MEDICAL GRAND ROUNDS

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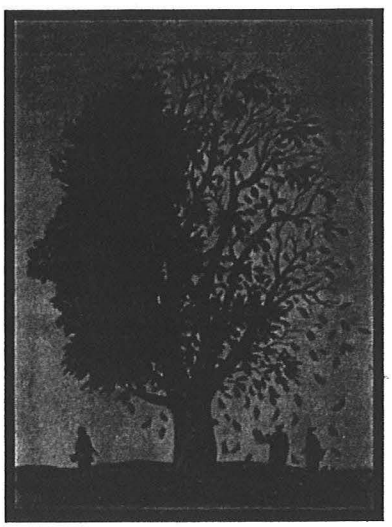
Losing it:

Mild Cognitive Impairment, Is it Alzheimers?



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Losing it: mild cognitive impairment, is it Alzheimer's?

Introduction

LT, a 69 year-old semiretired faculty member, comes to you complaining of forgetfulness. He has been asked to take on a position of consultant to an international health organization and wonders if he should. He tells you that in addition to forgetting appointments, he recently had trouble doing his taxes and that a book chapter he has been working on has been more difficult than usual. He wonders if this is early Alzheimer's or just a normal part of the aging process.

What is it?

In the next 45 minutes I will discuss the continuum of cognitive aging and how it relates to the dementing illnesses we have learned to recognize so well. I will speak of cerebral reserve and the effect of co-morbidity on aging brain function. I will define the entity that the National Institute on Aging calls mild cognitive impairment, comparing it to the clinical criteria for the diagnosis of Alzheimer's disease. I will review treatment options and finally, in light of recent discoveries regarding neurogenesis and the ability of the brain to regenerate itself, I will discuss prevention or how we can avoid losing it as we age and prepare to enjoy the great things about getting older.

Normal aging

Normal aging of the brain is defined as aging changes that occur in individuals free of overt disease.

For most of us, these changes are not significant until past the 75th year. Indeed, our concept of who is old has changed as more and more individuals reach older ages free of disabling diseases. Geriatricians have recognized this demographic change by subdividing the elderly into the young-old, those under age 75, the geriatric old, those 75-85, and the wonderful oldest-old, those over the age of 85, many of whom continue to be productive into their 90's.

Genetics, experience, health, personality, and culture all contribute to changes in cognition across each adult's life span. Scientific investigation of age-related changes is complicated by these diverse factors. Indeed, many studies of cognitive aging reveal enormous variability among older adults. That is, some older adults exhibit only mild to moderate changes in cognitive function, whereas others, specifically 25% of those older than 80, exhibit significant and often devastating deficits.

What do we know about the aging brain?

Brain volume

As we age, there is a loss of neuronal diameter, neuronal shrinkage[1] and decreased synaptic density. More than neuronal cells drop out, these cellular changes are responsible for the brain volume loss observed over time in the healthy elderly.[2] Brain volume differences seen cross-sectionally at any age reflect small constant rates of volume loss with healthy aging.[3] When examined longitudinally, however, healthy oldest-old subjects do not show greater rates of brain loss when compared to younger elderly. In 1998 Mueller et al.[4] confirmed this finding after measuring volume on annual quantitative MRI's he performed on 46 rigorously healthy subjects over a five-year period. Of all brain regions, the rate of change in brain volume for the frontal lobes, 55% per year in healthy adults, was substantially the greatest.

Effect of Age on Regional Cerebral Volumes

Brain Region	% Decline per Year	Cranial area (cm^2)
Cerebral hemispheres	-0.00.23	0.0065
Frontal lobes	-0.00.55	0.0086
Temporal lobes	-0.00.28	0.0049
Amygdala-hippocampal complex	-0.0030	0.0035

Coffey – Neurology 1992

Synaptic density

Brain volume loss in healthy elderly is also due to regression and loss of dendritic arborization. This decreased density of synapses which occurs along the lifespan seems to be more prominent in frontostriatal, temporal and prefrontal cortical structures. It is not felt to be related to the neuronal cytoskeleton changes such as intraneuronal neurofibrillary changes that are associated to AD.[5] There is also evidence that although regression of dendrites is seen in some cells, dendrites of other cells are growing.[1]

Cortical blood flow

There is increasing evidence that in the healthy elderly, cortical blood flow remains unchanged. Under stressful conditions, however, effective blood supply for the task at hand may be diminished.[6]

This decrease in effective blood flow in normal aging is due to a thickening of microvascular basement membrane.[7] More pronounced thickening and deterioration of the membrane with breakdown in the blood-brain barrier may play an important role in AD.

Biochemical changes

Recent studies reveal that memory fields are constructed through the interaction of pyramidal and nonpyramidal neurons and their excitatory-inhibitory relationships. Biochemical changes studied include alterations in neurotransmitters and growth factors. Although it has been difficult to distinguish usual aging changes from the effects of disease and concomitant medication usage.

