

DEMENTIA PREVENTION & TREATMENT

If we were to screen everybody age fifty and older with computerized neurocognitive tests, we would identify an enormous number of people with mild cognitive impairment. An appropriate differential will exclude many, but a good number, if not most, would qualify for the “diagnosis” of MCI. What then?

If the patient has incipient cerebrovascular dementia (CVD), there will be prominent cardiovascular risk factors, numerous WML’s on the MRI and the funduscopic examination will often show arteriolar narrowing. The patient’s neurocognitive profile should show deficits in attention, reaction time and executive function. The appropriate next step would be a vigorous approach to cardiovascular fitness. Controlling vasculopathy risk factors, like hypertension and diabetes, obesity, smoking, homocysteinemia and low density lipoprotein cholesterol should reduce the occurrence of vascular dementias. The combination of a statin drug, effective BP control (thiazide, beta blocker, angiotensin converting enzyme inhibitor), folate (0.8 mg) and aspirin (75 mg) could “largely prevent heart attacks and stroke (by more than 80%) if taken by everyone aged 55 and older”.

Controlling cardiovascular risk factors is the most important approach to primary prevention, not only for CVD, but for dementia in general. As we have seen, the clinical expression of AD is largely influenced by comorbid cerebrovascular disease, and there is no reason to think the same is not true of the other dementias. In fact, many of the “treatments” we shall discuss in this chapter, ranging from Vitamin E to vigorous physical exercise, are said to be “preventive” not only of dementia, but also of cardiovascular disease.

If the patient has incipient AD the soundest early clues are a family history of AD and a neurocognitive profile of impairment in memory, processing speed or executive function. In table X.01, in Chapter X, we reviewed the cognitive profiles that are characteristic of other dementias. Subtle personality change or late onset depression and/or anxiety may also be early signs. But AD and the other dementias are not so easy to predict as CVD. Nor do they possess the same panoply of preventive measures, rigorously supported by clinical trials and prospective studies.

And this takes us back to the same old question: *why screen for MCI if you can’t do anything about it?* The answer is, maybe we can. True, an expert panel recently wrote: “there is no evidence that any intervention can prevent the onset of dementia” but I think they overstated the case. Think of it this way: in twenty years, when there is, at last, a solid evidence base to guide practitioners, a substantial number of us, and an even larger number of our patients, will be demented. Isn’t there *something* we should do right now? Evidence-based medicine should not be an excuse for paralysis. Sometimes, one has to rely on one’s best judgment.

So we shall review this interesting topic, dementia prevention and treatment, with an appropriate degree of scientific skepticism, but also with a measure of hopefulness, if not optimism. It would be strange, indeed, if none of the protectants, preventives and treatments available right now had any beneficial effect at all.

During this review we shall also encounter a common pattern. Lifestyle modifications, dietary supplements and pharmaceuticals are deemed helpful on the basis of theories of what is central to the pathophysiology of AD and the other dementias, or at least what we think is central. Examples are substances that mitigate oxidative stress or inflammation. What happens next is an observational study

or two that support the benefit of a relevant intervention. Such studies usually generate a risk ratio to measure the strength of the putative effect. The results are published in an (obscure) journal of epidemiology or nutrition. The information is picked up by the popular press and touted as a way to prevent cancer, atherosclerosis, AD or whatever. As it happens, a dietary supplement that fits the description is available at Whole Foods.

Years pass, a clinical trial is done to test the theory, and the results are negative. Ah, but the trial was not right; the doses were wrong, the patients began the treatment too late. Then a meta-analysis is done, and it seems that our time-honored but ineffective treatment actually carries a measure of risk. Hmpf, says the crowd. But, look here. There is a spice from the far Himalayas, and the tribesmen who use it on all of their food have never known a case of AD...

This sort of thing can go on forever. In fact, it *has* gone on forever. Peddling nostrums has always been a pretty good business. The only difference, today, is the sophistication with which they are garbed, and the speed the Internet affords for dissemination.

So we shall present the state-of-the-art with respect to dementia prevention and treatment. We shall try to keep it respectable, but there are probably going to be some real chestnuts.

PRIMARY PREVENTION

Primary prevention means reducing or eliminating dementia risk factors. We are already trying to achieve that end, but with mixed results. Consider the risk factors for Alzheimer's disease. A close look underscores the truism that medical progress just makes more business for doctors.

The incidence of severe brain injuries is decreasing, thanks to bicycle helmets and airbags; on the other hand, the number of severe brain injury patients who survive, thanks to improved emergency care and neurosurgical management, is increasing. Brain injuries will always be with us.

The incidence of Down syndrome is decreasing because of prenatal screening. The prevalence of the disorder, however, is increasing, because of better medical treatment and improved longevity.

Educational achievement seems to be relatively protective against dementia in general and AD in particular. Educational levels are increasing all over the world, and the so-called "Flynn effect" documents an improvement in population IQ. Mean population IQ is probably increasing because of changes at the lower end of the IQ spectrum, the result, one presumes of better nutrition and medical care, education and exposure to media, but it is the low end of the IQ spectrum that is most vulnerable to dementia. Presumably, a better-educated, higher IQ population will be less prone to dementia. A better-educated population is also likely to be healthier and to live longer; then they will be *more* prone to dementia.

Cannabis, cocaine, opiates, methamphetamine, NMDA ("ecstasy") and the hallucinogens are all neurotoxic, to one degree or another, and the cognitive impairments of heavy users range from subtle and hard-to-detect to overt and debilitating. AD pathology and white matter degeneration have been discovered in young people who were opiate abusers and polydrug abusers. The appropriate question is whether less-than-heavy users, who do not, as a rule, have overt neurocognitive impairments, might be more prone to dementia when they are elderly. Since heavy use of intoxicants (other than alcohol) among healthy middle-class people is a relatively new phenomenon, the cohort of patients at risk has not yet appeared on the dementia horizon. It will be interesting to see what happens.

Primary prevention is most likely of success with respect to cerebrovascular dementia. The reduced incidence of stroke, the result of modern hypertension control, has already had an impact on the

occurrence of post-stroke dementia. As we said, reducing cardiovascular disease will reduce the incidence of vascular dementia and reduce the clinical expression of AD and other dementias. One can hardly be sanguine about the likely success of cardiovascular protection, though, in light of the epidemic of obesity and the anticipated epidemic of type II diabetes.

Perhaps it is presumptuous for physicians to speak in terms of the primary prevention of AD, since the fundamental risk factor, longevity, is something that we actively promote. If we advise patients to stay healthy, fit and mentally engaged, and to drink with moderation, we shall reduce the incidence of CVD and probably AD as well. There is evidence, albeit limited, that this is already happening. The paradox is that by increasing the population of elderly people, we necessarily increase the number of people with MCI who are worried about AD.

