

## THE PATHOLOGY OF NORMAL AGING

---

### *SO-CALLED BENIGN SENESCENCE*

The trajectory of brain development is balanced, at the end, by a negative trajectory of physical shrinkage and functional decline. The changes are similar to those of early dementia, but the slope, though negative, is not so steep. For this reason, the events are referred to as "benign." A synonym for normal aging is senescence, with its implications of gentle decline, the inevitable price of an active and useful life. The opposite is "senility," the loss not only of one's mental powers, but also the ability to get on in the world.

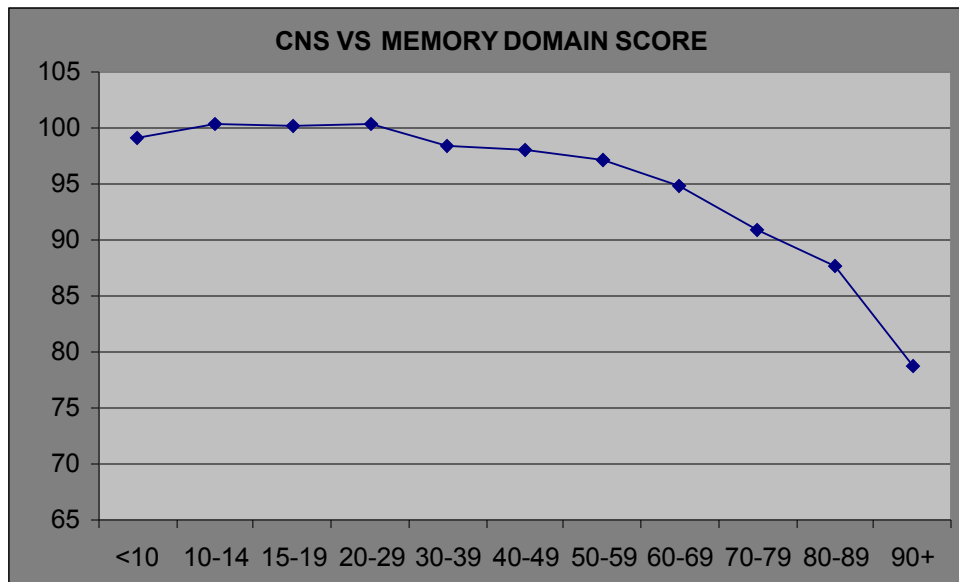
At one time, and not too long ago, "senile dementia" was thought to be an extreme variant of normal aging. In 1976, however, an influential editorial proposed that "Alzheimer's disease (AD) and senile dementia are a single process and should, therefore, be considered a single disease". Senile dementia was different from aging, not only in terms of the magnitude of cognitive decline, but also in the nature of the underlying processes.

However, the presumptions that these processes reflect the actions of a single disease, and that aging and dementia are altogether differentiable, are inconsistent with results of recent study. In the next several chapters, we shall visit the problems of normal aging, the dementias, and the intermediate state known as "mild cognitive impairment" (MCI). It is clear that the neuropathology of AD is central to understanding the nature of these conditions, but we shall show why it is not sufficient. The clinical study of dementia is more appropriate to a "systems" approach. The study of dementia is inseparable from the study of normal aging, with all its vicissitudes. Benign senescence is not a mild or indolent form of dementia, any more than dementia is just a severe case of aging. But it is not possible to understand dementia without taking into account the pathology of normal aging.

Benign senescence refers to the cognitive and behavioral correlates of normal aging, and these are well known. Memory decline, for example, is the most recognized feature of cognitive aging. Older adults score lower not only on laboratory tests of free recall, cued recall and recognition memory, but also on memory tasks with greater ecological validity, like memory for prose passages, medication instructions, the names of geographic landmarks, the appearance of common objects like coins or telephones, for the activities they have performed and for the names and faces of people.

