

THE PROBLEM OF DEMENTIA

Today we preach that science is not science unless it is quantitative. We substitute correlation for causal studies, and physical equations for organic reasoning. Measurements and equations are supposed to sharpen thinking, but...they more often tend to make the thinking non-causal and fuzzy. They tend to become the object of scientific manipulation instead of auxiliary tests of crucial inferences.

Many – perhaps most – of the great issues of science are qualitative, not quantitative, even in physics and chemistry. Equations and measurements are useful when and only when they are related to proof; but proof or disproof comes first and is in fact strongest when it is absolutely convincing without any quantitative measurement.

Or to say it another way, you can catch phenomena in a logical box or in a mathematical box. The logical box is coarse but strong. The mathematical box is fine grained but flimsy. The mathematical box is a beautiful way of wrapping up a problem, but it will not hold the phenomena unless they have been caught in a logical box to begin with.

It is a category error to regard dementia as a disease, like cancer or cardiovascular disease. Dementia is not a disease. Dementia is a functional state, rather as mental retardation is a functional state; both conditions have a host of possible etiologies. Dementia is unique, though, because its etiologies are not necessarily discrete; they can overlap and interact. “Mixed dementia” – dementia with multiple causes – probably accounts for the majority of cases.

Dementia is also unique because it develops in a brain that is undergoing gradual involution, and the processes that govern age-related cognitive decline are largely indistinguishable from the processes that cause AD. The lesions that typify AD are virtually ubiquitous in aging brain. Amyloid plaques and neurofibrillary tangles actually begin to form during the third and fourth decades. In autopsy studies, about 80% of the brains of people *who were never cognitively impaired during life* had at least some of the neuropathological signs of AD, and more than 50% met the neuropathological criteria for AD. The cortical load of amyloid plaques and neurofibrillary tangles is correlated with the degree to which the patient is demented, but the correlation is not perfect by any means and past age 90 (or 75) it is not correlated at all. There are well-documented cases of people with advanced disease, in terms of pathology, but who did relatively well on neurocognitive tests before they died and had no disability in their everyday lives. Patients with trisomy 21 (Down syndrome) develop prominent AD pathology when they are quite young, but they do not experience dementing changes until they are much older, if at all. Clinically normal individuals with and without AD neuropathology do not differ in rates of cognitive decline across a number of cognitive domains.

Taking AD as the prototype for the neurodegenerative dementias, we are confronted with a singular paradox. The disease has a neuropathological component, which is well defined, albeit obscure to all but the most highly technical methods, like PET scanning or CSF biomarkers. But it is possible to have a good deal of brain pathology, and yet to be cognitively and functionally intact. We are not sure why this is so. One reason is that, in most cases, the pathological

processes that ultimately lead to dementia are slow, and brain is pretty good at adjusting to the functional effects of a slow-growing lesion or a gradual process of decay. It is also likely that some brains are more resilient than others. People with Down syndrome, for example, over-express certain genes that seem to be neuroprotective. Well-educated people are less likely to develop AD than less well-endowed folk, but that seems to be because they can tolerate a higher load of plaques and tangles without being compromised functionally. Theoretically, they have more "cognitive reserve."

So, it is important to iterate this principle: Alzheimer's pathology is not Alzheimer's disease. And so it is for all the dementias. Neuropathology is a necessary condition for the development of dementia, but it is not sufficient. Functional impairment is imperfectly related to pathology. This is the first problem.

The second problem is that the progressive cognitive decline that characterizes dementia is superimposed upon another condition, aging, that is also characterized by progressive cognitive decline. Since Katzman, we have appreciated that dementia is qualitatively *and* quantitatively different from normal aging. But things can be different, yet have a lot in common, too. Normal aging brain is prone not only to neuronal and synaptic loss, but also to the development of amyloid plaques and neurofibrillary tangles, and to many other pathological events, like white matter hyperintensities, that are ordinarily attributed to the dementing conditions.

The third problem has to do with pathophysiology. It's not that we don't understand the pathological processes that contribute to dementia; we understand too much. We know a great deal about amyloid, *tau*, apolipoproteinE, reactive oxygen species, cytokines, etc. But we have not been able to establish a single point at which the pathological cascade begins, or to establish primacy to one element over another. If this is true of AD, the most intensely studied of all the dementing conditions, it is also true of the others. It is possible that the pathology of dementia is not a discrete process or an orderly cascade of events, but rather a complex of aberrant events that interact with each other, and also with pathological events of a systemic nature; with the natural brain changes that accompany normal aging; and with extrinsic events like stress, isolation and inutility. The issue may not be which pathological event or events cause dementia, but how multiple events participate in the dementing process.

In the preceding chapter we discussed, at some length, the pathology of normal aging. We shall not reiterate the molecular biology of AD and the other dementias, because that has been dealt with amply in the literature. Suffice it to say that the mechanisms that effect normal brain aging are also operative in dementia, although, in most cases, to a greater degree. In this chapter, we shall address a number of processes that participate in the genesis and the clinical expression of dementia, at a level that is several levels beyond the molecular. AD pathology is, for all practical purposes, ubiquitous. We are interested in the factors that influence the clinical expression of the pathology.

This is how we shall approach the problem. Usually, education and IQ, personality, mood and stress intolerance, and cardiovascular disease are spoken of as "risk factors" for AD. This terminology is appropriate to a "disease model" of dementia, where the assumption is that risk factors cause or aggravate the pathological process. However, in the case of dementia, the relationship between putative risk factors and dementia is ambiguous. In some cases, neuropathologic indices mediate the association of risk factors to cognitive disability. In other cases, risk factors modify the relation of pathology to cognition. Finally, some risk factors seem to be related to clinical AD and cognitive decline, in the absence of any association with extracellular

plaques, intracellular tangles, or other pathologic indices. In fact, in AD, risk factors that predict neuropathology are largely distinct from those related to the clinical expression of the disorder.

An alternative approach is the systems model. This model posits a more complex relationship, and is more relevant to the study of AD, not as a disease, but as a functional state that may or may not arise in a patient who has the requisite pathology. So, from epidemiological studies, we learn that education and IQ, personality, mood and stress intolerance, and cardiovascular disease are risk factors for AD in the conventional sense. But we also know, from clinical studies, that they are early signs of the condition. From yet another perspective, one might suppose that the risk factors in questions, and AD itself, are simply manifestations of an underlying systemic weakness. From this perspective, clinical expression would simply be a function of age and other extrinsic and intrinsic factors. The correct answer, in our opinion, is "all of the above."