It is likely that the patient who is worried about MCI is likely to have transcended these issues already. Such people are likelier to be interested in positive prevention strategies: what can I *do* to diminish risk? Well, this is what the public think they should do to prevent AD:

- Manage cardiovascular risk factors
- Drink more water
- Reduce stress, coffee, tea and alcohol
- Increase social and physical activity
- Eat foods high in omega-3 fatty acids
- Take antioxidants, estrogen, vitamin and nutritional supplements
- Avoid aluminium cookware

A few of these ideas are quite sound, and some of them are just silly. But none of them sprang from the clear air. All of them have been “recommended,” at one time or another, by some kind of medical authority, for some worthy purpose, at least. If you compare this list to the two lists of expert recommendations at the end of this chapter, you will see that only a couple of items overlap. The authors of this study, which was done in Australia, thought that it showed that the public were not very well-informed about dementia prevention. I think it shows that the public are optimistic, but they need better guidance.

PROTECTIVEFACTORS

There are a number of things a person may do in the way of lifestyle changes that could conceivably reduce the risk of developing dementia. The recommendations that we shall cite here are based almost entirely on observational studies. The method is to observe how a large group of people behave, retrospectively, or, less frequently, prospectively. Then, through statistical analysis, one determines whether some specific behavior is more or less likely to be correlated with cognitive decline or dementia. It is a powerful technique, but it is not the same as a clinical trial. Observational studies are useful because they point the way to possible interventions, but they can never prove that a given intervention is likely to be safe and effective when it is applied clinically.

Light-to-moderate **alcohol drinking** is protective against coronary heart disease, stroke and vascular dementia, and may also decrease the rate of progression from MCI to dementia. Light-to-moderate drinking seems to be protective against dementia in general, including AD, although studies vary widely in their definition of “moderate drinking.” In the USA, we believe it is up to 2 beers or 2 whiskeys or 2 glasses of wine. Drinking more than that can cause high blood pressure and is an independent cause of neurodegeneration. Alcoholic dementia is similar in its manifestations to AD. But

numerous epidemiological studies have shown that moderate intake of red wine in particular reduces the risk of developing AD. One of the components of red wine, resveratrol, will be discussed later.

The flavonoids in wine are powerful antioxidant substances, and similar compounds are found in tea, fruits and vegetables, **Ginkgo biloba** extract and curcumin. **Green tea**, in particular, is nearing legendary status as a weight loss agent (it is thermogenic), a cancer and stroke preventive and, of course, a neuroprotectant.

The polyphenolic compounds (flavonoids) in green tea are believed to be the active components. One green tea compound, (-)-epigallocatechin-3-gallate (EGCG), appears to be a versatile modulator of cellular responses that may contribute to disease pathogenesis. EGCG has been found to modulate protein kinase C (PKC) activity, to inhibit various activities of proinflammatory cytokines, and to promote cleavage of the alpha-C-terminal fragment of APP and thus elevate the N-terminal APP cleavage product, soluble APP-alpha. Green and black tea both inhibit human acetylcholinesterase and butyrylcholinesterase, actions associated with the Alzheimer's drug, rivastigmine. Green tea is also associated with lower concentrations of total cholesterol.

Recent studies have affirmed that green tea has a dose-response relation to reduced mortality due to all causes and due to cardiovascular disease, especially stroke, but not with reduced mortality due to cancer. Indeed, the thermal effect of drinking hot tea may actually increase the risk of oral-pharyngeal and esophageal cancers.

The beneficial effects of green tea on cognition are not explicable simply in terms of caffeine although caffeine, too, may be beneficial. In one case-control study, moderate caffeine intake was inversely related to AD (odds ratio 0.40). In a 10-year prospective cohort study from Finland, Italy and the Netherlands, coffee consumption was associated with less cognitive decline, with an optimal effect at 3 cups per day. Similar findings from a survey study in California indicated benefits from lifetime consumption of coffee, and the effect of decaffeinated coffee, though positive, was less strong.

In a community-based study comparing tea and coffee drinkers in Japan, using the MMSE as an indicator of cognitive decline with aging, the odds ratios for MMSE scores below 24 were calculated relative to consumption of green tea, black or oolong tea, and coffee. If the data are sound, then green tea is the best.

Table X.01 Beverage Consumption and Odds Ratio for Cognitive Impairment

Consumption	Green Tea	Black or Oolong Tea	Coffee
3 or fewer cups/wk	1.00	1.00	1.00
4-6 cups/wk	0.62	0.60	1.16
2 or more cups/d	0.46	0.87	1.03

Exercise: The public believe that exercise can prevent AD. Of course, only a minority act on that belief, but they seem to be right. There have been a large number of animal and human studies that support the potential of physical exercise to promote cognitive health later in life. Physical activity is associated with lower risks of cognitive impairment and dementia, with reduced risks of cognitive impairment (odds ratio, 0.58), AD (0.50), and dementia of any type (0.63). In a community-based, prospective cohort study of 1740 persons older than age 65 years without cognitive impairment, followed for 6.2 years, 158 participants developed dementia, and 107 developed AD. The age- and sex-adjusted hazard ratio for dementia in people who exercised regularly was 0.62. Of course, we already know that physical exercise has benefits for conditions that contribute to vascular dementia.

Physical exercise could support cognition in later life through a number of possible mechanisms, including neurogenesis, and anti-inflammatory effects like loss of body fat, reduced macrophage accumulation in adipose tissue and production of anti-inflammatory IL-6 in muscle. Regular physical activity also attenuates neural responses to stress in the brain circuits that regulate peripheral sympathetic activity, which could plausibly affect conditions like hypertension, heart disease, oxidative stress, and immune response.

Observational studies are equally supportive of the value of mental exercise but we have not found comparative studies on the relative merits of physical vs. mental exercise. However, in a study of amyloid precursor protein (APP)-23 mice (a mouse model of AD), animals who lived in an "enriched-environment" showed improved water maze performance, up-regulation of hippocampal neurotrophin (NT-3) and brain-derived neurotrophic factor (BDNF) and increased hippocampal neurogenesis. In contrast, mice that were exposed to a more physically challenging environment had increased bodily fitness, but no change in spatial learning or hippocampal neurogenesis and a down-regulation of hippocampal and cortical growth factors. Interestingly, the amyloid load was equal in the two groups of mice.

That mechanism exist for the beneficial effects of physical and mental exercise should come as no surprise. Whether they have a direct effect on with incident dementia is something else again. The data concerning the protective effects of physical activity derive almost entirely from correlational studies, not controlled trials. The problem with data thus generated is that people who are given to lifelong exercise, or who take up exercise in later life, may be different from people who do not. There is evidence that physical activity is not a random event. People with declining cognitive performance or poor health (e.g., cancer, high blood pressure, hip fracture, smoking) are less likely to engage in physical activities, and when they do, they perform poorly.

Yes, exercise improves one's physical and cognitive and emotional health. But the ability to exercise regularly, or one's willingness to, is also a function of one's physical and cognitive and emotional health to begin with. Physical and cognitive exercise improves the well-being of people in general, of people with depression and other chronic diseases. It even improves the lives of nursing home patients who have AD. With respect to dementia prevention, however, the question is this: is exercise protective, or are people who exercise protected?

Exercise is good, but the exercise effect, in my opinion, is too limited. Evidence continues to accrue that exercise need not be vigorous, or aerobic, to affect health and well being. Walking a corridor or simply expending a good deal of energy as part of a busy life is equally effective. What is essential is to be active and energetic. One should exercise one's physical and mental parts, yes, of course, but also one's social, spiritual and sexual parts. And not in a dim or perfunctory way, but in ways that are meaningful and involved.