The data in Figure X.1 represent age-related change in recognition memory, based on the performance of 1504 normal individuals whom we tested during the development of normative standards for CNS Vital Signs. The subjects were all in good health, with no history of neurological, psychiatric or developmental disorders, and free of any centrally-active medications. They ranged in age from 5 to 96, and their memory scores were derived from tests of visual and verbal memory.

Figure X.1 Age-related Change in Memory in Normal Subjects



**Figure X.1 Note.** Data from 1504 normal subjects, age 5-96, on the verbal and visual memory tests on the CNS Vital Signs computerized battery. The scores from both tests are added to generate a composite memory score.

In normal people, performance on memory tests begins to decline at age 40 and continues, gradually but inexorably thereafter. Normal people begin to notice memory problems by age 50. Dysnomia – forgetting names or words – is usually the first sign. It is embarrassing sometimes, and some people worry about it, but it carries no pathological significance whatever.

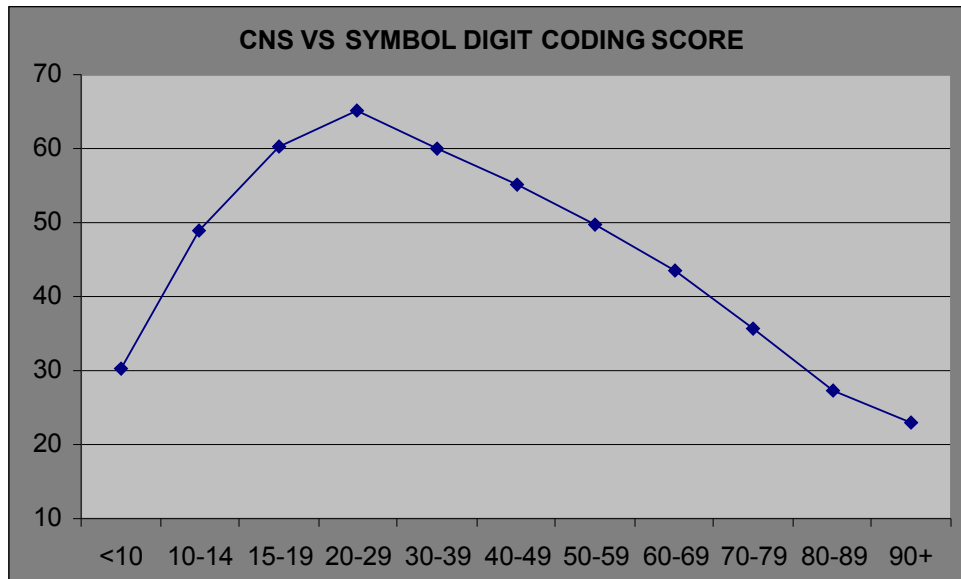
"Slowness of behavior" or psychomotor slowing is also a characteristic of becoming old. Peripheral sensory-motor factors make a small contribution to slowing -- even peripheral nerve conduction is slower -- but the CNS, especially its subcortical structures, is the primary locus for slowing of reaction time, evoked potentials and information processing speed. Psychomotor slowing begins at age 30 and may be apparent to the patient by age 40.

Slowing is most clearly demonstrated in tests of visual-motor performance. This age-related change is so robust it has been incorporated as a "correction factor" in most standardized tests of visual-motor function. For example, on the WAIS-R Symbol-Digit Coding subtest, a timed measure of visual-spatial scanning, a 35 year old male with a raw score of 56 is given the same scaled score (10) as a 70 year old male with a raw score of 33. \*

---

Translation: the average 35 year-old can code 56 figures in the same time it takes the average 70 year-old to code 33.