The early-life environment and its effect on growth and maturation of children and adolescents are associated with several adult chronic diseases, and research findings during the past 20 years suggest that Alzheimer disease (AD) may have its origins in early life. The areas of the brain that show the earliest signs of AD are the same areas of the brain that take the longest to mature during childhood and adolescence. A poor-quality childhood or adolescent environment could prevent the brain from reaching complete levels of maturation. Lower levels of brain maturation may put people at higher risk for AD. Socio-economic and familial risk factors identified in community-based, case control studies include fathers who were unskilled manual laborers (odds ratio = 1.80, 95% confidence interval = 1.19--2.73) and household size (for each additional child in the family the risk of AD increases by 8% (OR = 1.08, 95% CI = 1.01 to 1.15)), and head size.

Early-life risk factors for pathology include genes, chromosomal abnormalities, head injury, insulin resistance, oxidative stress and inflammation. It has been suggested that latent expression of specific genes can be triggered very early in life; that environmental agents (e.g., heavy metals), intrinsic factors (e.g., cytokines), and dietary factors (e.g., cholesterol) can perturb gene regulation in a long-term fashion, beginning at early developmental stages; but that these perturbations do not have pathological results until significantly later in life.

It is likely that the risk of AD is not determined in any single time period or by any single factor, but results from the complex interplay between genetic and environmental factors, local and systemic pathology, intrinsic and extrinsic events; and that this interplay persists throughout the course of life. When we address the risk factors and early signs of dementia, we are addressing the multiple inputs to a complex system that can be understood, first, by themselves, but, more importantly, as they interact in the life of an individual. As we have seen, all of these factors are operative during the course of normal aging. Now we shall address their relationship to dementia.

EDUCATION, IQ AND AD

Education is an early life risk factor for dementia. There is an inverse correlation between educational attainment and the risk of dementia. People who are less well educated are more likely to develop dementia (relative risk 2.6) and AD (relative risk 1.7); people with high educational attainment are relatively protected. At first researchers thought this finding was the result of detection bias; standard neuropsychological tests were simply more likely to detect dementia in patients with low educational backgrounds. In fact, the association has withstood

rigorous consideration of confounding variables, like detection bias, other socioeconomic indicators, health problems or lifestyle factors.

That educational background is associated with dementia risk has given rise to theories of a “reserve” that protects against dementia. Katzman, for example, proposed a “brain reserve” theory that increased neocortical synaptic density could delay the clinical expression of AD by five years. He based his idea on evidence that synaptic loss was the biological basis of cognitive disability in dementia, and on speculation that education increased brain reserve by increasing synaptic density. In 2001, he wrote that:

In the course of normal aging from about age 20 to 100, the population density of neocortical synapses declines toward, but not reaching, the level found in Alzheimer disease. A deficiency of synapses at birth or due to inadequate childhood education would theoretically cause the synaptic slope to reach the Alzheimer level early. The normal slope would cross into that dementia range at about age 130, resulting in true primary senile dementia without regard to the presence of plaques and tangles.

The term “cognitive reserve” is used more frequently, now. This theory proposes that innate intelligence or aspects of life experience like educational or occupational attainments supplies reserve in the form of skill sets or repertoires, and that these allow people to cope better with progressive AD. Support for the cognitive reserve theory comes from epidemiological evidence that high-level occupation and a lifestyle characterized by engagement in intellectual and social activities is associated with slower cognitive decline in healthy elderly and thus may reduce the risk of incident dementia. Meta-analysis of studies involving more than 29 000 individuals over seven years follow up indicates that education level, occupational complexity and mentally stimulating lifestyle pursuits are associated with a lowered risk for incident dementia (summary odds ratio, 0.54). Increased complex mental activity in late life is associated with lower dementia rates independent of other predictors; a dose-response relationship is also evident between the extent of complex mental activities in late life and dementia risk. Evidence from functional imaging studies also shows that people who engage in such activity can tolerate more AD pathology.

People with high levels of education are less likely to develop dementia but when they do, the progression of the condition is more rapid. Pathophysiological and imaging evidence indicates that AD-related pathologic changes in the brain are more advanced among subjects with dementia who have a high level of educational attainment than in those with a low level of education, given similar clinical dementia severity. Autopsy-verified studies have documented that education does not affect the pathologic course of AD. Collectively, these observations suggest that education influences the clinical expression of AD, but does not affect the underlying pathologic process .

There is something about educational success, therefore, that has a bearing on the development of dementia five or six decades later. That intelligence (or IQ) mediates the association is a likely explanation, and, as we shall see, strengthens the theory of brain reserve. It is easier to quantify years of education in dementia patients than it is to measure premorbid IQ, and that is why more research reports address education rather than IQ. IQ tends to be stable until very late in life,¹ but patients with dementia, even early dementia, do poorly on IQ tests, and the scores they generate are not good indicators of what their premorbid state was. Researchers are forced to rely on indirect methods, like estimating IQ on the basis of education and occupation, or administering a reading test, since reading skills are roughly correlated with IQ and do not decline in early dementia. However, when rigorous efforts are made to measure

¹ IQ has a high stability coefficient ($r=0.63; 0.73$) between age 11 years and 77 years.¹⁹

premorbid IQ, for example, by consulting the results of tests administered early in life, premorbid IQ proves to be the better predictor of dementia than education level. Not that it makes a great deal of difference, though. In modern societies, education, social class and intelligence are highly correlated, with correlation coefficients in excess of 0.80, and, in psychometrics, $r > 0.80$ is virtual identity. But it is important to acknowledge the primacy of intelligence because of where it takes us, in theory.

DIGRESSION: INTELLIGENCE

Intelligence is a psychological construct, but it is probably the most effective construct ever to have emerged from that field. That is because it speaks to something essential to human adaptation. A good definition of intelligence is that it is *the ability to deal with complex cognitive problems*, and people have recognized its importance for thousands of years. It is why Odysseus, not Achilles, is the hero of Homer's saga, and it is why God preferred Esau and not Jacob. Intelligence is an innate ability of the brain. Its functional components include working memory and attention, coordination of goal-directed cognitive processes and inhibition of goal-irrelevant processes. Classical psychometric theory posits the existence of *g*, a statistical expression of "pure fluid intelligence" and which IQ tests approximate, but never fully capture. Theoretically, at least, *g* should have a biological correlate, but, for many years, it was difficult to come by.