AGENTS THAT MAY BE PREVENTIVE

The drugs and supplements we shall discuss are all "rational" therapies, in the sense that they address specific aspects of AD pathology, or at least, what we think that may be. They are all "empirical," because they have been used for years, are more-or less safe and inexpensive. One would have few qualms about recommending them to patients at risk, if they worked. They are, however, none of them supported by an incontrovertible evidence base.

As I discuss each agent in turn, I shall give it two grades. One will be for the quality of the evidence that supports it as a preventive, and the second will be for the degree of risk entailed. For evidence, the grades are:

- A. Probably effective as a preventive, based on clinical trial data
- B. Possibly effective, on the basis of observational studies
- C. Speculative, but not outlandish.
- D. Evidence to the contrary: don't waste your time.

For degree of risk, the grades will be:

- A, No risk at all.
- B. A small degree of risk, but not much.
- C. Risky, but not dangerous.
- D. Evidence of substantial risk.

Consider, for example, a preventive measure like "mental exercise." In my opinion, its evidence grade is **B**, and its risk grade is **A**. Green tea, moderate alcohol, fruits and vegetables would get the same grades. Cardiovascular risk reduction, on the other hand, has an evidence grade of **A** and a risk grade of **A**.

I shall also, at the end, characterize each measure as an example of conservative or aggressive prevention. The former is what everyone should consider, even people without special AD risk factors, once they reach Middle Age. This category includes measures that may be unproven, but they carry no risk at all. Most of the protective factors listed in the previous section could be considered a form of "conservative prevention."

"Aggressive" prevention is what you might elect for yourself or a family member, in the face of clear risk: that is, AD risk factors like a strong family history, possession of the ApoE4 allele or a history of severe brain injury. It is what one might consider for a patient who had MCI. In such cases, it might be worthwhile to take a chance on an unproven preventive, even if it carried a small degree of risk.

The assessments are subjective, of course. I can't make enlightened judgments on any of these matters on the basis of multiple controlled trials. The evidentiary base is just too skimpy. One is painfully aware that when such studies have been done in the past, they sometimes demonstrate that dangers inhere to even the most venerable "treatments" – examples are estrogen and Vitamin E. Only longitudinal assessment can establish whether a treatment is safe or effective over the long run.

ANTIOXIDANTS AND OXIDATIVE STRESS

In the course of normal cellular metabolism, molecular oxygen is transformed into free radicals (e.g., hydroperoxides, superoxide and hydroxyl free radicals). Free radicals are highly reactive chemical species with an odd number of electrons, and they react with other substances that have an odd number of electrons. The intrinsic reactivity of free radicals, and their ability to generate even more potent oxidants when they interact with peroxides, constitutes a constant threat to cellular integrity. In normal circumstances, the generation of free-radicals is a steady-state phenomenon, prooxidant forces balanced by cellular antioxidant systems. When the normal balance is upset, either by the loss of reducing agents or protective enzymes, or by increased production of oxidizing species, tissue is considered to be under "oxidant stress".

Oxygen free radicals act as chain carriers in chemical reactions. When a free radical reacts with a nonradical compound, other free radicals are formed, thereby producing chain reactions. This kind of reactivity may lead to reversible or irreversible damage to compounds of all biochemical classes, including nucleic acids, proteins, lipids, carbohydrates and connective tissue macromolecules. Oxyradicals are capable of reacting with polyunsaturated fatty acids in lipid membranes, leading to lipid peroxidation chain reactions. The CNS is particularly sensitive to oxyradical damage because of the high levels of polyunsaturated lipids that comprise neuronal cell membranes.

The uncontrolled production of free radicals is a primary cause of many pathophysiological reactions, but since oxyradicals are difficult to study, the precise role they play as etiological agents has been viewed with a certain amount of skepticism. However, new experimental methods have generated evidence that oxidative damage does occur, and that the highest degree of oxidative damage occurs in heart, brain and skeletal muscle, which are composed primarily of long-lived postmitotic cells. These tissues are also the targets of several age-related degenerative disorders in which oxidative stress has been implicated, including atherosclerosis, stroke, age-related macular degeneration and cataracts, Parkinson's disease, AD and some forms of arthritis.

The proposition that free radicals are an important factor in ageing remains to be rigorously proven, but the presence of increased amounts of oxidized proteins in ageing biological systems supports the notion. According to the membrane hypothesis of ageing, chronic free radical damage may lead to changes in the composition and integrity of cell membranes. As a result, membrane fluidity decreases and intracellular density increases with age, which can finally lead to dramatic alterations of many membrane-bound mechanisms relevant to brain function.

Tissue damage due to oxidative stress accumulates with age. Aging itself is normally associated with an increase in the rate of generation of oxygen free radicals, a decline in the antioxidant defenses, and a decline in the efficiency of repair or removal of damaged molecules. Relatively longer life expectancy within and between species is associated with a correspondingly lower accrual of oxidative damage. The brain is particularly vulnerable to oxidative stress due to a relatively high rate of ROS generation without commensurate levels of antioxidant defenses. In fact, there is a progressive increase in the steady-state concentration of oxidatively modified DNA and proteins in the brain during ageing.

Therapeutic & Protective Effects of Antioxidants

The chain reactions that characterize oxidative stress stop when two free radicals react with each other or when they are quenched by reacting with an antioxidant. The major antioxidant defense systems include enzymes like superoxide dismutase, catalase and glutathione peroxidase; and chemical reductants like ascorbate (Vitamin C) which is water soluble and present in the cytosol, and α -tocopherol (Vitamin E), which is lipid soluble, and localized to lipid membranes. The chemical antioxidants act by donating a hydrogen atom to the radical; simultaneously, a stable tocopherol or ascorbate radical is formed. They are referred to as "free radical scavengers," and Vitamin E is the major chain-breaking lipid antioxidant. Dietary components contain an array of micronutrients that play direct roles in the enzymic and non-enzymic means of free-radical defense.

Drugs, vitamins or dietary supplements that are "free radical scavengers" or that contribute to the activity of antioxidant enzymes, are considered to be "neuroprotectants." These include Vitamins C and E, retinoic acid (Vitamin A, beta-carotene), deprenyl or selegiline, an MAO-B inhibitor, pramipexole, ginkgo biloba extract, selenium, zinc and riboflavin and resveratrol. Regular intake of antioxidant vitamins and minerals is often recommended to ward off illnesses like cancer, cardiovascular disease, and neurological conditions associated with ageing.

Atherosclerosis & Stroke

Experimental studies indicate that the oxidation of low-density lipoproteins (LDL) in the vascular endothelium plays a role in the development of atherosclerotic lesions. The resistance of LDL to oxidation is increased by antioxidant supplementation, at least *in vitro*. That antioxidant supplements, especially vitamins C and E and beta-carotene, might have cardiovascular benefits of antioxidants was supported by studies of users of vitamin E supplements, who seemed to have lower rates of coronary heart disease and myocardial infarction. However, clinical trials of Vitamin C and beta carotene supplementation have not shown cardiovascular benefit, with evident risk associated with the latter

Further, recent studies have failed to demonstrate that a high intake of antioxidant supplements leads to a decreased risk of coronary heart disease. Vitamin E at high levels (i.e., > 200 IU/d) may actually increase the occurrence of myocardial infarction. "Wide-spread use of antioxidant vitamins in cardiovascular protection should not be instituted" and "and cannot be recommended for the normal population." In a large prospective study of a normal, low risk group (physicians), however, supplement use was associated with neither increase nor decrease in cardiovascular events or mortality.

