the point of ligation had grown to bypass the ligature, in response, he suggested, to a 'stimulus of necessity' arising in the tissue supplied.

That observation emboldened Hunter [117–119] to try to avoid amputation of the lower leg, in cases of aneurysm of the popliteal artery, which runs behind the knee joint to supply the leg. Such an aneurysm threatens the patient's life, by hemorrhage should it burst. Surgeons would ligate the artery to prevent the hemorrhage but, for fear that the leg below would become gangrenous, they also amputated the leg. Hunter persuaded his next patient with this aneurysm to let him try just ligating the artery, trusting that the small articular arteries around the knee joint would respond to the leg's need for blood. The leg did survive in this and later cases; and Hunter's operation has influenced vascular surgeons ever since. Arteries respond to the needs of the tissues they supply and can grow (and shrink) in response to changes in those needs.

This early concept has evolved, for the brain, into the concept of the neurovascular unit [11], which summarizes the complex interaction of these brain tissue and the tissue of the cerebral vasculature, tissues which, as noted above, have different embryological origins. The interaction is adaptive, matching blood delivery to tissue needs.

Not all remodeling is well-adaptive, however. Iadecola [11] summarized maladaptive responses of cerebral vessels, including stenosis of large arteries, small vessel arteriosclerosis, vascular rupture,

and amyloid deposition in vessel walls as breakdowns of the 'neurovascular unit', the molecular conversation between cerebral vessels and the brain tissue they supply. Lehoux [116] distinguished volume- and pressure-driven aspects of remodeling. Pressure-driven responses include maladaptive changes: hypertrophy and hyperplasia of vascular smooth muscle cells, increased deposition of collagen, increased distention of vessels, and vessel rupture.

Molecular response: Signaling pathways

The effects of shear forces, caused by laminar flow over cells, and of mechanical stretch have been studied in endothelial cells. In cultured endothelial cells (reviewed [116]) shear stress induces the formation of reactive oxygen species (ROS) by regulation of the enzyme NADPH oxidase. The induction is transient at physiological levels of stress, but sustained at high stress levels. The damage caused by shear-induced ROS production is limited by the cells' upregulation of endogenous anti-oxidants, including glutathione, and the superoxide dismutases. Mechanical stretch of endothelial cells also upregulates their production of ROS [116], and again there is evidence that the damage caused is limited by anti-oxidant mechanisms. Vascular smooth muscle cells also respond to stretch with the production of ROS; in these cells, prolonged exposure to stretch can, in environment-dependent ways, change their contractility, and arguably [116] their phenotype. In addition, the induction of ROS by stretch and shear stress, and the accompanying induction of anti-oxidant pathways, have been demonstrated in isolated arteries, in which endothelial, smooth muscle, and other cell classes remain in their normal relationships.

ROS activate several signaling pathways, including the mitogen-activated protein kinase, and the oxidant-dependent phosphorylation of ERK1/2 and JNK. These pathways can lead to a range of downstream responses, by regulation of cytosolic and nuclear pathways.

These insights provide ways of thinking about how a breakdown in the neurovascular unit can lead to vessel pathology, although they do not yet identify specific pathways. Lehoux [116] stresses the balance between oxidant and anti-oxidant reactions of endothelial and vascular smooth muscle cells, suggesting that pathological remodeling results from a breakdown in that balance [117].

Relating arterial stiffness to dementia

Arterial stiffness is difficult to measure directly, *in vivo*, and investigators have estimated stiffness indirectly. They use non-invasive ways to record the waveform of pulse in a superficial artery, and from those waveforms they calculate three (at least) measures of arterial stiffness: PWV (usually measured between the carotid and femoral arteries), the augmentation index (AI), and the windkessel function. Each is a value derived from the arterial pulse waveform, so they are not independent.

Fujiwara and colleagues [120] related PWV to cognition in an elderly cohort in a Japanese community, and concluded that PWV is a 'potent risk factor' for cognitive loss, even after controlling for age, education, blood pressure, and cholesterolemia. With comparable controls, Hanon and colleagues [121] in France, Scuteri and colleagues [122] in Italy, and Elias and colleagues [123] in the USA reached similar conclusions. PWV, their work suggests, may be a direct cause of cognitive loss. Recently, in an Australian cohort, Singer and colleagues [124] reported the same inverse correlation between PWV and cognitive performance among men, but not among women.