In 1998, at Brookhaven, Nora Volkow[8] confirmed the relation between measures of brain dopamine activity and indexes of motor and cognitive function in healthy individuals. To do this, she studied thirty healthy volunteers aged 24-86 with positron emission tomography. All subjects underwent a neuropsych test battery. She found that there were age related decreases in brain dopamine activity that were associated with a decline in motor function and impaired performance on tasks that involve the frontal brain regions. This change may account for decreases in motor performance in older humans and explain the susceptibility to dopamine blocking preparations seen in this cohort.

Decrease in neuronal plasticity

It is said that the aging process involves circuitry rearrangements and loss of what is broadly referred to as synaptic plasticity.

Learning and memory promote plasticity of synapses notable in the hippocampus. There are also pathological conditions that trigger plasticity. For instance, in ischemic stroke damaged neurons sprout and re-establish connections.

Thus, one could suggest a theoretical model in which there are two populations of neurons in the normal aging cortex, one a group of dying neurons with shrinking dendritic trees, the other a group of surviving neurons with expanding dendritic trees. In normal aging, the latter population prevails. With the passage of time, there would be a shift of individual neurons from the surviving population to the dying population. The rate at which this shift takes place is probably a function of genetic and non-genetic or extrinsic factors.[1]

Successful plasticity may be a finite event. So, older persons suffer larger lesions after stroke. They are more sensitive to neurotoxins and the effects of psychotropic medication. In the face of acute illness, older individuals display impaired resistance to hypoxic and hypotensive conditions.

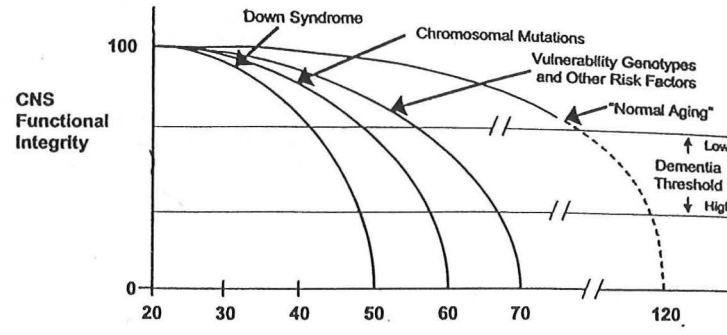
Decreased functional reserve

Because of this decreased functional reserve, old brains are easier to hurt. The **cognitive reserve hypothesis** posits that individuals manifest different thresholds for symptom occurrence with brain dysfunction. Those with a greater reserve can sustain more brain disturbance before manifesting symptoms, whereas those with little cognitive reserve become symptomatic with more limited functional insults. An individual with more neuronal connections than another, for instance, can sustain a substantially greater amount of neuronal dysfunction before becoming symptomatic.

In a study of aged patients with normal cognitive function who were found at autopsy to have neocortical plaques, Katzman et al. noted that asymptomatic patients with AD changes had greater brain weights and larger number of neurons compared to age-matched controls.[9] The reserve hypothesis predicts that these patients were able to sustain a degree of neuropathological change consistent with early AD but had sufficient cognitive reserve to remain asymptomatic. In 1995, Snowdon described the fascinating case of Sister Mary, a 101-year old nun whom upon her death and autopsy showed pathological evidence of multiple plaques and neurofibrillary tangles, yet clinically seemed asymptomatic until her death of cancer of the colon.[10] Upon autopsy, what distinguished her brain from those of other sisters with symptoms and pathological findings consistent with AD was the total absence of vascular changes.

Thus, AD patients with greater brain reserve can sustain more cerebral dysfunction before becoming symptomatic.

Figure 1 shows the interaction of Alzheimer's disease with cognitive reserve and symptom thresholds.[11] At one extreme is normal aging with its very gradual production of A beta and slow rates of neuronal degeneration, such that dementia does not occur within the normal life span. At the other end of the spectrum are patients with down syndrome who have both cognitive reserve and over production of A beta leading to occurrence of the dementia syndrome early in life. Next most severely affected are those with the inherited autosomal dominant forms of AD in which AB is generated in unusual quantities leading to the appearance of the dementia syndrome in late midlife. Next in order of appearance are patients who have normal AB production but are genetically at risk because of the presence of the Apo-E-4 genotype or other disease promoting factors such as hypertension. These lifetime trajectories interact with thresholds such that those who have had a history of head trauma, small heads, low intellectual function or little education become symptomatic at earlier times than those whose life has become more propitious.



Effect of disease

To date, physical illnesses have generally not been shown to be potent independent influences of cognitive functioning once age has been taken into account. Among the physical conditions most studied, hypertension is a weak predictor of cognitive function, as are depression[12,13] and stroke. Diabetes has been associated with poorer performance on some memory-related tests compared to non-diabetics and may aggravate the usual changes that occur with aging. Diabetics, however, do not have increased Alzheimer-type pathology compared with age-matched control subjects.[14-16] As a risk factor for cognitive impairment, DM seems to interact with other disorders, particularly hypertension and dyslipidemia and perhaps the apoprotein E genotype suggesting the likelihood of at risk subgroups. Some preliminary data suggests some benefit to cognition can be gained by improved glycemic control.[17]