In contrast, many epidemiological studies antioxidant rich foods do point in the direction of a preventive effect. Foods rich in antioxidant micronutrients contain other forms of tocopherol, for example, as well as other constituents that may be protective. They also provide dietary fiber, and diets rich in fruits, nuts and vegetables are usually low in lipid-rich foods.

Although some studies have suggested a modest effect, the weight of the evidence is that supplemental vitamins C or E and beta-carotene do not have a role in stroke prevention.

Dementia

Direct and indirect indicators of free radical injury in AD include: increased iron, aluminum and mercury, which stimulate free radical generation; increased lipid peroxidation and decreased polyunsaturated fatty acids; increased protein and DNA oxidation in the AD brain; diminished energy metabolism in the AD brain; increased concentration of oxidation by-products in neurofibrillary tangles and senile plaques; and evidence that amyloid itself is capable of generating free radicals. The overall

peroxidation activity of brain tissue from people with AD is elevated, and the levels of antioxidant enzymes are substantially reduced. It appears that oxidative damage occurs not only before the first symptoms arise, but even before the formation of amyloid-containing plaques and neurofibrillary tangles.

There is evidence that AD patients have below-normal levels of ascorbate in their CSF, despite normal dietary Vitamin C, and no clinical evidence of Vitamin C deficiency. In fact, the degree to which they are Vitamin C deficient correlates with their degree of cognitive impairment. CSF ascorbate levels can be corrected by supplemental C and E.

Oxidant stress is related to aging and AD; that is widely accepted. What is not so widely accepted, however, is whether antioxidant supplements are, in fact, capable of preventing AD, delaying its onset or slowing its progression. The Rotterdam Study, a prospective examination of 5395 participants, reported that high intake of dietary Vitamins C and E was associated lower risk for AD, and that the "rate ratio" per 1 standard deviation of intake was 0.82. In Chicago, however, a prospective study of 815 participants discovered a protective effect for Vitamin E, but only for people who were ApoE4 negative. The Cache County (Utah) study actually found that vitamin E and C supplements *in combination* were associated with reduced AD prevalence (OR 0.22) and incidence (0.36). A trend toward lower AD risk was also evident in users of vitamin E and multivitamins containing vitamin C, but there was no evidence of a protective effect with use of vitamin E or vitamin C supplements alone, with multivitamins alone, or with vitamin B-complex supplements. In the longitudinal Study of Health and Aging (Canada) combined use of vitamin E and C supplements and/or multivitamin consumption at baseline were significantly less likely (OR 0.51) to experience significant cognitive decline during a 5-year follow-up period. Subjects reporting any antioxidant vitamin use also showed a significantly lower risk for incident vascular cognitive impairment (OR 0.34). A reduced risk for incident dementia or AD was not observed, however. In New York, a similar study of 980 elderly people discovered no effect from dietary or supplemental antioxidants.

In one influential trial, supplemental Vitamin E was compared to the monoamine oxidase inhibitor selegiline in patients with AD of moderate severity. 341 patients were treated for two years either with selegiline (10 mg), vitamin E (2000 IU), the combination of the two, or placebo. Compared to placebo, all three treatment conditions were associated with slowing the course of deterioration to a significant degree. In a second trial, Vitamin E (2000 IU) compared to donepezil and placebo in patients with amnesic MCI, there were no significant differences in the rate of progression to AD between the vitamin E and placebo groups.

The epidemiological data is compelling, but the results of clinical trials are not. So, it is possible that vitamin E has no effect at all. It is also possible that people who take supplementary vitamin E are different from people who don't bother. Maybe the tocopherol isoforms and flavonoids present in fresh fruit and vegetables are effective, but pure alpha-tocopherol is not. Maybe vitamin E has an effect, but in circumstances different from those represented in the trials. It is arguable that vitamin E should always be taken with vitamin C, but that is not always done in trials. Some authors have suggested trials of "antioxidant cocktails" or antioxidants combined with other drugs.

It is also possible that antioxidants are only effective in the pre-MCI stage. Since the effects of oxidative stress in the CNS occur early in the course of neurodegenerative disorders, the timing of treatment administration may be crucial. For example, in one study transgenic mice (Tg2576) were administered Vitamin E before or after the amyloid plaques formed. The mice that were treated at a younger age showed a significant reduction in A β levels and amyloid deposition. In contrast, mice who received Vitamin E at a later age did not show any significant difference in either marker when compared

with placebo. Antioxidant therapy, therefore, may be beneficial only if given at an early stage of the disease process.

Vitamin E

Two families of fat-soluble compounds, the tocopherols and the tocotrienols, constitute Vitamin E. Alpha-tocopherol is the most biologically active of these compounds, and CSF levels correlate with serum levels. Natural-occurring α -tocopherol is found only in the D isomer, while synthetic α -tocopherol is a racemic mixture of the D and L isomers, with approximately 75% of the biologic activity of the pure D- α -tocopherol. One milligram of the racemic form is the equivalent of one IU of Vitamin E activity. The primary dietary source of Vitamin E is vegetable oil, specially soybean, corn, safflower and cottonseed oil. It is also found in wheat germ, nuts and green leafy vegetables.

The neurological problems associated with Vitamin E deficiency respond to oral doses of 1600 mg of synthetic α -tocopherol. Children with cystic fibrosis are advised to take 100 mg/d. The RDA is 4 mg/d and the average diet contains about 8 mg/d .

Vitamin E as a nutritional supplement has relatively few side effects. The most common are gastro-intestinal: nausea, flatulence or diarrhea. Other reported (rare) adverse reactions are necrotizing enterocolitis, gonadal dysfunction, elevated cholesterol and triglycerides. In patients who are vitamin K deficient, perhaps because of anticoagulation therapy, high doses of α -tocopherol may increase the bleeding tendency. Until recently, the weight of opinion was that normal, healthy people taking Vitamin E 400-800 IU/d will not experience serious adverse effects, although there have been dissenters. The effects of long-term treatment with high doses (> 1000 IU/d) are not known, but in double-blind studies with large numbers of subjects, doses as high as 3,200 IU/d led to consistent adverse effects.

The problem, though, of potential cardiovascular toxicity with Vitamin E has chastened supporters of what was once considered an essential treatment for early cases of AD. In the HOPE trials, patients taking 400 IU of Vitamin E had a higher risk of heart failure (OR, 1.13) and hospitalization for heart failure (OR 1.21). In post-infarction patients, vitamin E treatment was associated with a 50% increase of congestive heart failure in patients with left ventricular dysfunction.