The psychologist Karl Lashley proposed that the biological basis of intelligence resided in the *mass action* of functioning cortical tissue, and that the loss of intelligence, for example, following brain injury, was a function of decreased efficiency in cortical operations. Several observations in recent years have tended to support Lashley's definition of intelligence as a manifestation of brain efficiency. For example, there is a commonly observed correlation between reaction time (RT) and intelligence, a correlation that only grows stronger when the complexity of the RT task is increased. In experiments using both visual and auditory stimuli, the RT of low intelligence subjects *increases* as more stimuli are added. In contrast, the RT of high-IQ subjects *decreases* with more complex stimuli. Not only are their RT's quicker, but the variance is smaller. Not only do they respond to stimuli more quickly, they do so more consistently.

Inspection time (IT) is a psychophysical measure like RT that does not require a speeded response. In IT research, people with higher levels of intelligence are able to make more accurate judgments when stimuli are visible for very brief periods. Largely on the basis of RT and IT experiments, one general theory of intelligence holds that individual differences in *information processing speed* functionally determine individual differences in general intellectual ability.

Intelligence, however, is not simply a function of the speed of mental operations. This is clearly evidenced in evoked potential (EP) studies, in which response latencies are only weakly correlated with subjects' IQ. What characterizes the EP's of more intelligent subjects is diminished intrastimulus variability; that is, a more reliable waveform from one trial to another. This occurs, even though high-IQ subjects generate more complex waves in response to the stimulus, and they fire more neurons in responding to it. They bring more resources to bear on the task, and they do so with a high degree of electrophysiological reliability.

Another pertinent observation, in PET studies of mentally retarded and normally intelligent people, is that brain glucose metabolism in response to a cognitive task is *inversely* correlated with the subject's level of intelligence. That is, the brains of more intelligent people work less hard to deal with the cognitive task than the brains of less intelligent people.

The neural operations of an intelligent brain, therefore, are Lashleyan, in that they are characterized by efficient operation. The intelligent brain reacts quickly and consistently, mobilizes a greater mass of neuronal tissue and, at the same time, utilizes less energy. On an ultrastructural level, one assumes that these attributes of intelligence must be represented in superior neuronal connectivity and bioenergetics.

Hebb's rule defines learning in terms of synaptic plasticity. Hebb proposed that learning and memory are comprised of modifications in synaptic strength among neurons that are simultaneously active. In modern terms, the Hebbian model is expressed in studies of long-term potentiation (LTP) and depression (LTD), which are experience-engendered changes in synaptic efficiency. Recently, proteins have been described that facilitate LTP and LTD within the synapse. Genetic modifications or chemical interventions that block proteins like Src and PSD-95 interfere with LTP and LTD, and thus impair learning. "Learning," of course, is not synonymous with "intelligence," but theories of the latter have also been advanced in terms synaptic efficiency: *"intelligence...is the summation of all of the factors which can affect the synaptic recognition process"*.

High intelligence is a manifestation of functionally efficient cognitive networks. Intelligence is associated with synaptic density, and this is supportive of the brain reserve hypothesis. It is directly correlated and with gray matter thickness in frontal, temporal, parietal and occipital lobes; in males, more parietal, and in females, more temporal. The general intellectual impairment that accompanies dementia is associated with marked changes in neuronal number and synaptic density. The connectivity of neural assemblies is compromised and there is a generalized reduction in the efficiency of central processing.

High IQ is directly correlated with brain size, and brain size is inversely related to dementia risk. Individuals with higher intelligence are more likely to be employed in fields that are intellectually stimulating, and are more likely to continue working when they are old. They are also more likely to be engaged in leisure activities that are active and stimulating. It is important to distinguish, if one can, the effects of intelligence from the effects of occupation, social experience or leisure activities, because the latter are behavioral indices, and subject to all the variability that characterize human life, while intelligence is rooted in the biology of the central nervous system.

INTELLIGENCE AND MORTALITY

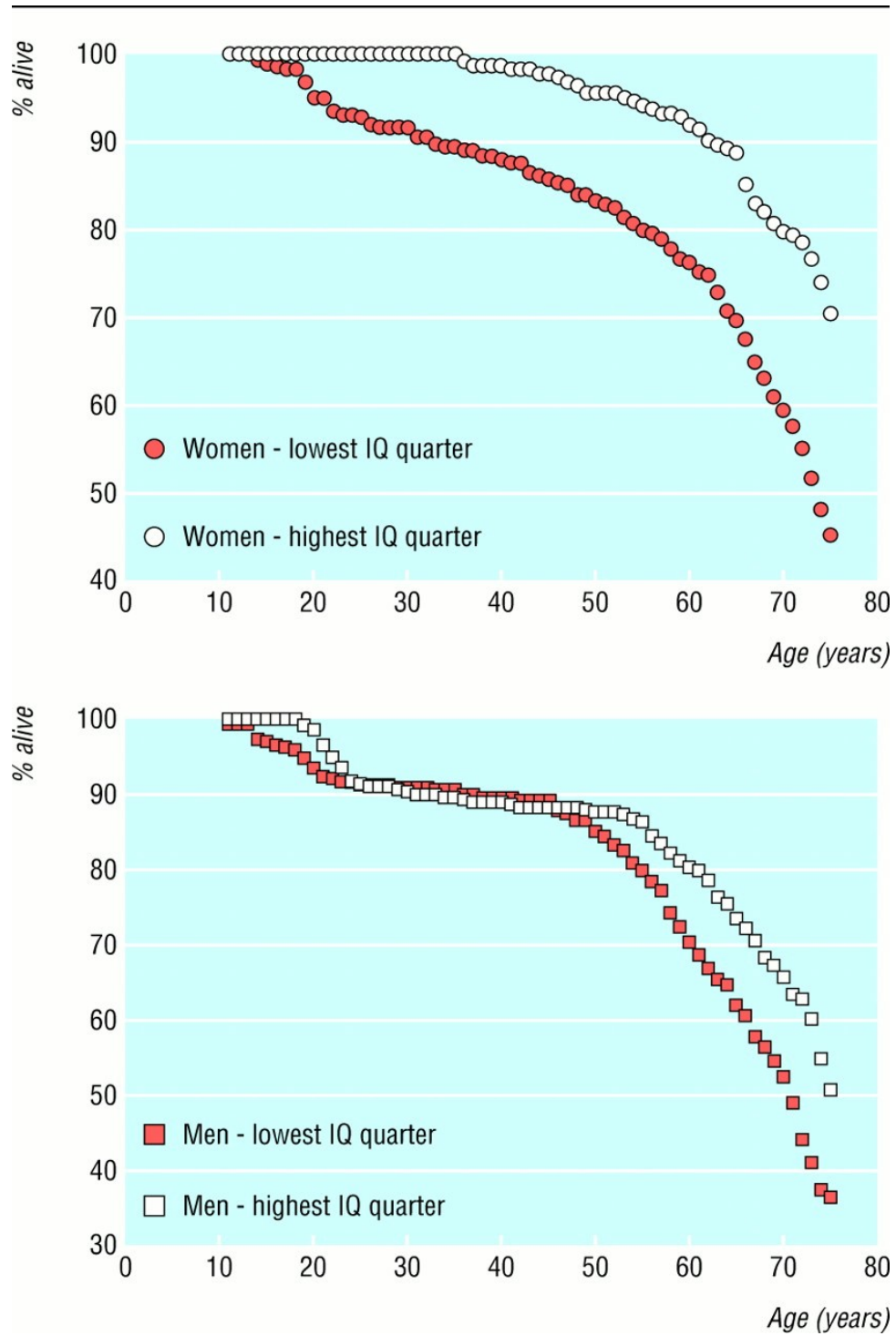
Intelligence, therefore, is likely to be the event that mediates between the clinical expression of dementia and education, occupation and stimulating leisure activities. But that is only part of the story. Early-life intelligence scores are inversely correlated not only with the likelihood of developing dementia, but also with the likelihood of development of disease in late life, and with mortality.