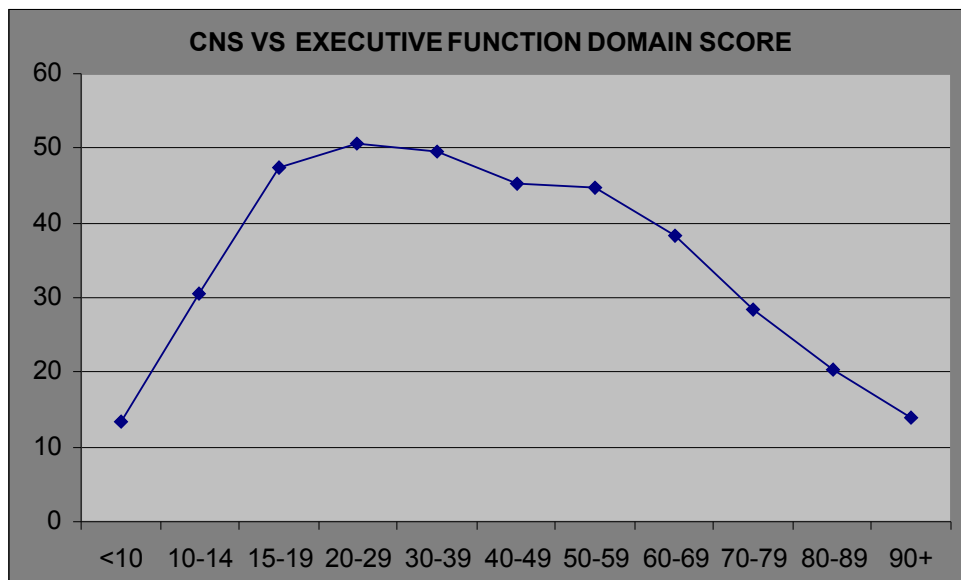
Figure X.2 Age-related Change in Visual Motor Performance in Normal Subjects



**Figure X.2 Note.** Data from 1504 normal subjects, age 5-96, on the symbol digit coding test on the CNS Vital Signs computerized battery. Symbol-digit coding is a variant of the digit symbol substitution test.

The cognitive abilities known collectively as "fluid intelligence" are especially vulnerable to the effects of aging: nonverbal reasoning, rule discovery and concept formation. Neuropsychological deficits in frontal lobe function, like cognitive flexibility, tend to be more pronounced.

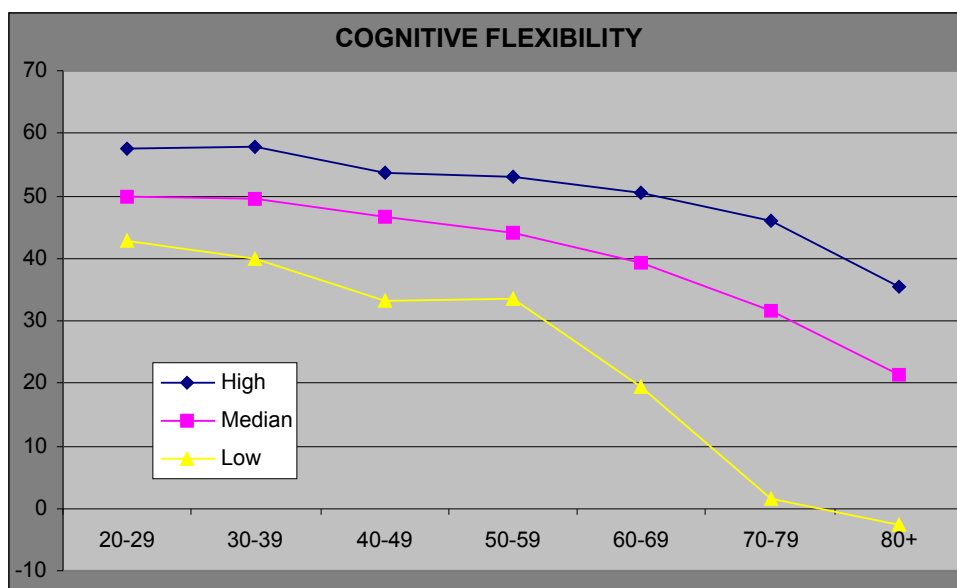
Figure X.3. Age-related Change in Executive Function in Normal Subjects