An ordinary multivitamin contains about 30 mg of vitamin E, and an ordinary "antioxidant formula" contains 200 mg. What dose should one take, for the purpose of "neuroprotection"? The Alliance for Ageing Research recommends 250-1,000 mg/d of α -tocopherol. Fahn used 3200 IU/d in patients with early PD (along with 3 gms of Vitamin C). The Alzheimer's Disease Cooperative Study found substantial benefit from 2000 IU/d, *sans* C.

Should a patient who was at high risk to develop AD take more than the RDA? Several years ago, when we visited this issue with respect to patients who had had severe brain injuries, we proposed that 400-2000 mg/d of tocopherol was not an outlandish dose. Now we have our doubts. Higher doses of Vitamin E should not be recommended to patients with cardiovascular disease. Whether it should be recommended to patients at low risk for cardiovascular disease is an open question.

Table 00. 2. Vitamin E

EVIDENCE GRADE	B
RISK GRADE	C

Vitamin C

Vitamin C is synergistic with Vitamin E. One of its primary roles in vivo is the regeneration of oxidized tocopherols, recycling them to the reduced state that is essential for an antioxidant effect. A patient who chooses to take vitamin E as a preventive antioxidant preventive should also take vitamin C.

The association between vitamin C intake and protection from cancer, heart disease, cataracts and arthritis is based, almost entirely, on epidemiological studies. On the basis of this research, it is virtually impossible to discern whether the protective effect is due to vitamin C, to vitamin E, or carotene, to the combination thereof, or to some unmeasured constituent, like the bioflavonoids. Nevertheless, the epidemiologic evidence does suggest a protective role for dietary, if not supplemental, vitamin C.

Specific mental changes that occur in Vitamin C deficiency (scurvy) include lassitude, depression and personality change. Excluding scurvy, the health consequences of inadequate vitamin C intake are not well characterized.

Brain has the highest concentration of vitamin C in the body. Ascorbate in the CNS influences the actions and the metabolism of dopamine, norepinephrine, serotonin, acetylcholine, NMDA and glutamate. The clinical importance of these actions is not known. High doses of vitamin C have not been demonstrated to alter the course of neuropsychiatric disorders or the effects of neuroactive drugs. There is no evidence of a Vitamin C effect on dementia, independent of Vitamin E. It merits an "evidence grade" of B only as a cofactor with vitamin E.

Treatment of scurvy in adults requires 1 g/d of Vitamin C for about a week, which is usually sufficient to replenish body stores of 2-3 gms. The RDA for adults is 60 mg/d, and the average diet contains about 80 mg/d. Linus Pauling recommended 1-5 g/d for prevention of colds. The Alliance for Ageing Research recommends daily intake of 250-1,000 mg/d. The ordinary multivitamin has about 60 mg and the "antioxidant formula" has 250 mg.

The consensus is that large amounts of Vitamin C (up to 10 gm/d) are not associated with side effects in healthy people, although there is anxiety about oxalate stone formation, uricosuria, Vitamin B₁₂ destruction, mutagenicity and iron overload. You can probably take as much Vitamin C as you can stand to swallow. After all, a lot of people have been taking megadoses of Vitamin C since the 1970's, and there is no fallout yet. One or two grams per day is not an outlandish dose.

Table 00.3. Vitamin C

EVIDENCE GRADE	B
RISK GRADE	A

OMEGA-3 FATTY ACIDS

That fish are good for you first came to the attention of the medical world in 1980, when Bang, Dyerberg & Sinclair suggested that the low rate of coronary artery disease in Greenland Eskimos might be due to their high consumption of seafood. Since that time, more than 15 cohort studies have been done to address the topic, and the majority supported a cardioprotective role from the consumption of a small amount of fish.

Fish are high in omega-3 polyunsaturated fatty acids (omega-3FA), which have antiarrhythmic and antihypertensive properties. They decrease platelet aggregation and sometimes lower serum triglycerides. They also have anti-inflammatory effects. Low levels of omega-3FA are associated with neuropathy and impairment of the immune system. So, it's good to eat fish. But is it *brain food*?

The lipid fraction of human milk is the main energy source for the newborn infant, and supplies essential nutrients, including the polyunsaturated fatty acids. The essential fatty acids in milk, linoleic and linolenic acid, are necessary for normal growth and development. Linoleic and linolenic acid are precursors of the long-chain polyunsaturated fatty acids, such as arachidonic acid (an omega-6 omega-3FA) and docosahexaenoic acid (DHA, an omega-3FA). The long-chain omega-3FA are indispensable structural components of all cellular membranes, and they are incorporated in relatively large amounts during early growth of the brain. Some long chain omega-3FA are precursors of eicosapentanoic acid (EPA), an omega-3FA with potent biological activity. DHA and EPA together are referred to as omega-3FA, or "Fish Oil," since they are found in high concentrations in fish, especially fatty fish like salmon, tuna and mackerel.

The composition of cell membranes is to great extent dependent on dietary omega-3FA.. They are necessary for the maintenance of normal brain function. Deficiencies of DHA are associated with learning deficits in infants and children, while inclusion of plentiful DHA in the diet improves learning ability. Learning deficits are demonstrated in animals deficient in omega-3FA. In animals, diets with less omega-3FA and more omega-6FA accelerate aging-related changes of dopamine and serotonin in the frontal cortex and the brain stem.

There have been several reports of reduced omega-3FA levels in psychiatric patients and clinical improvement when supplements are added to the diet. One learned committee decided that "the preponderance of epidemiologic and tissue compositional studies supports a protective effect of omega-3 FA intake, particularly EPA and DHA, in mood disorders. Meta-analyses of randomized controlled trials demonstrate a statistically significant benefit in unipolar and bipolar depression."

Low serum DHA and high dietary intake ratios of omega-6 to omega-3FA have been linked to cognitive impairment and are said to be a "significant" risk factor for AD. The brain membranes of AD patients have been found to be deficient in DHA. There are lower levels of omega-3FA in the parahippocampal cortex of patients with AD. In the mouse model of AD, omega-3FA have an anti-amyloid effect.

Several epidemiological studies show a protective effect against AD associated with increased fish consumption and intake of unsaturated fats leading to low omega-6/omega-3FA ratios. The evidence for a protective effect is mostly based on biological, observational and epidemiological studies. One clinical trial published in 2007 reported that omega-3FA supplementation in patients with mild or moderate AD had marginal effects, improving agitation and depression but not caregiver burden or activities of daily living. In another controlled study in AD patients, omega -3FA supplementation did not affect cognitive decline, except if patients with very mild AD.

The oxidative transformation of omega-6 and omega-3FA in brain by free radical species may adversely affect neuronal function and oxidative products of essential fatty acids are elevated in demented patients. Theoretically, then, if someone elects to take omega-3 supplements, he or she ought to take a supplemental antioxidant as well.