Epidemiological studies of socioeconomic effects on health and mortality have traditionally focused on external events, like education and income, physical exposures in the living and working environment, and health related behaviors like smoking and diet. } Controlling for such plausible mediating risk factors, however, does not eradicate socioeconomic differentials in health. This has prompted speculation that as yet unmeasured psychological factors need to be taken into account in order to explain the health effects of low SES. The hypothesis that intelligence might be 'fundamental cause' of social class inequalities in health is based on observations that low IQ scores ascertained in childhood, early adulthood, mid-life, and older age are associated with elevated rates of later death and disease. A link also exists between functional literacy (a correlate of IQ) and health related behaviors, injuries, and self management of illness.,

In a study of 1347 people aged 56 in 1987 in the west of Scotland, SES indices (childhood and current social class, education, income, and area deprivation) were significantly associated with negative health outcomes. The greatest risk of ill health and mortality was evident in the most disadvantaged groups. After adjustment for IQ, however, there was a marked attenuation in risk for poor mental health (range of attenuation in risk ratio across the five socioeconomic indicators: 15-58%), long term illness (25-53%), poor self perceived health (41-56%), respiratory function (44-66%), coronary heart disease mortality (31-111%), and total mortality (45-131%). That the effects of IQ are persistent, even when extraordinary measures are taken to mitigate the physical effects of poverty and disadvantage, may explain why the socio-economic gradient in mortality has actually widened during the past 25 years in Scandinavia.

A dramatic demonstration of this effect is presented in Figures X.1a and X.1b. Under the auspices of the Scottish Council for Research in Education, an intelligence test was given to all Scottish children who were born in 1921 and attending school in June, 1932. This was called the Scottish Mental Survey 1932 and provided a unique record of intelligence test scores for a complete age group of school children. Test data were obtained for 87 498 children (44 210 boys and 43 288 girls). The data showed that high intelligence in childhood reduced the chances of death up to age 76 years. For example, women with a deficit in IQ of 15 points at age 11 had less than 75% survival and those with a deficit of 30 points were about half as likely to survive.

Figure X.2a&b. Cumulative Mortality by IQ, the Scottish Mental Survey 1932



There is no ready explanation for this association. The authors of the West of Scotland study could offer no more than an analogy. Intelligence, they suggested, is a function of the efficiency and resilience of complex functional systems in the nervous system. Its relationship to health and mortality suggests that it is an index of system integrity in the multiple complex systems that comprise the *soma*. One presumes that the genes that encode for aspects of intelligence confer efficiency and resilience to other complex systems in the body.

A glib definition is that intelligence is what IQ tests measure. It is true that intelligence is a psychological construct, but it is more than that. It represents an attempt to address something real and meaningful – the comparative ability of individuals to solve complex problems quickly and efficiently – and to describe it quantitatively. On a practical level it has proven to be a useful and enduring concept. On a biological level, we can appreciate that the processes that contribute to intelligence are operative in relative protection, not only from dementia, and also systemic disease. Later, when we discuss another dementia risk factor, cardiovascular disease, we shall expand on this point.

The efficiency and resilience of a complex system is properly referred to as “integrity.” Intelligence is a measure of the integrity of the higher cortical functions, and also of deeper systems that contribute to health and longevity. In the next section, we shall propose that emotional regulation and temperament are also measures of system integrity in mind and body. Both have a bearing on dementia development and clinical expression.

TEMPERAMENT, MOOD AND PERSONALITY

Like problem-solving, the regulation of emotion and stress-response are elements central to the individual's ability to interact effectively with his environment, especially one's social environment, and also to come to terms with the enduring problem of self-consciousness. The complex mental systems responsible for these functions are subsumed under the terms “temperament” and “personality,” old Latin words that psychologists appropriated for the purpose of systematic study, just as they appropriated “intelligence.” Attempts to quantify temperament and personality have been less successful, however. Ad hoc distinctions, for example, Type A and Type B, introversion and extroversion and easy, difficult and “slow to warm up” have been useful for specific purposes, but no measure of temperament or personality has achieved the transcendent importance of the IQ score. (Google “measure your emotional IQ” and you will get 1,190,000 hits; “measure your IQ” gets 1,130,000.)