Recent reviewers [125, 126] have discussed the AI as a factor in vascular aging; this index measures the extent to which systolic pulse wave is increased (augmented) by a wave of pressure reflected from the peripheral arterioles, mainly from the lower limbs. The speed at which this wave is reflected increases with the square root of the elastic modulus (stiffness) of the walls of the great arteries, so that in advanced years the reflected wave becomes superimposed on the primary pulse, increasing the amplitude of the pulse, measured as the pulse pressure (systolic minus diastolic). Shimuzu and Kario [127] reviewed the definition of the AI, and how it is measured in practice. In a meta-analysis, Vlachopoulos and colleagues [128] concluded that the AI is a strong predictor of cardiovascular events, and all-cause mortality.

Other workers have used the term 'windkessel function', imported from general fluid dynamics, to describe the elastic expansion of the aorta and great vessels, and 'windkessel dysfunction' to describe the loss of elasticity. In particular, Henry-Feugeas [89, 129] proposed that windkessel dysfunction induces an encephalopathy of aging, comprising cerebral hemorrhage and general cerebral hypoxia; and Bateman and Levi [114] argued that windkessel dysfunction is a component of both normal aging and senile dementia.

However it is measured or expressed, there is considerable agreement that arterial stiffening increases the intensity of the pulse, and, when both are quantified, correlates with cognitive decline during aging.

Two corollaries

This step of our hypothesis—that the pulse induces the small vessel hemorrhage, which causes insidious-onset dementia—raised several questions, which initially seemed esoteric, yet to provide a test of the hypothesis.

Why are kidney failure and dementia closely linked?

The co-occurrence of dementia and nephropathy in the aged is so common clinically that reviewers have begun to discuss the idea of 'clinical interaction' between small vessel disease in the kidney and brain [130]. Weight-for-volume, the kidney receives even more blood than the brain (3.7 l/kg/min, as against 0.54 l/kg/min for the brain). The kidney receives this high flow not for the oxygen in the blood (oxygen saturation in the renal veins is close to arterial levels [131]), but for its role of eliminating toxins from the blood. As with the brain, the high flow is achieved by the low resistance of the kidney's vasculature, and the pulse penetrates through the capillary bed. O'Rourke and Safar [132] commented that "these 2 organs throb with each beat of the heart, and their venous efflux ... retains pulsations transmitted through the capillary network" [132]. Mogi and Horiuchi [130] noted that "the kidney and brain are low resistance end-organs that are exposed to high-volume blood flow throughout the cardiac cycle".

Kidney function (for example, creatinine clearance [133]) breaks down with increasing arterial stiffness, and several workers [130, 134, 135] have noted a relationship between age, renal dysfunction, and cerebral dysfunction, suggesting ideas (e.g., the 'strain artery' hypothesis [134]) to explain the relationship. We note below that, as death rates from coronary artery disease and cancer decline, dementia and kidney failure are emerging as top-ten causes of death. Whether or not there is an interaction between them, it is striking that small vessel disease in high-flow, low-resistance organs such as kidney and brain is increasingly a cause of morbidity and death. We suggest, following [132], that the link from age to small vessel disease in the kidney, as in the brain, is the stiffening of the arterial tree.

Why does short stature predispose to cardiovascular disease and dementia?

The risk of cardiovascular disease is related to stature, being greater in those with smaller stature (reviewed [136]). The risk of dementia in old age is also related to stature, also being greater in those with smaller stature (reviewed [137]). The influence of height on cognition during aging is considerable. In one study [138], the frequency of cognitive loss among men in the tallest quartile was 59% of the frequency among men in the shortest quartile; another [139] concluded that "... ..after adjustment for age, the prevalence of poor cognitive performance declined consistently with increasing height from 25% in men shorter than 154 cm ... to 9% in those taller than 174 cm".