CNS Vital Signs computerized battery. The shifting attention test is a measure of cognitive inhibition/dis-inhibition, one of the executive functions.

aging-related cognitive decline is not uniform. Memory decline may be the hallmark of aging, but the figures demonstrate that changes in psychomotor speed and executive function are, if anything, more dramatic. There are also marked inter-individual differences in aging-related decline. Illustrative data are presented in Figure X.4. We divided the normative sample of 1151 adults (age 20-96) in the CNS Vital Signs database into thirds, on the basis of their overall neurocognitive performance (the Neurocognition Index). All three groups demonstrated aging-related decline, but the trajectory of the lower third was significantly steeper than the median third and the higher third. Now, these are cross-sectional data, not longitudinal data. But they demonstrate a fact that is well-known in psychometrics: performance on neuropsychological tests show increased variability with aging, even among people who are perfectly healthy.

Figure X.4. Age-related Change in Cognitive Flexibility in Three Groups of Normal Adults



**Figure X.4 Note.** Data from 1151 normal adults, age 20-96, on the cognitive flexibility domain score. The subjects are divided into three groups on the basis of their overall Neurocognition Index. The cognitive flexibility score is calculated from the Stroop test and the shifting attention test

aging is always associated with cognitive decline, but aging does not affect all cognitive functions uniformly, and the cognitive decline that accompanies normal aging – even if it reaches criterion for MCI – is not necessarily debilitating. Many older patients can compensate as well as they need to in the face of cognitive decline. Education level is a reliable predictor of that. People who are well-educated and intellectually active tend to be relatively stable on tests of language and memory. Nevertheless, they deteriorate as rapidly as less educated people do on measures of visual-perceptual ability like Coding.

On the behavioral level, healthy old people frequently have a stooped posture and a slowed gait, with some parkinsonian features. Hand steadiness is reduced, postural tremor is frequent, coordination and balance are impaired. There are mild delays in movement initiation, decrements in complex somesthetic tasks like writing and aiming, and complaints of excessive fatigue during testing. There may be a patchy loss of light touch perception and a generalized reduction of deep tendon reflexes. Simple tests of motor speed, like the Finger Tapping Test, gradually decline with age.

Such changes, of course, are rarely overt in healthy individuals during the fifth and sixth decades of life, but in studies of athletes it is clear that speed, strength and endurance begin to decline during the fourth decade. In marathoners, for example, there is a linear decrement in maximum performance from age 30 to 70 by about 1 per cent per year. This pattern of change in neuro-muscular performance is only indirectly reflective of events in brain. A more direct example is the experience of patients who have experienced mild brain injuries. The severity and persistence of post concussive symptoms is much more problematic in older patients, and the statistical dividing line is around age 40. The gradual decline in cerebral reserve during middle age accounts for a wide range of clinical and sub-clinical phenomena, like the relative intolerance to the effects of intoxicating drugs, the development of fatigue-related hypacusis, the increased severity of neuroleptic-induced neurotoxicity and the late clinical manifestations of encephalitis lethargica.

It is striking that in Figures X.1, X.2 and X.3, peak performance occurs at age 20-35. It may be discomfiting to be reminded that one's cognitive powers converge, sometime between age 30 and 40, on a downward course that is inexorable and unstoppable. It is also counter-intuitive. Most of the sixty year olds I know look back on their twenties as an era of ignorance and fecklessness. "If only I knew then what I know now," is a common lament. When the musician Eubie Blake turned 90, he said, "If I had known I was going to live this long I would have taken better care of myself."