Table 00.4. Omega-3 Fatty acids

EVIDENCE GRADE	B
RISK GRADE	A

ANTI-INFLAMMATORY DRUGS

An interesting contribution of anti-inflammatory drugs, including dapsone, indomethacin, nonsteroidal anti-inflammatory drugs (NSAID's) and COX-2 inhibitors may be to inhibit the course of AD. The idea originated with the pathologic demonstration of acute phase reactants and other markers of immune processes, absent or present at very low levels in normal brain, in the post-mortem brains of AD patients. Plaques in brains from AD patients are filled with reactive microglial cells. The activity of microglial cells is not an innocent event, a form of neuronal housekeeping, as it were, but potentially toxic in its own right. Microglial cells are prone to secrete complement proteins and other biochemical weapons, like COX-2, that are, by themselves, potentially neurotoxic. In various experimental models, ischemia, for example, and neurotoxic injection, microglial cells are induced to generate COX-2 and pro-inflammatory prostanooids. COX-2 induction is also a component of the cascade of events that surround neuronal Excitotoxicity. Brain injury, itself, induces the expression of several genes, including the gene for COX-2.

A series of epidemiologic studies have consistently demonstrated lower rates of dementia in patients who take anti-inflammatory drugs for the usually medical indications. A number of observational studies have also demonstrated that AD occurs at a lower rate in patients who have been treated long-term with NSAID's, for example, people with rheumatoid arthritis or osteoarthritis, and that a course of treatment with anti-inflammatory drugs may slow the progression of dementia in patients with AD. In the Rotterdam study of about 8,000 elderly people, the relative risk of AD among users of NSAID's (and of aspirin) was 0.38. These data were later amended to show risk reduction with short-term NSAID's at 0.83 and with long term use, 0.20.

On the other hand, treatment studies with ibuprofen and indomethacin have not been strongly supportive. No benefit whatever was noted for rofecoxib in patients with mild-to-moderate AD. or MCI; or for rofecoxib or naproxen in older people who were cognitively intact but who had a family history of AD.

Drugs that inhibit the activity of COX-2 should, theoretically, interrupt or attenuate a series of inflammatory processes that are potentially neurotoxic in their own right, and that aggravate the impact of the original pathogenic event, be it *tau* protein, ischemia or traumatic injury. As we see all too often, theories of pathogenesis complement the results of epidemiological studies, but clinical trials fall short of the mark.

Table 00.5. NSAIDs

EVIDENCE GRADE	C
RISK GRADE	C

In addition to well-known GI side effects, high doses of NSAID's interfere with other biological processes not dependent on prostaglandins, the activity of various enzymes and transmembrane ion fluxes. Nor is the inhibition of COX-2 inevitably beneficial for the health of one's brain. The expression of COX-2 is a normal component of brain development, and the basal production of prostaglandins through COX-2 may "participate in neuronal homeostasis." Patients taking traditional NSAID's, especially elderly patients, have had a variety of mental problems, including depression, forgetfulness, difficulty concentrating, paranoia, mania and frank psychosis; the COX-2 inhibitors are no different in this regard. Even young, healthy patients of NSAID's may experience mental slowing or "fuzziness" at high doses.

ASPIRIN

Aspirin is an NSAID but a special case. Its benefit as a prophylactic after a thrombotic event was first observed 30 years ago, and its use after coronary or cerebral thrombosis, and in patients judged to be at increased risk of a thrombotic event, is said to be "virtually mandatory," unless there are signs of intolerance. In the UK, one study indicated that 80% of patients with cognitive impairment and vascular risk factors were prescribed aspirin.

Large scale prospective studies have shown reduced stroke incidence in women treated with low dose (100 mgm every other day) aspirin, and in men, reduced cardiovascular mortality with 325 mg every other day. Low doses are sufficient to reduce platelet aggregation, which may have a bearing on white matter disease, but they do not exert an anti-inflammatory effect. It is not clear whether the benefits of aspirin are confined to the former. Prospective studies of older individuals indicate cognitive sparing with low-dose aspirin, and perhaps more so in smokers and patients with high lipid levels – suggesting an antiplatelet effect. In another prospective study, users of high-dose aspirin had lower AD prevalence and better-maintained cognitive function than non-users. The benefits to low-dose users and users of other NSAIDS were positive but not nearly so strong – suggesting an anti-inflammatory effect. Anti-inflammatory doses of aspirin, but not low doses, are found to decrease tau protein phosphorylation.

Aspirin and the older NSAIDs are nonselective inhibitors of both COX-1 and COX-2. Among the NSAIDs, only aspirin has been proven to significantly reduce cardiovascular risk, primarily through inhibition of COX-1-mediated platelet aggregation. It has been suggested that other nonselective agents, especially naproxen, may provide some lesser degree of cardioprotection, but conclusive evidence is lacking. Conversely, there are concerns that the COX-2 inhibitors may increase cardiovascular risk.

Some, but not all NSAIDs decrease the production of Abeta42, the major component of senile plaques of the AD brain, and counteract the progression of Abeta42 pathology in transgenic mouse models of AD. The inhibition of Abeta42 production is independent of the anti-cyclooxygenase (COX) activity and is related to the chemical structure of the compounds, with some NSAIDs being active (ibuprofen, sulindac, flurbiprofen, indomethacin, diclofenac) and others not (naproxen, aspirin, celecoxib). It is not clear whether combining aspirin with other NSAIDs might compromise the beneficial antiplatelet effects of aspirin.

Table 00.6. Aspirin

EVIDENCE GRADE	B
RISK GRADE	C

STATINS

The “statins” (3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors) are drugs of choice for lipid lowering and prevention of cardiovascular disease. They are among the most frequently-prescribed prescription drugs. It is intuitive that lipid lowering agents (LLA’s) should reduce the risk of cerebrovascular disease as well, and, indeed, they do. What surprised the scientific community, though, was information that statins may have a protective effect against the occurrence of AD. The magnitude of risk reduction, based on observational studies, might be as high as 70%. Meta-analysis of data from seven studies indicates an odds ratio for statin therapy of 0.43. In a clinical trial of 67 patients with mild-to-moderate AD, with a significant positive effect on cognitive performance after six months of atorvastatin therapy, the effect was more prominent among individuals entering the trial with higher MMSE scores, cholesterol levels above 200 mg/dl or an apolipoprotein-E-4 allele.

The mechanism of this putative “protective” effect is not understood. It is not because patients who take LLAs are more prosperous and better educated, and it is not because they lead healthier lifestyles to begin with. The anti-dementia effect of non-statin LLA’s is not nearly so robust.

Cholesterol in the CNS is mostly endogenous; lowering serum cholesterol has a negligible impact on cholesterol available to neurons. A statin drug, crossing the blood-brain barrier, reduces the amount of endogenous cholesterol available to neurons. There are several mechanisms by which it may do this. Decreased brain cholesterol tends to inhibit the pathway by which Abeta-amyloid peptide (Abeta) is derived from the amyloid precursor protein (APP). Reducing the activity of Abeta can inhibit a number of events that are central to the pathology of AD, including fibril formation and activation of pro-inflammatory pathways. A clinical study of simvastatin also indicated a direct action on the processing of APP by inhibiting both the alpha- and the beta-secretase pathways.

Other statin effects that are cholesterol-independent may be more directly neuroprotective, including anti-inflammatory and antioxidant properties and preservation of endothelial nitric oxide synthase activity in the cerebral vasculature and improved cerebrovascular reactivity.

Table 00.7. Statins

EVIDENCE GRADE	B
RISK GRADE	C

In light of all this, the occasional reports of acute memory impairment in patients treated with statins ought to be addressed. This putative side-effect has been widely reported, and has given pause to many likely patients. As we have noted on other occasions when medication-related cognitive impairment is at issue, the acute effects of a drug may be different from the long-term effects, and the effects of a drug on groups of patients does not necessarily preclude a different kind of effect on individuals.