The pulse wave is affected significantly by height. Specifically, height affects the latency of the pressure wave that is reflected, with every systole, from the peripheral arteries of the limbs back into the aorta. The latency is shorter in shorter bodies [136, 140, 141] and this shorter latency may be the parameter that affects cognition. In the tall young, the latency of the reflected wave (300 ms), means that it reaches the aorta in diastole. When its latency is reduced, the reflected wave can arrive at the aorta while the heart and pulse are still in systole; it then sums with ('augments') the primary systolic pressure wave, lifting systolic pressure by as much as 40%. Seeking an explanation for the effect of height on cardiovascular disease, Smulyan and colleagues [136] concluded that "The early systolic arrival of reflected waves in short people ... acts to stiffen the aorta and increase the pulsatile effort of the left ventricle, even at the same mean blood pressures. Short stature also induces a faster heart rate, which increases cardiac minute work and shortens diastole."

We suggest that the effect of short stature in reducing the latency of the reflected pulse wave sums with the effect of arterial stiffening in reducing the same latency, accelerating one feature of the aging vasculature, and predisposing to cardiovascular disease and to cerebrovascular disease, and its sequelae—cognitive loss.

TOWARD THERAPY

The implications of these ideas for treatment are several, and to a considerable extent beyond the present scope. Briefly, the implications are, first, that the search for therapy should now include the aging of the arterial tree, and how it can be countered and mitigated; and that, until the damaging effects of the pulse can be countered, pulse-induced breakdown of cerebral vessels will occur, and attention should be focused on limiting the damage done to brain tissue.

Mitigation of age-related stiffening of the arteries

O'Rourke and Hashimoto [109, 110] reviewed options for reducing arterial stiffness and Henry-Feugeas and Koskas [129] argued similarly, that

countering the effect of arterial stiffening on the pulse should be an effective approach to the prevention of late-onset cognitive decline. One effective strategy is to reduce amplitude of wave reflection by drugs, such as nitroglycerine, that dilate conduit arteries. Nitroglycerine reduces augmentation of both pulse pressure and flow [142]. The mechanism of this reduction has been investigated for some time. In one possible mechanism [143], smooth muscle in the conduit arterial wall is in series with collagen elements in the wall, but parallel with elastin fibers, and maintains arterial tone through its attachment to collagenous elements. Relaxing the smooth muscle causes the artery to dilate, and the transfer of tension to elastin elements. The artery is then more dilated and more distensible, reducing wave reflection from the peripheral vascular bed. Surgical approaches to dampening the pulse could also be important.

Mitigation by neuroprotective conditioning

A growing body of evidence indicates that central nervous tissue (retina, brain) can be pre-conditioned by a range of interventions (infrared radiation [144–146], low-level gamma radiation [147], phytotoxins [148], caloric restriction [149], remote ischemia [150], exercise [151], dietary saffron [146, 152–154]) to be resistant to damage. These interventions upregulate endogenous mechanisms of cellular repair, some identified at the mitochondrial level, and reduce neural degeneration in models of parkinsonism, dementia, and macular degeneration. In clinical trials, dietary saffron has been reported [155–157] to restore vision partially and to stabilize the macular region of retina in age-related macular degeneration; transcranial infrared radiation has been reported to reduce functional deficit after stroke [158], and direct infrared radiation to mitigate age-related macular degeneration [159, 160]; and remote ischemic preconditioning is under trial in stroke, cervical myelopathy, and subarachnoid hemorrhage [161, 162]. With all techniques, larger trials and more development of the interventions must follow, but it is remarkable that the brain and retina can be protected or, more accurately, can be induced to self-protect, by a range of low-impact interventions.

Can the vasculature be rejuvenated?

Vascular endothelial growth factor-induced angiogenesis

Several reviewers have followed the analysis pioneered by de la Torre, which emphasizes 'hypofunction' of the cerebrovascular capillary bed as the central pathology of ARD, precipitating and reinforcing a breakdown of the functional relationship between blood supply and the neuropil (subsequently termed the 'neurovascular unit'). The functional relationship is complex and dynamic [163, 164], and can account for many of the features of the progression and neuropathology of ARD. Goldsmith [164] reviews case studies of attempts to improve cognition by implanting strips of omentum, still connected to their abdominal blood supply, over the cerebral cortex, initially as a treatment for stroke, then as a potential treatment for ARD. The pia is removed in this surgery, the omental tissue contacts the neuropil and vessels form from the omentum and extend into the brain, the author suggests, because reduced perfusion of cortex induces an upregulation of the potent angiogenic factor, vascular endothelial growth factor. Encouraging evidence of improvements in cognitive performance has been reported, though not yet in controlled trials.