When I lecture to groups of doctors about our research, these normative curves are usually met with a nervous shiver. People at the height of their powers and the pinnacle of their careers are vaguely embarrassed at the idea that they are, in fact, well on their way on a downward slide. They know that it is true, but they don't care to be reminded. Anyway, does it really matter if my reaction time is 50 milliseconds slower? If the pinnacle of cognitive performance is achieved at age thirty, why don't we choose thirty-year olds to be CEO's or prime ministers? Would you choose a thirty-year-old brain surgeon, or a fifty-year old? Don't you feel more secure if the pilot of your 747 has a few gray hairs?

Psychologists draw a distinction between "fluid intelligence" (e.g., memory, perceptual-motor speed) and "crystallized intelligence" (e.g. general information, vocabulary). The former change with aging but latter do not, and may even improve, because they represent the effects of learning and experience. The normal aging brain never loses its capacity to learn new things. It remains capable of growing dendritic spines, establishing new synaptic connections, and even growing new neurons. Judgment and wisdom are the fruits of experience, and are only indirectly influenced by the molecular processes that comprise neurocognition.

## THE PATHOLOGY OF NORMAL AGING

The functional changes that characterize normal aging are reflected by morphological, histological and biochemical changes in the brain. There is a decrease in brain size with thickening of the meninges. Brain weight decreases by about 2% per decade after the age of 50. At least some of that is water loss, but atrophy of nervous tissue also occurs: atrophy of both

gray and white matter, sulcal widening, flattening of the convolutions and ventricular dilatation. The regions of brain that are most likely to undergo aging-related changes are the medial temporal lobes, especially the hippocampal formation, and the prefrontal cortex. Hippocampal atrophy is correlated with memory impairment. By age 80, brain weight is reduced 10% relative to healthy young adults.

On the histological level, there are changes in neurons that are regarded as characteristic of normal aging and are not correlates of dementia: shrinking of neurons, loss of dendritic spines with attendant loss of synaptic junctions, and the depletion of neurons. By age 90, nearly 10% of the twenty billion neocortical neurons have been lost. Astrocytes undergo hypertrophy and hyperplasia, particularly at sites of neuronal depletion. Neuropathological hallmarks of cell degeneration, like neurofibrillary tangles and neuritic plaques are seen in normal aging as well as in Alzheimer's disease (AD); "the distinction is quantitative rather than qualitative." In fact, only 17% of brains from normal individuals show few or none of the microscopic findings characteristic of AD and about 50% of brains from nondemented elderly people meet neuropathological criteria for the diagnosis of AD.

In normal aging as well as in dementia there is loss of neurons in most regions of brain and regression of dendrites in cells that have not yet died. The interesting contrast, however, is that in normal aging, the remaining neurons retain the capacity for compensatory dendritic growth, whereas dementia is associated with an apparent failure of this growth, and thus a more dramatic regression of the dendritic tree.

There is an age-related decline in neuronal numbers, varying with neuronal type and brain region; down by as much as 54% in the superior frontal, superior temporal, precentral and striatal cortices. Of particular interest is the age-related decline in the brain stem nuclei containing the neuromodulatory monoaminergic neurotransmitters: a decrease, for example, in noradrenergic neurons of the locus coeruleus (but not in the cerebral cortex), from about 19,000 cells in youth to about 10,000 cells in neurologically normal 80 year-olds. At birth, there are about 400,000 dopamine-containing neurons in the substantia nigra; by age 60, about 250,000.

Three hormonal systems show decreasing circulating hormone concentrations during normal aging: estrogen (menopause) and testosterone ("andropause"); dehydroepiandrosterone ("adrenopause"); and growth hormone ("somatopause"). Even the posterior pituitary hormone, vasopressin, declines with aging.

Females are more susceptible to AD than men, and it may have something to do with estrogen. The estrogen receptor in brain promotes neuronal growth during development and, in adults, after brain injury. It prevents cell death and promotes the growth of interneuronal connections. The estrogen receptor is found on neurons that degenerate in AD. The female brain is abruptly deprived of estrogen after menopause. The male brain continues to be bathed in testosterone, which is partly converted to estradiol in the brain, though at a slower and slower rate as the years go by.