Depression and anxiety are mood states that everyone has experienced at one time or another. Prolonged and disabling states of depression and/or anxiety are abnormal, although not uncommon, and are considered to be pathological states. Anxiety and depression are not only transient states (“I feel anxious about that,” “I have depression”) but also traits, enduring parts of one's personality (“I am an anxious person,” “He is a chronic depressive”). The conventional nosology takes cognizance of this, but only to a limited degree. Major depression, generalized anxiety and all of their respective variants are dealt with, nosologically, as if they were distinct entities, but, in fact, they are intimately related. Three-fourths of lifetime GAD cases also have MDD, and about half of lifetime MDD cases also have GAD. The two conditions are more appropriately considered as variants of an individual's capacity to regulate “distress,” and the diagnostic manuals may be amended soon to accommodate this fact. “Chronic dysthymia” is not the same as “depressive personality,” but it might as well be. “Anxious personality” is implicit in categories like “obsessive-compulsive personality disorder.” The correlation between depression

and anxiety and concepts of temperament and personality is imperfect, although "introverts" are more prone to distress disorders than "extroverts," for example.

As psychiatric disorders, anxiety and depression are transient or long-lasting derangements of a complex functional system that regulates emotion and stress response. Personality traits or temperamental traits that incorporate a lifelong tendency to anxiety and/or depression are indices of the integrity of that system. The stress response is characterized, in different individuals, by a comparative degree of the resilience and efficiency in response to environmental events.

Personality is an enduring complex of cognitive and temperamental traits that does not change very much at all when individuals grow old. In fact, personality change is among the earliest behavioral alterations exhibited by patients who develop AD. Personality change is an important prodromal sign of developing dementia, and often occurs well before overt cognitive decline. A significant change in personality in old age always warrants careful neuropsychiatric examination. The most common personality changes associated with AD are diminished initiative/apathy, relinquishment of hobbies, social withdrawal and increased rigidity. Frontotemporal dementia (FTD) is associated with loss of emotions and insight, selfishness, disinhibition, personal neglect, gluttony and sweet food preference.

Personality change may be an early sign of dementia. But it is also true certain personality characteristics typify people who are bound to develop dementia. The data are based on retrospective studies, and are compromised by our ability to measure personality as accurately as we can measure intelligence, but there is consistency in the recognition that people who ultimately develop AD have personality structures characterized by "neuroticism," stress intolerance and rigidity.

Persons who later become AD patients tend to leave important daily-life decisions to their partners (or other persons of reference). Prior to the onset of the very first neuropsychological deficits, persons who later became Alzheimer patients are found to stay in a lasting situation in which they were subject to a treatment that could be designated as "caring tutelage." Subsequently, most patients became subject to an increasingly patronizing and restricting treatment. People suffering from dementia have personality traits (higher than controls) such as passivity, avoidance, obsessive features and alexithymia.

Among patients who have both mild cognitive impairment (MCI) and anxiety symptoms, 83.3% developed AD over follow-up, as opposed to 6.1% of cognitively intact persons and 40.9% persons who had MCI but not anxiety. Among patients with MCI, the 3-year risk of progressing to AD almost doubled with each anxiety symptom (relative risk [RR] = 1.8 [1.2 to 2.7] per symptom). Conversely, among cognitively intact subjects, only symptoms of depressive mood were related to AD development (RR = 1.9 [1.0 to 3.6] per symptom).

The conventional "risk factor" view is that certain personality attributes, like stress intolerance, are independent variables that contribute to the pathological evolution and clinical expression of dementia. The hormones and other physiological agents that mediate the effects of stress on the body have protective and adaptive effects in the short run but can accelerate pathophysiology when they are over-produced or mismanaged. Prolonged stress produces opposing effects on structural plasticity, notably dendritic atrophy and excitatory synapse loss in the hippocampus and prefrontal cortex, and growth of dendrites and spines in the amygdala. Stress-induced structural changes in brain regions such as the hippocampus have clinical ramifications for disorders such as depression, anxiety and individual differences in the aging process.

The converse is that there is something about the early-life pathology of dementia that renders an individual neurotic or rigid or stress intolerant. An analogy is the rigidity, anxiety, depression and mood instability that characterize the personalities of patients who have had brain injuries or stroke. In the case of people who are bound to develop dementia, emotional dysregulation, or rigidity in the face of internal stress, may represent an adaptation to latent pathology.

These two positions are not orthogonal. Both points of view suggest that the integrity of the stress-response system is compromised in people who are more likely to develop dementia.

DEPRESSION AND DEMENTIA

Depression is easier to measure than temperament or personality. Arguably, it is easier to measure than anxiety, which can occur as excessive emotionality or as rigid suppression of emotionality. For this reason, the literature concerned with the relationship between depression and dementia is much richer. It begins with an old problem in differential diagnosis: is this elderly patient depressed because he is dementing, or is he cognitively impaired because he is depressed?

A generation ago, the concept of "pseudodementia" was current. The rationale for pseudodementia was straightforward: because cognitive impairment is a symptom of depression, and depression is a symptom of early dementia, distinguishing one from the other is not always possible. The only reliable differentiator is treatment response. If an elderly patient presented with cognitive impairment and depression, and if treating the latter led to resolution of the former, then the patient had "pseudodementia". The term is used less often now, as new knowledge has accrued concerning the nature of depression and its relationship to medical illness in general and dementia in particular. It is not simply an "either-or" question.

The study of "late-onset" or "late life" depression (LLD) has shed new light on the relationship between depression and dementia. LLD is a term reserved for patients who experience their first depressive episode after age 50 or 65. Several aspects of LLD are of particular interest to students of dementia: cognitive impairment is a more prominent symptom than in early depression, especially deficits in memory, processing speed and executive function. These also happen to be the earliest cognitive signs of dementia. LLD frequently characterized by symptoms reflecting hypofrontality (blunted affect, apathy, defective initiative, etc.) and psychosis, which are also early signs of dementia. LLD shares with dementia the cardiovascular risk factors, inflammatory markers and the ApoE4 genotype. LLD has a strong association with medical morbidity, especially cardiovascular pathology.

Patients with LLD are at risk for dementia. In a study of 44 patients with "pseudodementia" who were followed for 4 to 18 years (average, 8 years), 39 (89%) developed Alzheimer's disease (AD). In another study of 27 elderly patients with depression accompanied by cognitive impairment, 43% developed dementia within 3 years. Patients with mild cognitive impairment (MCI) and depressive symptoms are twice as likely to develop AD as MCI patients without depressive symptoms. Robert et al described a strong correlation between the onset of AD and a first episode of depression occurring during the preceding year.

In older patients who develop depression, cognitive impairment is likely to persist even after depression is successfully treated. In fact, a "substantial proportion" of older depressed individuals who are cognitively intact when depressed are likely to be impaired one year later, even though their depression has remitted. Not every patient who develops LLD will develop

dementia; not every case of pseudodementia will develop AD. However, the co-occurrence of LLD and cognitive impairment is likely to be an early sign of dementia. .