Endothelial stem cells [165]

Other authors have emphasized the damage called to endothelial cells by the stress of blood flow, and have suggested that an age-cumulative failure to self-repair may be important in the vascular dysfunction which seems to be important in the genesis of ARD. In addition, there is evidence of a reduction in ARD patients in the number of circulating angiogenic stem cells [166]. One potential therapy that follows from this analysis is the infusion of endothelial/angiogenic stem cells, to accelerate the normal process of vessel repair.

These vascular-oriented therapies are still under test, their value yet to be established. More generally, when understanding of the cause of a disease shifts, in this case to a vascular-focused idea, some opportunities for therapy (such as amyloid clearance) lose their rationale, and others come to be considered. Because all science is uncertain, we may never quite know when the cause of ARD has been correctly identified; doubt will always remain. But the need is urgent and growing, and there is a need to continue and broaden the search, in spite of that doubt.

THE CHANGING FACE OF DEATH AND THE LIMITS TO LONGEVITY

The inevitability of death is a constant, but the nature of human death has changed [167, 168]. In the mid-19th century, even in societies now economically

advanced, much of the dying was done by the very young in epidemics of infectious diseases, and the deaths of so many children held the average age at death to 40 years [169]. Since then, the control of infectious diseases, and growth in the power and range of specific medical treatments, have steadily increased longevity, shifting the burden of dying to the very old and changing the major causes of death—how we die. By the year 2000, average age at death had reached 75 or more in 42 nations and in, for example, the United States [170], only one of the top-ten causes of death was infectious (pneumonia and influenza). Heart disease and cancer in adults had replaced infectious diseases among children, as the major causes of death.

Since 2000, these trends have continued. From 2000 to 2011, the number of nations in which life expectancy at birth was $\geq$75 rose to 68; death rates among the very young continued to fall from their already-low 2000 levels; and rates of death from heart disease, stroke, influenza, and pneumonia also continued to fall.

Strikingly, two top-ten causes of death were on the rise in this decade. 'AD' (up by 62% from 2000 to 2010 in US data) and chronic kidney disease (up by 33%) (data from [170, 171], for a summary, see [167]) were becoming larger features on face of death (Fig. 3). Similar trends are apparent in Australian statistics (Fig. 4). These two fast-increasers are failures of the two organs most vulnerable to pulse-induced damage. It seems that degeneration of the brain is becoming, along with kidney failure, a default form of death; increasingly it is how we die, if we survive the gamut of disease and accident that still inflicts, on a decreasing minority, the tragedy of early death.

The present analysis suggests that, for the majority who survive into our eighth decade and beyond, one of our high-profile organs, the heart, will destroy the most complex, powerful and critical of our organs—the brain, thumping it until it bleeds in a thousand places, becomes littered with inert scar tissue, seethes with inflammation, and shrinks *in situ*, its surviving neural machinery struggling to function. Alzheimer described hallmarks of dementia, the scar-tissue (plaques and tangles) and inflammation. But what he identified was not really a disease; it was the end stage of internal trauma.

Ways will be found, have already been found, to protect the brain from the pulse, by relaxing the arterial tree, controlling blood pressure and diabetes, minimizing arteriosclerosis and atherosclerosis; investigators have begun to ask whether arterial stiffening can somehow be slowed, reducing what may be the key change that links age to dementia; extensive work is being done on neuroprotection, how to condition the central nervous system to resist damage when hemorrhage does occur; and pioneering work is being done on angiogenesis, to rejuvenate the vasculature, and on neurogenesis, to reconstruct the degenerating brain.

Even so, this analysis of dementia leads us not to a cure, but to sobering consideration of the changing nature of death and of the limits to longevity, for a species whose brain has overcome so many forms of death, without altering its inevitability.