Basal levels of plasma catecholamines, a measure of the activity of the sympathetic-adrenal medullary system, are elevated in aged animals and humans, and the regulation of the catecholamine response to stress appears to be less efficient. One of the natural functions of estrogen is to neutralize the effects of glucocorticoids released in response to stress.

On the biochemical level, there is clear evidence of age-related effects on dopaminergic neurons. For example, between the ages of 28 and 91, there is a linear regression of dopamine and its metabolite 3-O-methyl dopamine. The number of dopamine receptors declines in striatum and in frontal cortex. The enzymes that catalyze the synthesis of dopamine in the substantia

nigra and the striatum decline with age, and the activity of the catabolic enzymes, monoamine oxidase A and B, increases with age.

When dopaminergic function is measured dynamically by PET and compared to levels of functioning measured by neuropsychological tests, the age-related decline in parameters of dopaminergic brain function correlates directly with measures of motor and cognitive function. Neuropsychological measures of frontal lobe function, the so-called "executive functions," are the cognitive measures most closely related to the decline in DA activity.

Evidence for age-related declines in the noradrenergic system is less clear although there is evidence for reduction in concentration of adrenergic receptors. There is also evidence for increased 5HT turnover and reduced density of 5HT-1 and 5-HT-2 receptors.

A cholinergic hypothesis for geriatric memory disturbance is based on the (inconsistent) finding of reduced cholinergic markers in aging brain (eg, choline acetyltransferase, muscarinic receptors). Anticholinergic drugs are known to impair cognitive performance in healthy young subjects and cholinergic drugs enhance short term memory; the former is true of healthy elderly subjects, but the latter has been difficult to demonstrate consistently.

There is also an age-related decline in the activity of enzymes of the glycolytic pathway. In dementia, the glycolytic turnover drops well below the "critical threshold" of 40-50% of the functional reserve capacity; in normal aging, the decline, after age 70, is no more than 20-30%, well within functional reserve capacity, but sufficient to account for the subclinical changes of benign senescence. The glycation of proteins is something that occurs in diabetes, and glycated endproducts trigger inflammatory reactions in endothelial cells. Glycation and the accumulation of glycated endproducts, however, is also a function of aging.

The proposition that oxygen free radicals are central to aging remains to be rigorously proven, but the presence of increased amounts of oxidized proteins in aging biological systems supports the theory of oxidative stress. There is at least a degree of agreement that oxidative stress is associated with neuronal degeneration under acute pathological conditions, like stroke and brain injury, and also in brain aging. Tissue damage due to oxidative stress is thought to accumulate with age, and mitochondrial DNA is particularly vulnerable to oxidative stress. Mitochondrial energy production is markedly diminished in aging animals and humans, and the loss of mitochondrial energy production is thought to contribute to senescent changes and aging-related disease.

Since cerebral blood flow (CBF) is coupled to cerebral functional activity, measures of CBF are proportional to the metabolism of oxygen and of glucose. Observations of reduced CBF with aging were first made by Kety. More recent studies have demonstrated a loss of the hyperfrontality of CBF that characterizes healthy people during the fifth and sixth decades. Decreased gray matter CBF has been found to correlate with impaired performance on neuropsychological tests in a sample of elderly patients, both healthy and demented.

## IS AGING A DISEASE?

Modern times have blessed us with longevity, but the price we pay is the natural involution of our *soma* and our *psyche*. This was always so. Life expectancy in prehistoric times was probably in the range of 20 to 30 years, as has been inferred from very slow population growth rates. By 1500 or 1600, when data on mortality first become available, mortality levels

were still very high, and life expectancy rarely exceeded 35-40.\* Thirty years is not very long by our standards, but it affords sufficient time for propagation, and that is what counts to Nature.