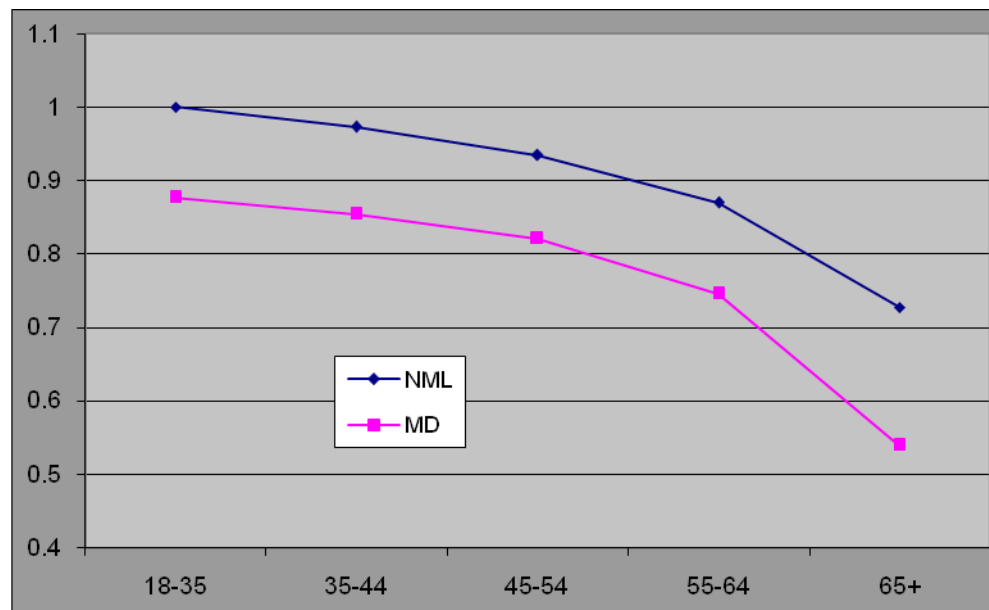
There is a second dimension to the relationship between depression and dementia. Depression is more than just a prodrome of dementia. In fact, mood disorders – at any age -- are a risk factor, albeit a weak one, for the development of AD . Even depression occurring when the patient was young (more than 25 years prior to ascertainment) is associated with the eventual development of AD . The hazard ratio for patients with bipolar affective disorder to ultimately develop dementia is 1.92, and for patients with unipolar depression, 2.13. The risk of developing dementia increases with the number of prior depressive episodes in both depressives and bipolar patients .

There is overlap between the cognitive deficits that are specific to depression and the cognitive deficits that characterize early dementia. In MCI and early dementia, cognitive deficits exist in on memory, the executive functions, processing speed and complex attention . By the same token, cognitive deficits that are specific to depression reside in the domains of executive function, processing speed and effortful attention .

Memory impairment frequently occurs in association with mood disorders , and depressed patients are aware of memory impairment in their day-to-day lives . The relationship between depression and some specific component of the memory system, however, is ambiguous. Although studies have demonstrated problems with encoding as well as retrieval, recall as well as recognition , the common element is probably difficulty with tasks requiring sustained effort rather than with memory *per se* . Interestingly, when depressed patients are memory impaired, the problem is independent of the patient's current mood state, but is related to the past course of the patient's illness – for example, the number of prior depressive episodes. Thus, memory impairment is at least to a degree trait-related, in contrast to attentional dysfunction, which appears to be state-dependent .

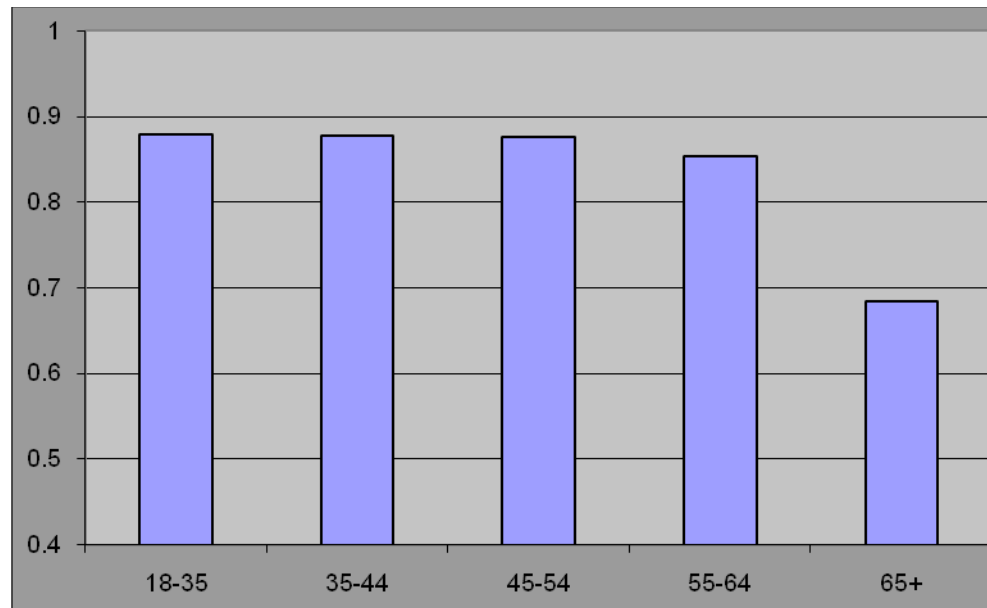
Data from the CNS Vital Signs research project examined the age-related change in cognition in 455 patients with mood disorders compared to 1003 normal controls from age 35 to 90. We generated a standard score for the four domains of memory, psychomotor speed, reaction time and cognitive flexibility by relating the average score of each age group to the average score generated by normals at age 18-35, when performance is optimal. A Neurocognition Index was calculated for each age group by averaging the standard scores of all domains. The change in neurocognition in normal controls and mood disorder patients is represented in Figure X.2. The two lines run in parallel from age 18 to 54, begin to diverge between age 55 and 64, and then diverge sharply past age 65.