Longitudinal studies, like the Framingham and Honolulu Heart Program cohorts, have reported a modest inverse association between mean blood pressure and cognitive function measured 12-15 years later.[18,19] Treating moderate hypertension with either a diuretic or beta-blocker does not seem to influence cognitive function. To date, there is no evidence that treating hypertension benefits cognitive function in older adults.[20] However, cognitive functions measured at Framingham were mostly memory tests,[21,22] and not tests of frontal lobe function, which perhaps would be expected to be more vulnerable to microvascular injury. There is some evidence that the control of systolic blood pressure within the range of borderline hypertension may delay the progression of brain atrophy in elderly patients with essential hypertension and no history of stroke.[23] Cognitive impairment is more likely, of course, in individuals with stroke.[24]

Cognitive function changes

Because of the above described changes, the most consistent alterations in cognition are the impairment of memory, slower speed of cognitive and motor performance, and the impairment of the frontal lobe's function called executive function.

Memory is not a unitary phenomenon. It involves an extensive array of processes some that remain stable with aging and others that show aging-sensitive changes.[25]

Memory Functions and Aging

Stable memory functions with aging
Remote memory
Crystallized abilities (world knowledge, vocabulary)
Remembering the gist of information
Aging-sensitive memory functions
New learning (learning occurs at a slower pace for many types of information)
Dept of processing (elderly tend to process information at a more superficial level)
Recall of details of new information and events
Nonverbal memory (eg. Misplacing things)
Cullum, JAMA 1998

What is the cumulative effect of these neuroanatomic and cognitive changes? How is this picture of mild cognitive losses different from Alzheimer's?

Recently several investigators have attempted to establish the benchmarks of this continuum.

In 1998, **Rubin** et al.[26] reported on the results of a fifteen-year longitudinal examination of clinical and psychometric performance of a group of older healthy adults. On average, there was no longitudinal decline in psychometric performance in non-demented elderly who remained non-demented. However, forty percent of participants in the study (ages 64 to 83 years) experienced cognitive decline within twelve years of enrollment. Cross-sectionally, the older an individual was the first time the battery of tests was administered, the lower the score. Interestingly, those patients developing dementia had initially lower performance levels that still fell within normal limits for their age.

In 1999, **Petersen**[27] reported on a sample of 76 consecutively evaluated Mayo Clinic patients who filled criteria for mild cognitive impairment and compared them with 234 healthy controls and 106 patients with mild Alzheimer's disease. The three groups underwent an extensive battery of neuropsychological testing. He found that the primary distinction between control subjects and subjects with mild cognitive impairment was memory. However, when the subjects with mild memory loss were compared to those with very mild Alzheimer's, memory performance was similar. AD patients, however, were impaired in other cognitive domains. This study, therefore, validated criteria for distinguishing what he called mild cognitive impairment from AD. In this study, the rate of conversion from MCI to AD was higher than that from control to MCI/AD 12% vs 1% to 2% per year.

Criteria for MCI

1) memory complaint
2) normal activities of daily living
3) normal general cognitive function
4) abnormal memory for age
5) absence of dementia

As defined by these criteria, individuals with mild cognitive impairment are at an increased risk for developing AD ranging from 1% to 25% per year. The Peterson cohort, however, was not controlled for co-morbid illnesses, such as hypertension or diabetes, and they could be taking medications for these disorders. So is the story different in populations who have been screened for disease?

In 1993, Howieson[28] et al. examined two groups of healthy community dwelling volunteers. Two age groups were studied: the oldest-old, n =34 and the young old n=17. Rigorous exclusion criteria covering all diseases "that might affect the brain" were applied. Exclusions included alcoholism, past or present, psychiatric illness, risk factors for vascular disease and history of trauma with loss of consciousness for greater than 5 inutes. Present or past hypertension was the greatest exclusion. Vision and hearing testing were performed as well. Again, two groups of subjects emerged indicating that in this group of super elderly, substantial cognitive decline is

not inevitable. Relatively spared were verbal measures of learning and reasoning. The effect of aging itself was greatest on visual, perceptual, and constructional tasks.

The Continuum of Cognitive Changes of Aging

Test	Normal Young	Normal Age	MCI[1]	AD	OLD-OLD[2]
Vocabulary	↔	↑	↔	↓	↑
Naming (BNT)	↔	↔	↓	↓↓	↓
Story Recall (WMS-R)	↔	↓	↓↓	↓↓↓	↓
MMSE	28	28	26	22.6	26
Exec. Function	↔	↔	↓	↓↓	↔
Speed of Processing	↔	↓	↓	↓↓	↓
Learning Retention	↔	↓	↓	↓↓	↓

1. Petersen 1999
2. Howieson

But is memory the only element of cognitive decline we have to worry about? Remember that Dr. T's most bitter complaint is being unable to do things he had been doing easily before.

Research on age-associated cognitive impairment has focused on memory function. However, several authors[29,30] have suggested that many age-related cognitive losses unmask when frontal lobe function is impaired. The frontal lobe has been associated with higher-level cognitive functions, such as working memory (the mental sketchpad), organization, and executive control of complex mental processes.