It is appropriate to take an evolutionary/phylogenetic approach to the study of longevity and dementia. The areas of brain that are most vulnerable to the pathology of AD, for example, are the latest to mature, and the neocortical lesions of AD and Parkinson's disease (PD) are densest in areas with the highest cortical differentiation and hierarchical refinement.

Involution and death are biological necessities; the mystery of the human condition is why we age so slowly. That is a subject that we shall address at another time. Sufficient for this discussion is the fact that we do, and the reason why is the extraordinary resilience of our biological systems. Long-lived organisms, like whales and redwood trees and human beings tend to procreate rather slowly. Our evolutionary bargain has been to devote more energy to cell maintenance, and less to procreation. Thus we are capable of withstanding years of exposure to trauma and to disease, and we have to, to keep the species alive. The resilience of long-lived organisms resides in the three principles of resistance, capacity for self-repair and redundancy.

The human brain is characterized by an extraordinary degree of redundancy. If you lose a chunk out of your brain, other parts take over. If you lose a function, other functions will develop to compensate for the deficit. When we work with patients who have had brain injuries or stroke, treatment aims to support re-learning or to teach compensatory strategies. What we try to do is to take advantage of the resilience of a system that is, if anything, over-engineered.

So, it is true that elements of fluid intelligence begin to decline during the fourth decade of life, and never stop going down until we die. It is true that we lose neurons and synapses. But the loss is gradual, and we have ample time to make the necessary adjustments. A system that is well-engineered, with built-in redundancy, can afford to lose some of its capacity, and still run perfectly well.

The brains of young people are organized for learning. That is why their memory functions are so advanced, relative to all the other neurocognitive domains. The brains of young people also have pluripotentiality; that is, the capacity to adapt the wide range of different events the future may bring. That is why young people do so well in psychological tests that measure set-shifting. The brains of older people, however, are perfectly adapted to the tasks evolution has assigned to them.

Longevity, in historic terms, is life past 40. In prehistoric societies, very few people lived to that age, although some did (although there has never been a skeleton unearthed from this period that was older than 54). The role of such individuals we must assume had to do with the transmission of culture. Thirty years is more than enough time to teach the next generation to dig up roots and grubs or to hunt small animals. More time is necessary, however, to convey all the vicissitudes of living in harsh environments, raising crops, hunting large animals and competing with other groups; or how to predict the movements of the stars or the antics of the spirit world. We value the experience, judgment and high skill of older people, and the aging brain must be well adapted for these purposes. It has lost some of its resilience and much of its pluripotentiality. But the successful older brain is liked a honed instrument. It can do a few things very well, and what it can do is of great value to the group.

That is why we don't mind presidents or surgeons or pilots who are old.

The trajectory of benign senescence is most apparent after the age of 70. By this point, the cognitive and behavioral changes enumerated above often are starkly apparent, as cellular and molecular changes indistinguishable from AD proceed apace. It is common wisdom to ascribe to elderly people the attributes of poor memory, slowness, diminished flexibility, reluctance to engage in novel pursuits, emotional dependence or lability, depression etc. It is also clear, from cross-sectional studies and from the complaints of patients that behavioral and cognitive changes occur as early as the fifth or sixth decade of life. After age 85, nearly half of all individuals are cognitively impaired and at least 20% are incapacitated by dementia. Only a third of nonagenarians and centenarians are considered cognitively "normal," despite considerably reduced expectations.

However, the extent to which a healthy old person manifests the cognitive, motoric and behavioral characteristics of "normal aging" is quite variable. Most elderly people maintain cognitive and functional good health in spite of neuronal loss, oxidative stress, inflammatory cytokines, etc. Within the broad swath of normal aging, therefore, there are relative degrees of health and impairment.

aging is not a disease any more than dementia is normal. But the involution of tissue is the inevitable accompaniment of aging, and it is upon this matrix that aging-related diseases work their ill effects. The factors that influence the impact of senescent change and how these relate to the early signs of dementia are dealt with in the next chapter.