Figure X.2. Age-related Change in Neurocognition from Age 18, Normal Controls and Patients with Mood Disorders



In Figure X.3, the neurocognition scores of patients with mood disorders are presented as a percent of normal control scores at each age group. In age groups 18-35, 35-44 and 45-54, mood disorder patients' neurocognitive index scores are 87.9%, 87.7% and 87.6% of control scores. During age 55-64, they are 85.3% of control scores. Beyond age 65, they are 68.4% of control scores.

Figure X.3. Difference in Neurocognition between Normal Controls and Mood-Disorder Patients



Although this was a cross-sectional study, the data suggest an acceleration in age-related cognitive decline in patients with mood disorders in compared to normal controls. It is likely, then, that as people age, the ones who develop depression, or who fail to recover from early episodes of depression, include a substantial number of patients with preclinical dementia. This is consistent with the fact that LLD is a prodrome of dementia.

But we also know that mood disorders are a risk factor, albeit a weak one, for the development of dementia. There is something about the pathophysiology of mood disorders, therefore, that aggravates the process of aging-related cognitive decline and predisposes individuals to dementia.

DEMENTIA AND DEPRESSION: DIGRESSION

One suggestion about how this may occur is from the work of Heneka et al in studies of transgenic mice with a low amyloid load following chemical ablation of the locus coeruleus (LC). Noradrenergic projections arising from the LC to the cerebral cortex play a direct role in selective attention, general arousal, and stress reactions and an indirect role in memory. A recent study showed a facilitator role of NA in the retrieval of spatial and contextual memories, and the role of NA in long-term potentiation is well-established.

It has been known, for decades, that AD (but not CVD) is associated with degeneration of noradrenergic projections from the LC and decreased cortical levels of norepinephrine (NA). Loss of LC neurons occurs early in AD and attenuates the allocation of NA to respective projection areas. LC degeneration correlates with the clinical and histopathological changes of AD.

Hypothetically, loss of NA innervation could cause microvascular dysfunction and ischemia. The preclinical studies in mice, however, suggest alternative mechanisms. Six months following LC degeneration, the relevant projection areas showed a robust elevation of glial inflammation and augmented amyloid plaque deposits. NA depletion in combination with amyloid deposits led to a decrease in neuron number and in neuronal function as determined by micro-PET and behavioral studies *in vivo*.

In addition to its function as a classical neurotransmitter, NA exerts potent anti-inflammatory effects in the brain. It is possible, therefore, that NA functions as an endogenous immunosuppressor that normally counteracts amyloid-induced inflammation.

Two types of LC-derived axonal terminals have been described: conventional synaptic structures and varicosities. These varicosities are believed to release NA extrasynaptically, which allows for its diffusion into the microenvironment where it may act on surrounding neurons, glial cells, and blood vessels. Extrasynaptic NA is thought to execute additional functions apart from its role as classical neurotransmitter. NA blocks the expression of inflammation-induced proteins, including major histocompatibility complex class II, tumor necrosis factor- α , interleukin-1 β (IL-1 β), and inducible nitric oxide synthase (iNOS) in astrocytes and microglia. *In vivo* noradrenergic depletion reinforces the increase of iNOS, IL-1 β , and cyclooxygenase 2 evoked by intracortical injection of A β . Therefore, it has been proposed that NA serves as an endogenous anti-inflammatory agent.

Another candidate mechanism that links emotional dysregulation, the stress response and AD pathology is cortisol. Prolonged elevation of serum cortisol is associated with synaptic loss in the hippocampus. Depression is associated both with hypercortisolemia and hippocampal atrophy, and certain personality traits, like perfectionism, are associated with exaggerated responsiveness in the hypothalamic-pituitary-adrenal axis. This brings us, neatly, to the next section. Like IQ, depression is also associated with cardiovascular disease and cardiovascular risk factors.

CARDIOVASCULAR DISEASE

Cerebrovascular dementia (CVD) is an entity unto itself, the second most common form of dementia, after AD. CVD is clinically and neuropathologically distinct from AD, but the two disorders are also related. Most striking are the observations that, in AD patients, the presence of CVD risk factors aggravates the course of the disorder and that, in patients disposed to develop CVD, the presence of the ApoE4 genotype accelerates the course of the disorder. In simple terms, when the aging brain is assailed from without and within, dementia is more likely to occur and to be more severe.

Epidemiological data show that main vascular risk factors are also risk factors for AD. Some of those risk factors accelerate the progress of AD lesions, mainly by acting on the amyloid cascade. Polymorphic genes associated with AD delineate a clearly defined pathway related to cerebral and peripheral cholesterol and lipoprotein homeostasis and have also been implicated in atherosclerosis. Abnormal lipid, cholesterol and glucose metabolism are consistently indicated as central to the pathophysiology, and possibly the pathogenesis of AD.

Coronary artery bypass surgery, atrial fibrillation, aortic/mitral valve damage, hypertension, hypotension, congestive heart failure, cerebrovascular-carotid atherosclerosis, and transient ischemic attacks produce chronic brain hypoperfusion. In people whose cerebral

perfusion is already diminished by their advanced age, further cerebral blood flow reductions seemingly increases the probability of AD. A neuronal energy crisis brought on by relentless CBH is responsible for protein synthesis defects that later result in the classic AD neurodegenerative lesions.

Cardiovascular disease, and cardiovascular disease risk factors are so intimately associated with the development of dementia that at least one writer has suggested that AD is a vascular disorder with neurodegenerative consequences rather than a neurodegenerative disorder with vascular correlates. That is a rhetorical position, but it the inevitable consequence of a certain kind of thinking. Linear thinking requires a primary and then a secondary. But there is nothing linear about Nature, or evolution, or the clinical expression of dementia.

The cardiovascular system and the central nervous system are two complex systems whose functions are deeply intertwined. Both systems are characterized by relative degrees of resilience and efficiency, and these differ markedly among individuals. The integrity of the vascular system can be measured early on, with simple indices like blood pressure, cholesterol, homocysteine, C reactive protein, etc. On a practical level, cognitive impairment is frequently noted in patients with cardiovascular risk factors, an issue that we shall deal with at some length in the next chapter. Like low IQ, this can lower the threshold for the clinical expression of dementia.

Measures of CNS integrity, like emotional dysregulation, stress intolerance and intelligence, have profound cardiovascular consequences. For example, recent studies indicate a relationship between intelligence and cardiovascular disease. In the Danish Birth Cohort study, childhood intelligence was inversely related to CHD with the highest rate apparent in adults with low childhood test scores (HR(lowest vs. highest quartile), 2.70; 95% confidence interval: 1.60, 4.57; P(trend) = 0.0001). After adjustment for paternal social class and birth weight, the association was attenuated but only to a small degree.