Frontal lobe dysfunction may antedate the diagnosis of dementia. In 1997, Hanninen and Soininen[31] in Finland compared 43 individuals with age-associated memory impairments according to NIMH criteria to 47 age-matched healthy controls. Four neuropsychological tests and MRI's were performed on all subjects. Investigators found that in subjects thought to be normal except for memory problems, there was impairment in three of the four tests assessing frontal lobe function. (Interestingly, frontal lobe volumes on MRI remained unchanged in both groups suggesting that maybe functional changes antedate structural changes and that functional testing such as SPECT would be more useful in early diagnosis of frontal lobe dysfunction.)

Since 1994, Royall in San Antonio has been studying a cohort of well, elderly, air force retirees looking at other measures of cognitive function in an attempt to predict future changes in ability to perform activities of daily living and live independently.[32] Using tools, such as a modified clock drawing, he has managed to identify individuals with intellectual losses that cannot be easily attributed to early AD.[33]

In Dr. T's case, inability to keep appointments made several weeks in advance may reflect a mild organizational or executive dysfunction. However, his clock drawing was intact, and formal neuropsychological testing revealed only slowing of neuroprocessing.

Diagnosis of Alzheimer's disease and related disorders

As currently defined by the NIH, then, mild cognitive impairment, perhaps better called mild memory impairment, is a disorder of predominant memory loss. In that way, it probably resembles a pre-Alzheimer's dementia syndrome more than the normal changes of aging do.

The relationship between neuropathological lesions and this mild "preclinical" dementia is not fully understood. In the case of the commonest kind of dementia, Alzheimer's, it is unclear whether the classic neuropathological features of the disease, neurofibrillary tangles (NFT's), dendritiv neuropil threads (NT's), and neuritic plaques (NP's) seem to precede the clinical diagnosis of AD.[34,35] However, there are patient's in the early stages of disease with severe dementia symptoms while others in the final stages have only minimal dementia.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) INCDS-ADRDA work group, under the auspices of the Department of Health and Human Services task force on Alzheimer's disease, produced consensus criteria for the clinical diagnosis of Alzheimer's disease.[36] Fifteen years later, as the use of these criteria and clinicopathological skills has evolved, it has become apparent that the group of disorders that we call AD is a truly a heterogeneous one.

Criteria for Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Min-Mental Test, or some similar examination;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40-90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease , after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

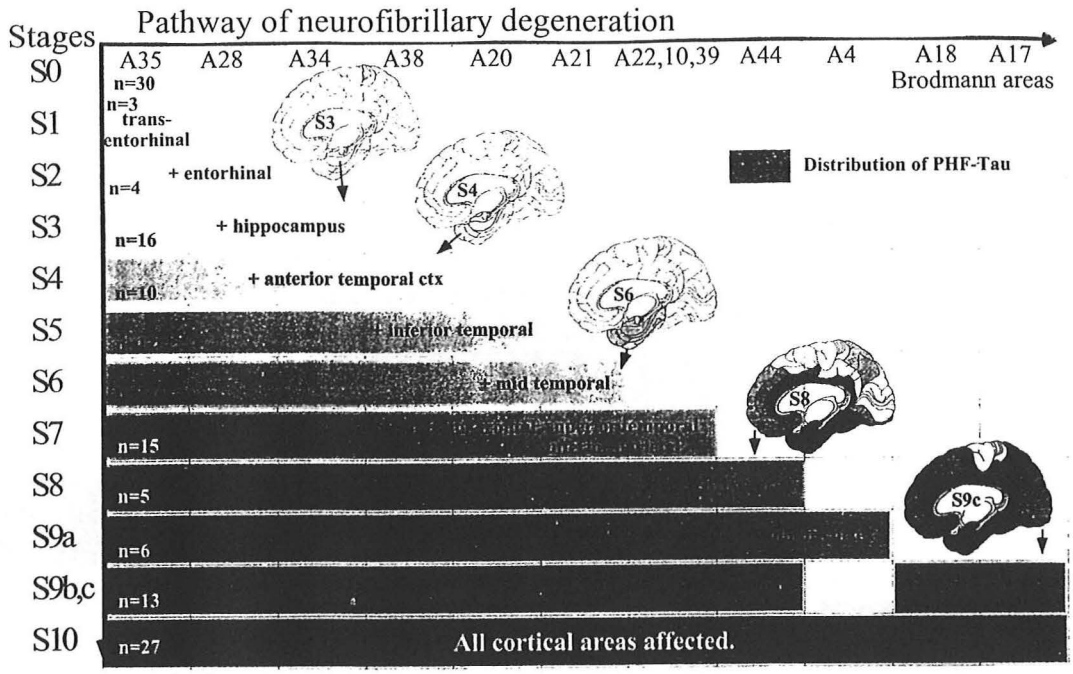
familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

Neurology 1984



Proposed pathway of neurofibrillary degeneration (NFD) in aging and AD. Paired helical filaments (PHF)-tau in the different brain areas, as a function of the stages, is shown in gray. Aged control subjects and non-AD patients were found at stages 0 to 3. Up to stage 6, NFD could be asymptomatic. All patients above stage 7 and with two association brain areas affected by NFD were patients with AD or mixed dementia. Note the heterogeneity of stage 9, with either the occipital areas or the frontal motor cortex affected.