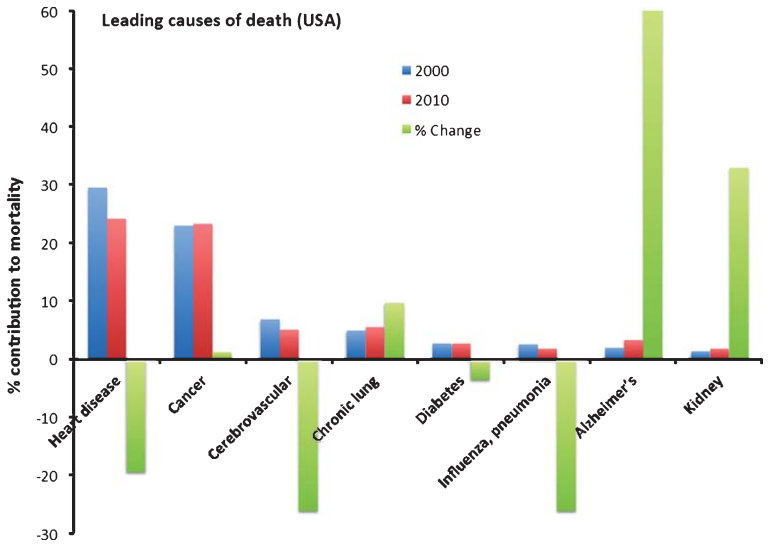

Fig. 3. Leading causes of death in the USA in 2000 and in 2004; and (in green) the percentage changes over that decade. The two fast-increasers are dementia and kidney failure. Data from [172].

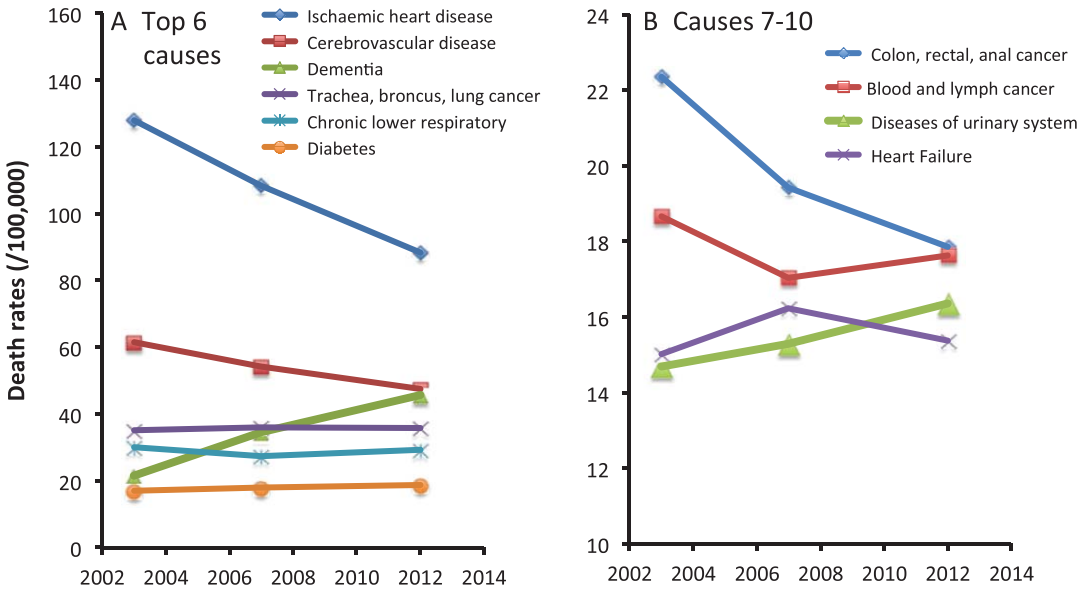

Fig. 4. Leading causes of death in Australia 2007-2012. A) Among the top 6 causes, the one increasing cause is dementia. B) Among causes 7–10, one is increasing, diseases of the urinary system. Data from [173].

In the meantime, it may be inevitable that, for those who live beyond the biblical three score years and ten, a strong pulse will still change from the easy thump of vigorous youth, to the lethal beat of aged death, which will kill us quickly if stops and slowly if it continues.

We are left then with questions that contain an element of existentialist angst: if we could, in the aged, restore the elasticity of the great vessels, how long might we then live? And of what would the gamut-survivors then die?

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