In the Scottish study, childhood IQ was negatively correlated with diastolic and systolic blood pressure, and positively correlated with height and respiratory function in adulthood. The risk of vascular disease, heart disease or stroke was increased with every 15 point (one standard deviation) decrease. in childhood IQ. Again, adjustment for risk factors attenuated the childhood IQ-CVD relationship but only by a small amount.

The fact that the risk factors for cardiovascular disease are largely the same as the risk factors for AD may be interpreted to mean that the two conditions are the same ("aging-related disease"), or variants of a single process (e.g., inflammation), or that one is primary and the other is secondary. We prefer to be less concrete in our approach, less quantitative, as it were, and more qualitative. Logically, what we see in the life of two complex and deeply interrelated systems is that similar processes participate in the phase of involution. The same markers indicate resilience or vulnerability to decay.

AD GENETICS

In autosomal dominant early-onset AD (Familial Alzheimer's disease, FAD) mutations in 3 causative genes are associated with prominent AD pathology, early clinical expression of the disorder and rapid decline. FAD is the prototype of dementia *qua* disease. It accounts, however, for only a small proportion (1-5%) of the dementias. In most dementias, clinical expression is the consequence of multiple, interacting processes.

The goal of genetic study is to tease out the precise nature of pathological processes that participate in the development of dementia. In fact, studies of the genes that code for apolipoprotein E isoforms suggest that the complexity of interacting systems is manifest even at the genetic level. The $\epsilon 4$ isoform of apolipoprotein E is related to late-onset AD, but mainly in association with other risk factors.

ApoE is a major component of circulating lipoprotein and an important regulator of lipid storage, transport and metabolism. The three major isoforms of ApoE in the human body, E2, E3 and E4, are encoded by three alleles on chromosome 19, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. About 90% of the population have one $\epsilon 3$ allele and 60% have two. Genetic linkage and association studies have indicated that the $\epsilon 4$ allele is overrepresented in patients with AD and $\epsilon 2$ is underrepresented ; people with two $\epsilon 4$ alleles are eight times more likely to develop AD than people with two $\epsilon 3$ alleles, and people with two $\epsilon 2$ alleles are relatively protected against late onset AD . The accumulation of beta-amyloid protein is more extensive in people with the $\epsilon 4$ allele, regardless of whether they have AD, and the presence of the $\epsilon 2$ allele is associated with less deposition .

The $\epsilon 4$ allele is an established risk factor for the development of AD and AD patients with $\epsilon 4$ experience accelerated decline . Possession of one or two $\epsilon 4$ alleles is associated with a greater rate of conversion from MCI to AD ; greater vulnerability to the effects of drugs that impair memory , greater impairment and slower recovery following brain injury ; and the development of dementia in people with Down syndrome and cardiovascular disease .

In studies of healthy, cognitively intact individuals with the $\epsilon 4$ allele, young people, middle aged people and relatives of AD patients with the $\epsilon 4$ allele have reduced blood flow and decreased glucose metabolism in the same regions of brain as AD patients . Healthy, cognitively intact adults with the $\epsilon 4$ allele experience more memory decline over time and generate increased brain activation in response to cognitive testing, which is interpreted as a sign of compensation .

The $\epsilon 4$ allele, however, is not specific to AD and is only a weak predictor of AD and/or cognitive decline . ApoE genotyping has neither the sensitivity nor specificity necessary for a medical screening test, although, in company with other information, like memory impairment, it has a degree of usefulness .

THE PROBLEM OF DEMENTIA -- SUMMARY

Aging is the most important cause of dementia. Aging is not a "risk factor" for dementia, it is the *sine qua non*. Like neuropathology, aging is not sufficient cause for dementia, but it is necessary.

By the age of 85, estimates of dementia prevalence are as high as 50% . On the basis of arithmetic alone, therefore, it is as reasonable to say that dementia is normal and preserved cognition in old age is an aberration as it is to maintain the converse; just as it is equally valid to refer to age-related brain changes as "pathological" or "normal aging." Even "early onset" AD arises at an age that was advanced and exceptional during most of humanity's history.

For generations, "senile dementia" was thought to be an entirely normal consequence of aging. We are not about to resurrect that old canard, but we cannot accept what has arisen, in some quarters, at least, as the alternative: that the only proper approach to the problem of dementia is the pathology of AD.

Aging is not dementia and dementia is not aging, but aging is the set and dementia is a subset. They are both complex phenomena that incorporate three processes: the gradual winding-down that characterizes all complex systems, something that physicists call “entropy” ; the integrity, or resilience, that is built into every successful system, but is subject to inter-individual variation; and pathology that arises here or there, like weeds in a garden, and that interacts with the first two processes. This logical framework is appropriate to the study of aging, to dementia, and to life itself.

Forty years ago, medicine moved away from the idea of “senile dementia” and embraced the idea that dementia was understandable as a disease. The approach has been magnificently productive. For every single publication about AD prior to 1976, there have been a thousand since. We have treatments now for the symptoms of AD, and we are on the verge of developing treatments for the pathological processes that contribute to AD. It is ironic, therefore, that as we anticipate ultimate success, we discover the limitations of the premises under which we have been operating. Eliminating AD pathology will not eliminate dementia, any more than eliminating pellagra and neurosyphilis has eliminated schizophrenia. All of the processes that contribute to the evolution of dementia have to be addressed.

Because we know that accumulation of amyloid in the brain begins early in life and afflicts 80% of the population, sooner or later, an appropriate treatment will have to begin early in life and be universally administered. The appropriate model would be childhood vaccination, or supplementing the grain supply with folate or milk with vitamin D.

The stress disorders, anxiety and depression and all their variants; the cardiovascular risk factors; low intelligence, low education, and psychosocial disadvantage, all contribute to the evolution of dementia. All of these elements have to be addressed in the course of effective dementia prevention. They are being addressed, in some societies more than others. Even the global population IQ is steadily rising. There is evidence, too, that the incidence of dementia in particular, and aging-related disability in general, is actually going down.

In the next chapter we shall address the issue of dementia screening. If prevention strategies and treatments are to be effective, there has to be a way to establish an early diagnosis, or at least to identify groups of people who are high risk. At the present time, the best way to screen for dementia is neurocognitive testing. We shall consider the method, and its limitations.