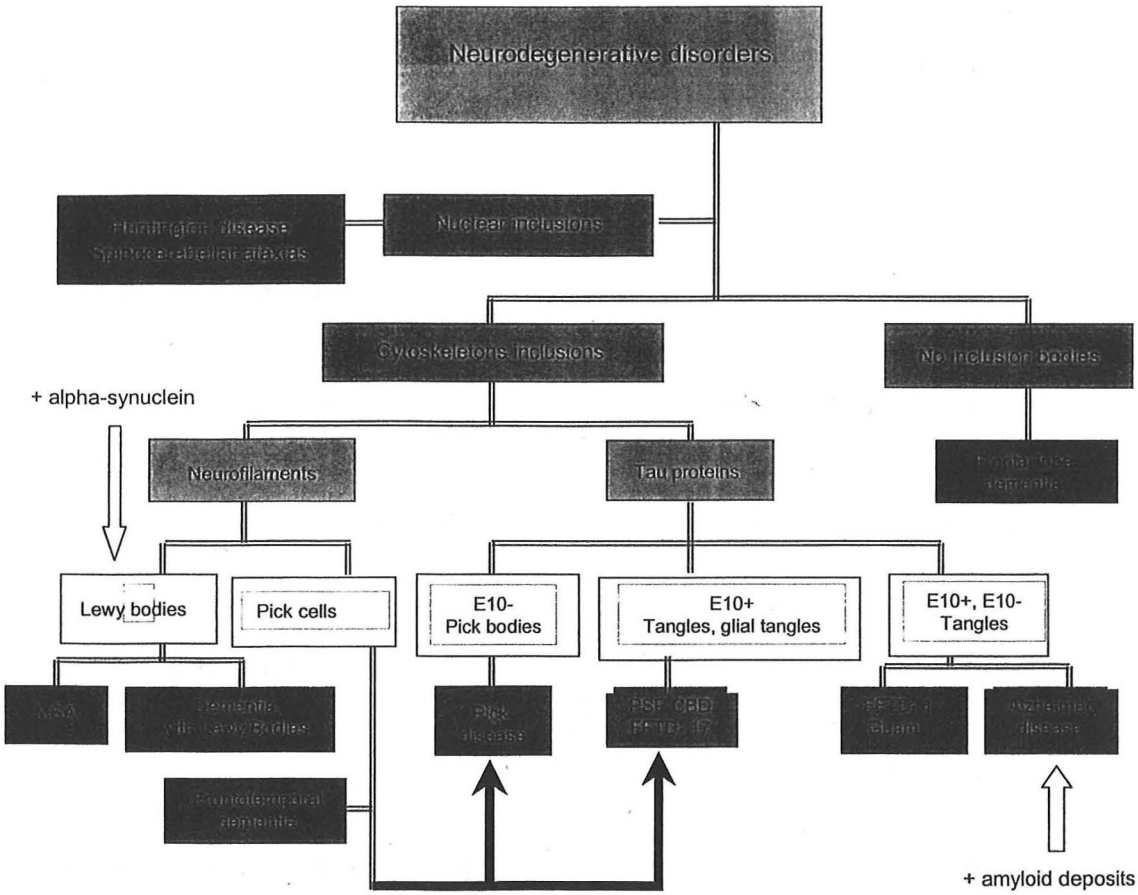
For instance, we know that 10 percent to 20 percent of all patients with pathological confirmation of AD have also been noted to have cortical Lewy bodies. These pathological findings in **Lewy Body Dementia (LBD)** coincide with the clinical picture of early delusions and hallucinations, fluctuations in mental status, and mild extrapyramidal signs or neuroleptic hypersensitivity.

Compared with patients with AD alone, those with LBD have somewhat better recall on clinical evaluation and a significantly lower frequency of neurofibrillary tangles on autopsy. There seems to be no difference in survival time.[38]

After expanded clinicopathological experience, we can also now talk of **frontotemporal dementia syndromes (FTD's)** in contrast to classical Alzheimer's disease, which initially shows a predilection for the entorhinal, hippocampal, and temporal regions. The FTD's comprise a group of disorders with a common, basic degenerative pattern. Pathological changes in this group of disorders are relatively bland when compared to the amyloid containing plaques and NFT's characteristic of Alzheimer's disease. They are characterized by atrophy and a striking loss of synapses with mild gliosis, and mild loss of myelin that may be invisible on gross

inspection. Clinically, the patients present between the ages of 45 and 70 with change of personality and behavior, affective symptoms, and a progressive speech disorder. Signs of disinhibition often appear early as hyperorality, restlessness, impulsivity, irritability, and excessive sentimentality.