ESTROGEN

Estrogen Replacement Therapy (ERT) is effective in alleviating the cognitive problems – mainly, memory and attention – that accompany the climacteric. The number of significant findings favoring ERT considerably outnumbers the rare findings of better performance in controls. Experimental studies demonstrate a consistent beneficial effect on verbal memory, at least in short-term studies. Observational

studies suggest that there may be a long-lasting effect of continued ERT on cognitive functioning, but these studies need to be interpreted with caution because of the lack of random assignment and a possible "healthy user bias." Five observational studies and 8 trials have addressed the effect of estrogen on cognitive function in nondemented postmenopausal women. Cognition seems to improve in perimenopausal women, possibly because menopausal symptoms improve, but there is no clear benefit in asymptomatic women.

Biochemical and neurophysiologic studies suggest several plausible mechanisms by which estrogen may affect cognition: promotion of cholinergic and serotonergic activity in specific brain regions, maintenance of neural circuitry, favorable lipoprotein alterations, and prevention of cerebral ischemia. ERT is similar to the effects of statins and omega-3FA in enhancing nitric oxide synthesis and suppressing the production of proinflammatory cytokines. ERT has antioxidant and antiatherosclerotic properties and neuroprotective activity.

Observational studies have also suggested a role for ERT in the prevention of dementia in general and AD in particular. At least ten observational studies have measured the effect of postmenopausal estrogen use on the risk of developing dementia. Meta-analysis of these studies suggests a 29% decreased risk of developing dementia among estrogen users. Four trials of estrogen therapy in women with AD have been conducted and have had primarily positive results, but most have been small, of short duration, non-randomized, and uncontrolled.

It has subsequently been established that ERT or estrogen/progestin replacement does not lower the risk of coronary heart disease postmenopausal women and may actually *increase* the risk of CHD, thromboembolic events and breast cancer. In fact, ERT may actually *increase* the risk of cognitive decline.

Table 00.8. Estrogen

EVIDENCE GRADE	C
RISK GRADE	C

THE B VITAMINS

Vitamin nomenclature is an historical accident more than anything else. When researchers were trying to identify the "growth factors" that were at issue in early vitamin research, one could be extracted from certain foods with organic solvents ("fat soluble A") while another was extractable with water ("water soluble B"). We now refer to fat- and water-soluble vitamins, but the letters live on. "Water soluble B" was originally thought to be only the *antiberiberi vitamine* (thiamine, or Vitamin B1); later, the term "B Complex" was used to refer to the numerous other vitamins, in addition to thiamine, that could be partitioned from "water soluble B": riboflavin (B2), niacin or nicotinic acid (B2 or B5), pyridoxine (B6) and pantothenic acid (B3). Cobalamin (B12) was isolated from another source entirely, but it is a "B" vitamin because it is water-soluble. Ascorbate is water soluble but not a B vitamin, because it was designated before the B complex was partitioned. Folate was originally known as vitamin Bc; it is a B vitamin, because it is water soluble and its metabolic activity is associated with B6 and B12; but folate, or folic acid, is easier to say than B_{anything}. The term B complex definitely has a cachet and it has survived, even as some other famous complexes (e.g., Oedipus Complex, Inferiority Complex, Military-Industrial Complex) have withered. It is used very loosely now, primarily as a marketing tool, and you never know

what you're going to get in a bottle of vitamin B complex. Theoretically, the B complex also includes biotin, and the quasivitamins, choline, inositol, carnitine (Bt), and para-amino benzoic acid, but (hopefully) not the non-vitamins pangamic acid (B₁₅) and laetrile (B₁₇).

B vitamin deficiency can cause dementia: thiamine in the Wernicke-Korsakoff syndrome, and niacin in pellagra ("dermatitis, diarrhea and dementia"). The B vitamins that are pertinent to this discussion, however, are cobalamin (B₁₂), pyridoxine (B6) and folate. With respect to these three, there is still controversy surrounding the issue of subclinical deficiency and about their putative therapeutic benefit in conditions that are not overt deficiency states.

Measuring serum levels of folate and vitamin B₁₂ is a recommended part of the standard dementia workup. Deficiencies of either of these micronutrients are associated with neurodegeneration, which is fully reversible, if caught early enough. Measuring serum levels of homocysteine may indicate the presence of an important risk factor for cardiovascular disease, and, therefore, vascular dementia. Is that all there is to it, or do the B vitamins play an additional role in the prevention of dementia?

Folate & Vitamin B₁₂

Folic acid and vitamin B₁₂ (cobalamin) are essential in several metabolic pathways in the CNS and a close relationship exists between them. Both are involved in single carbon transfer reactions necessary for the production of monoamine transmitters, phospholipids, and nucleotides. Deficiencies of either vitamin produce characteristic hematological abnormalities and neuropsychiatric symptoms.

The RDA for B₁₂ is 2 µg/d, and the average diet contains about 20 µg/d. Treatment of pernicious anemia usually begins with intramuscular injections of 100-1000 µg of B₁₂ for five days, and monthly thereafter. There is a prejudice against oral B₁₂ among American physicians, because it is poorly absorbed in the absence of gastric acid and Intrinsic Factor (IF), which is usually what causes B₁₂ deficiency in the first place. A daily dose of 1000 µg by mouth will allow absorption by passive diffusion (absent HCl or IF) of 10 µg, which exceeds the RDA. The ordinary "B Complex" one buys at the health food store or a "high-potency" multivitamin ordinarily contains only 25-75 µg of B₁₂.

Folate is a generic term that refers to folic acid and related compounds. Foliates are widely distributed in foods, especially green, leafy plants. (*Folium* is Latin for leaf; hence, *folio*.) The RDA is 200-400 µg/d. The average diet contains 200-300 µgm of folate, and most supplements contain 50-400 µgm. Nutritional deficiency results in impaired biosynthesis of DNA and RNA, and thus in reduced cell division, which is manifested clinically as anemia, dermatologic lesions and poor growth. An oral dose of 5 mg/d is used to treat patients with pernicious anemia. Increasing dietary intake of folate by 200 µgm/d is said to reduce the risk of cardiac death.

Low serum vitamin B₁₂ concentrations are found in more than 10% of older people. Folate deficiency is less common, especially since the vitamin has been added to our grain supply to prevent neural tube defects. Folate-responsive homocysteinemia, however, can be demonstrated in people who are apparently healthy, suggesting prevalent undiagnosed suboptimal vitamin status.

Changes in mood and cognition may accompany low levels of B₁₂ or folate, even in the absence of hematological abnormalities. Such patients may present to neuropsychiatry clinics with undiagnosed deficiencies, and their conditions may improve dramatically with replacement therapy. Psychiatric abnormalities associated with cobalamin deficiency include depression, paranoia, organic psychosis, obsessive-compulsive disorder, personality and mood changes. B₁₂ deficiency is, of course, a cause of

reversible dementia. It is a subcortical dementia typified by processing speed deficits, memory and visuospatial impairment. But not all of the neurocognitive deficits improve after replacement therapy.