Genetic studies and biochemical analysis of neuronal inclusions have helped us to refine diagnosis criteria for the degenerative dementias. The present challenge is to fit clinical with neuropathological features better. Advances in neurochemistry and molecular biology may give us clues to this moving domain.[39]



The biochemical composition of neuronal inclusions seen on brain autopsy often gives precise information linked o the etiology. Nuclear Inclusions are seen in some familial diseases with repeats of nucleotides, such as in Huntington's disease or spinocerebellar ataxias. They correspond to the translation of the CAG repeats into polyglutamine chains that accumulate in the nucleus. Many brain diseases are affected by neurofibrillary degeneration, which corresponds to the accumulation of abnormal Tau proteins into pathological filaments [paired helical filaments (PHFs) in Alzheimer's disease, straight filaments in corticobasal degeneration (CBD), random colled filaments of Pick bodies in Pick's disease]. Tau proteins have a biochemical signature reflecting the subtype of degenerating process: a triplet in Alzheimer's disease; an upper doublet in progressive supranuclear palsy (PSP), CBD and most frontotemporal dementia (FTD)P-17; and a lower doublet in Pick's disease. Cortical Lewy bodies that characterize dementia with Lewy bodies (DLB) are composed of α-synuclein. Similar Lewy bodies are found in the substantia nigra of Parkinson's disease. Very recently, brain lesions in multiple system atrophy (MSA) were found to be composed of ∝-synuclein. Neurofilament epitopes have also been described in Lewy bodies. They are also found in Pick cells (also named balooned cells or swollen achromatic cells) found in FTDs (pick's disease, CBD and FTDP-17 with Pick cells). Other diseases are characterized by the complete absence of distinctive biochemical and neuropathological features, such as some frontal lobe degeneration types of FTD (Lund and Manchester criteria [2]).

Pasquier - Current Opinions in Neurology, 1999

Treatment of mild cognitive impairment

As the baby boom generation ages and Americans are faced with the certainty of a grayer society, concern about loss of cognitive faculties, and memory in particular, are skyrocketing.

There are no approved treatments for mild cognitive impairment. Trials are now underway to evaluate effectiveness of several formulations used for treatment of Alzheimer's disease and other related disorders. Most trials are predicated on the idea that mild cognitive impairment is a predementia syndrome and that, therefore, therapies that are to treat dementia should have comparable or greater beneficial effects.

Briefly then, these therapies are:

- Anticholinesterase inhibitors.
- Anti-inflammatories
- Estrogen.
- Anti-oxidants

Cholinesterase inhibitors

There is some evidence that memory is mediated by acetylcholine, a chemical neurotransmitter, which communicates electrical impulses between brain cells. In AD, there is depletion of acetylcholine in certain areas of the brain. The anticholinesterases, such as tacrine and donepezil, prevent the degradation of the naturally occurring acetylcholine in the gap between brain cells by obstructing the enzyme that degrades it. Therefore, there is more acetylcholine available. Disappointingly, clinical improvement seen in Alzheimer's patients treated with these cholinergic enhancers has been modest at best. To date, no definite disease modifying effects have been reported.

Recently, the National Institute on Aging announced a national, multicenter randomized, double-blind placebo-controlled trial in which individuals with mild cognitive impairment (as defined by a clear memory deficit without major impairments in other cognitive domains) will receive donepezil or Vitamin E for thirty six months. Efficacy will be determined by comparing the rate of conversion to AD for vitamin E or donepezil to that observed with placebo.

Anti-inflammatory treatment

Failure of the neurotransmitter enhancers to alter the underlying pathology of AD has led researchers to investigate agents that interfere with neuronal degeneration. Mounting evidence suggests that neuronal destruction in AD is mediated by inflammation involving free radicals and that anti-inflammatory drugs may delay the onset and progression of AD.

In 1997, Stewart[39] at Johns Hopkins reported on the results of a 16-year longitudinal study examining the 1686 participants of the Baltimore Longitudinal Study on Aging. They confirmed

that risk for AD decreased with increasing duration of NSAID use. No trend of decreasing risk was noted in those with increasing duration of aspirin use or with the use of acetaminophen. The diagnosis of Alzheimer's was based on a standardized neurological assessment applied to all participants in the cohort. No improvement in baseline cognitive function was noted.

A large multicenter trial is now underway to assess the efficacy of low dose ibuprofen in slowing normal loss in baby boomers. Previously, a smaller prospective trial failed to show any benefit of prednisone on patients with established Alzheimer's disease.[40]

Estrogen replacement

Estrogens have numerous effects on the brain throughout the lifespan, beginning during gestation and continuing on into senescence. They do so via multiple mechanisms in which both genomic and cell surface receptors appear to be involved. For genomic effects, both the ER alpha and ER beta genes are expressed in brain tissue, and mapping studies continue to reveal new estrogen containing cells in regions of the nervous system not previously thought to be estrogen targets.[41] For cell surface actions, receptors have not been well characterized; but, many actions have been described, including effects on neuronal excitability, and calcium ion homeostasis. In addition, estrogens are reported to have neuroprotective effects against free radical induced damage. In Alzheimer's disease, in cell culture of fibroblasts and neural cell lines, estrogen has been shown to suppress the toxic amyloid protein.

Estrogen exercises its benefits in post-menopausal women via effects on cholinergic and nerve growth factor-related systems in the brain. It also increases density of dendritic spines and the synthesis of acetylcholine transferase in area CA1 of the hippocampus. There are estrogen receptors at the neurotransmitter pathways as well as the hippocampus, the spinal cord, glial cells, and the blood brain barrier. One of the most surprising effects is the regulation of synapse turnover in the hippocampus.

Evidence in large population groups of women that estrogen treatment of postmenopausal women may have a protective effect toward dementia is controversial and somewhat confounded by the tendency of educated, healthier women to take ERT more often than not. In 1998, Diane Jacobs et al.[42] evaluated cognitive performance of 727 primarily Latino and African-American women participating in a community-based epidemiological study of aging in northern Manhattan. Participants were followed longitudinally for 2.4 years. Women who had used estrogen replacement scored higher at baseline than non-users, and verbal memory improved over time. The effect of estrogen on cognition was independent of age, education, ethnicity, and APOE genotype. Women with Parkinson's, dementia, and stroke were excluded from analysis. There have been no trials demonstrating the effect of estrogen on mild cognitive impairment.

Anti-oxidants

Concern about the efficacy, safety, and expense of cognitive enhancers, NSAID's and ERT has lead to a surge in the use of non-prescription anti-oxidants for the treatment of memory

disorders. It is estimated that on GB alone, US sales are as high as 125 million dollars per year. Unanswered questions remain about which antioxidants to recommend, at what doses they should be taken, and whether supplements increase the benefit of a normal dietary intake

In 1997, Le Bars et al.[43] reported on the results of a randomized, controlled double-blind placebo-controlled study using a standardized extract of gingko biloba preparation in a dose of 40 mgs tid. Conceivable action of EGB in AD includes free radical reduction, modulation of neurotransmitters, or an antidepressant effect. Results, which were comparable to the first RCT resulting in FDA approval of tacrine, suggests that they are equally effective in treatment of moderate dementia. While safe and effective in producing a 25% reduction in the short term cognitive and functional decline, long-term effect of this preparation on cognition remains unclear. Also untested is its effect as a memory enhancer, although a proposal for a large multicenter trial to test its effect on this cohort is currently being planned.

Sano and colleagues[44] were able to demonstrate the beneficial effects of high dose vitamin E–2000IU a day only after adjusting for the small differences in mental status between control and treatment groups. Significant outcome was a seven-month delay in institutionalization. There was no benefit on memory. Vitamin E will be part of the large multicenter trial also examining the effect of cholinergic enhancers in patients with mild cognitive impairment.

Prevention

Using the diagnostic criteria outlined earlier, Dr. T does not have dementia, nor does he have mild cognitive impairment. Because of slower performance skills, we advised him to take on shorter assignments with more flexible deadlines. Dr. T is aware of the fact that the incidence of dementia doubles approximately every five years after the age of 65.[45] *He wonders what he can do to prevent further decline.*

The age of onset or clinical detection of dementia may be delayed by several exogenous factors, many of which have been discussed in my review of current treatment options. Other protective factors are education and occupation, mental activity, and exercise.

There is strong evidence that **education** and **occupation** protect against cognitive decline. Dementia is a democratic process. Physicians and politicians, actors and musicians may become its victims. Yet a number of studies report that individuals with low education are more likely to develop dementia.[46]

In 1994 at **Columbia,** Stern et al.[47] examined 593 non-demented elderly in the Washington Heights and Inwood communities of New York City. Four years later 106 had become demented. The risk of dementia in this cohort was increased in subjects with either no education or low education. Risk was greatest for subjects with both low education and low lifetime occupational attainment. Stern concluded that increased educational and occupational attainment may reduce the risk for incident dementia either by decreasing ease of clinical detection or by imparting a reserve that delays the onset of clinical manifestations.

In an analysis of mental status examination scores in subjects in the Iowa, East Boston, and New Haven Established Populations for Epidemiological Studies of the Elderly **(EPESE)** cohorts over a 6-year period, education protected against a decline in performance. Higher test scores also were associated with greater occupational prestige, an effect that persisted when education was controlled.[48] There is inconsistency in this relationship once high school graduation is reached, no further effect being demonstrated in the EPESE studies.

Concerning appropriate temporal relationship, formal education occurs decades before the clinical presentation of dementia. It is possible that education-secondary school as compared to no education-increases brain reserve by increasing synaptic density in the neocortex leading to the delay of symptoms by four to five years.[46] Thus, it is possible that there is a decline in synaptic density with aging, but that learning stimulates neuroplasticity, augments cognitive reserve, and delays the onset of the dementia syndrome.

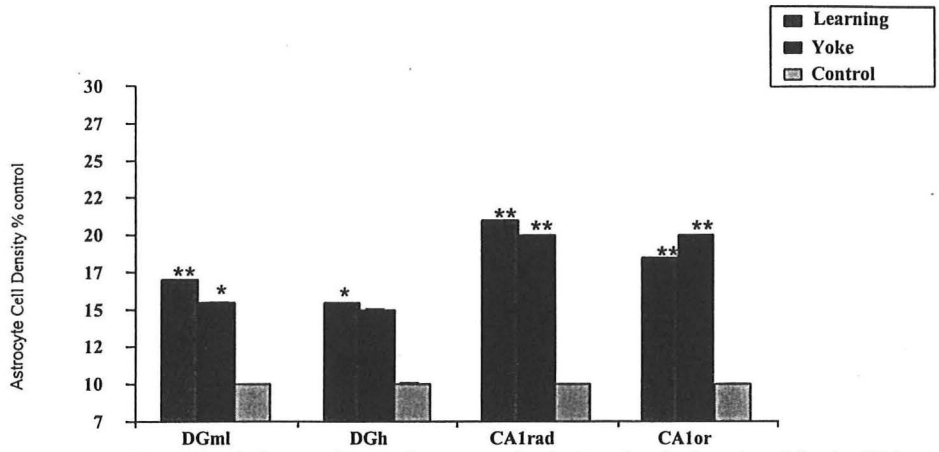
Because the median education level of the elderly is rising rapidly, the association between low education level and dementia may have important implications for future incidence rates of Alzheimer's disease and dementia. Over the past thirty-five years, the median education level of the US population of individuals aged sixty-five years or older has increased from 8.3 years to 12.8 years. At the same time, the increase in educational attainment among the elderly has paralleled improvements in nutrition of pregnant women, childhood and adult nutrition, and control of infectious diseases. It is possible then, in a manner analogous to other chronic diseases, that we are compressing the onset of clinical dementia to the end of life expectancy.[49]

Another intriguing possibility is that age related neurotransmitter alterations can be forestalled by increased **physical activity**. There is some initial evidence supporting this idea. In laboratory animals, changes in motor activity to a rich lifestyle led to D2 receptor changes. Routine exercise also improved certain cognitive skills and dopamine activity in sedentary humans 50-70 years of age.[50]

Neuroplasticity and neurogenesis

The possibility that learning and physical activity may stimulate cellular plasticity is a fascinating one.

Last year, Gomez-Pinilla at UC Irvine reported on the results of a fascinating experiment.[51] Following training in a water maze, the hippocampus and cerebellum of learning rats exhibited an increase in basic fibroblast growth factor messenger RNA. An active control group, which exercised for the same time as the learning group but with minimal learning of the task, exhibited only a minor increase in the BFMRNA. The intensification of the physical activity resulted in greater increases for both groups, but levels remained higher for the learning group. Changes in growth factor were accompanied by an increase in astrocyte density in the hippocampus. Results suggest that learning potentiates the effects of physical activity on trophic factor in select brain regions. Trophic factor involvement in behavior may provide a molecular basis for the enhanced cognitive function associated with active lifestyles.



Learning effect -- Graph shows an increase in astrocyte density in various brain regions following Water maze training compared with sedentary controls.

Gomez-Pinilla Neuroscience 1998

We have known of the possibility of neurogenesis since 1967, when Das presented evidence of new neuron formation in the guinea pig.[52] In November, Eriksson and Gage at the Salk Institute published the startling news that mature *human* brains can spawn neurons routinely at the hippocampus, an area vital to memory and learning.

For a long time, the question of whether humans posses a capacity for neurogenesis in adulthood seemed unanswerable. This was because usual animal techniques involving the staining of DNA in differentiating neuronal cells could not be applied to humans. The obstacle seemed insurmountable until Eriksson, a clinician, learned while on call with another cancer specialist, that the stains the institute had been using as a marker for dividing cells was coincidentally being given to some terminally ill patients with cancer of the tongue or larynx. These patients were part of a study to monitor tumor growth. Eriksson realized that if he could obtain the hippocampus of study participants who eventually died, analyses could identify the neurons and see whether any of them displayed the DNA marker. The presence of the substance; bromodieoxyuridine (BrdU) would mean that the affected neurons had formed after the substance had been delivered. In other words, the study could prove that neurogenesis had occurred, presumably through stem cell proliferation and differentiation, during the patients' adulthood. Between early 1996 and 1998, he raced to the hospital and was given brain tissue from five such patients, ages raging from 57 to 72. All five brains displayed the new neurons–in the hippocampus.

Now that human neurogenesis is apodictic, how does this change our view of the brain? For one, it extends understanding of neuroplasticity beyond synaptic growth and rearrangement to completely new cells entering neural pathways. Neurogenesis also opens up the possibility of repair and regeneration in case of synaptic or neuronal loss. Of course, the rate of neuronal proliferation is not high; and, the interpretation of the impact of neurogenesis assumes that the new neurons are functional. But, studies such as these are quite comforting to all as the baby boomer generation ages.

Conclusion

- Realize that all cognitive impairment is not AD.
- Pronounced heterogeneity within the MCI population suggests exercising caution when using this construct. At present, there seems to be significant differences between the pre-dementia Alzheimer's syndrome and those with normal aging. But, as functional brain imaging improves, these boundaries may be redefined.
- Follow therapeutic trial results closely realizing that most of them have been designed under the construct of AD prevention.
- Enhance and protect cognitive reserve.
- Treat chronic illnesses with an eye toward enhancing function.
- Avoid neurotoxic medications, such as dopamine antagonists and anticholinergics.
- Exercise your body and your brain, and learn new things. Today, more than ever, the old adage "if you don't use it, you lost it," seems to be the best way to go.

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