The common view is that the neurological manifestations of cobalamin deficiency are a late manifestation, occurring only after the deficiency and its hematological abnormalities are well established. In fact, neuropsychiatric abnormalities can occur even in the absence of low serum cobalamin levels, anemia and macrocytosis. Neuropsychiatric symptoms in the absence of anemia "should not be considered rare." ^{p1727}

Folic acid metabolism has also been connected to various neuropsychiatric disorders, including dementia, depression, schizophrenia, alcoholism and anorexia. Experimentally induced folate deficiency in normal volunteers can cause sleeplessness, irritability and memory deficits. The commonest neuropsychiatric complication of severe folate deficiency is depression, but depression is more likely to be correlated with hypercysteinemia than with low serum folate levels. Dietary intake may play a role, but the cause of folate deficiency in psychiatric patients, compared to normal controls, is unknown. Folate therapy, however, does not always lead to clinical improvement, although patients with low baseline folic acid levels tend to respond less well to antidepressants, antipsychotic drugs, lithium and anticonvulsants.

Cobalamin, pyridoxine and folate are co-factors in the synthesis of methionine from homocysteine, which is why homocysteinemia is indicative of B₁₂/B₆/folate deficiency. In the mitochondria, cobalamin catalyzes the conversion of methylmalonyl CoA to succinyl CoA, which is why elevated levels of methylmalonic acid are indicative of B₁₂ deficiency. Serum levels of folate and B₁₂ are customary in dementia workups, but serum levels of homocysteine and methylmalonate are a more accurate gauge of the patient's actual status with respect to these two micronutrients. The assays are expensive, however; considerably more expensive than a therapeutic trial of B₁₂ injections and a bottle of B complex.

High blood levels of homocysteine signals the hypomethylation of numerous substances, including DNA, proteins, phospholipids and various neurotransmitters. Thus, vascular structures and neurons are rendered more susceptible to damage and apoptosis. It is also possible that homocysteine, by itself, may be neurotoxic. Experimental folate deficiency has been shown to cause elevated plasma homocysteine concentrations, and the use of folate-containing multivitamin supplements is associated with low mean plasma homocysteine levels. Homocysteinemia is especially prevalent in the elderly (as high as 29%). Strong and remarkably consistent data have linked elevated levels of homocysteine with increased risk of cardiovascular disease.

Homocysteinemia is prevalent in patients with vascular dementia and there are numerous reports of increased levels of homocysteine and reduced levels of its metabolic product S-adenosylmethionine in AD patients. In a group of elderly patients with early dementia (mixed types), elevated levels of homocysteine were noted, and were corrected by a course of folate (2 mg) and vitamin B₁₂ (1 mg).

Elevated levels of homocysteine may be an early risk factor for cognitive decline and low/normal levels may be protective of dementia conversion in MCI patients. For these reasons, it was natural to investigate the effects of vitamin B₁₂ and folate in patients with MCI and dementia. In one study of patients with dementia, supplementation with B vitamins led to clinical and cognitive improvement in patients who had elevated levels of homocysteine at baseline, but not in patients who had normal homocysteine. In a study of patients with dementia and MCI, all with low serum B₁₂ levels, supplementation led to improvement among the latter but not the former.

Other trials of patients with AD showed no evidence for a vitamin B₁₂ treatment effect. Treatment with folate and vitamin B₁₂ can lower homocysteine concentrations in elderly patients with vascular disease but may not improve their cognitive status over the short or medium term.

Table 00.9. Vitamin B₁₂ & Folate

EVIDENCE GRADE	B
RISK GRADE	A

Folate toxicity is low. High doses (1-10 mg/d) may complicate the management of epilepsy or lead to zinc deficiency. Concomitant anticonvulsant therapy may increase the requirement for dietary folate, and estrogens, including oral contraceptives, may reduce blood levels of folic acid. High doses of folate (e.g., 15 mg/d) may cause irritability, overactivity, excitability, euphoria and altered sleep patterns. Folate therapy, of course, can mask the clinical manifestations of vitamin B₁₂ deficiency.

Pyridoxine (Vitamin B₆) and Thiamine (Vitamin B₁)

The role of other B vitamins in the genesis of dementia or its treatment is obscure. Pyridoxine is an essential homocysteine re-methylation cofactor, and deficiency is associated with increased blood homocysteine levels. It is also a co-factor in the metabolism of CNS neurotransmitters. Pyridoxine deficiency may be associated with peripheral neuropathy and neuropsychiatric disorders including seizures, migraine, chronic pain and depression. Epidemiological studies indicate that poor vitamin B₆ status is common among older people. Supplementation with B vitamins including vitamin B₆ has been shown to reduce blood homocysteine levels. Low pyridoxine is associated with atherosclerosis, but not AD. There is no evidence of benefit from pyridoxine supplementation on mood or cognition in elderly people.

Thiamine deficiency plays an important role in the Wernicke-Korsakoff syndrome, and low levels of thiamine have been observed in elderly people in general and in patients with AD in particular. Thiamine deficiency in elderly patients can be induced by parenteral hyperalimentation, diuretics, hemodialysis and surgery. In some old patients, it may just happen. It has been suggested that thiamine may have a beneficial effect for AD patients, but the results of controlled studies, thus far, have been inconclusive.

Table 00.10. Vitamins B₁ and B₆

EVIDENCE GRADE	C
RISK GRADE	A

The Rationale for Treatment with B Vitamins

Simply because a vitamin is essential to some aspect of metabolism in the CNS does not mean that supplemental vitamins will improve CNS function. Vitamins are taken up into the CNS by an active transport system that gives priority to the requirements of brain metabolism, and the synthetic steps in which the B vitamins participate are not usually rate-limiting bottlenecks.

Simply because vitamin levels are found to be low in patients with dementia doesn't mean that supplemental vitamins can prevent dementia or improve the status of a demented person.

Nevertheless, it is clear that subclinical deficiencies in B₁₂, folate and pyridoxine, are associated with elevated homocysteine and vasculopathy; that subclinical deficiencies of cobalamin and folate are associated with dementia; that non-alcoholic thiamine deficiency sometimes occurs; and that a course of intramuscular cobalamin may lead to nonspecific improvement in patients with a variety of neuropsychiatric conditions.

It is necessary to begin the dementia work-up by measuring blood levels of B₁₂ and folate. It is not sufficient. Serum homocysteine should be monitored on an ongoing basis, just as one monitors other cardiovascular risk factors. A normal B₁₂ level in a patient with MCI is an indication for a methymalonate level.

Supplemental intake of B vitamins during middle-age may or may not be preventive against dementia. The effect, if there is any, is likely to be small. But the risk is just as small or smaller.

A MISCELLANY OF ANTIOXIDANTS

Ginkgo Biloba

Ginkgo biloba is an extract from the leaves of the Ginkgo, or maidenhair tree, used in China as a traditional medicine. It is also used widely in Europe for “cerebral insufficiency,” a wide range of problems including absent-mindedness, difficulties with concentration and memory, confusion, lack of energy, fatigue, impaired physical performance, depression and anxiety, usually associated with aging. It is also used for intermittent claudication, because it is said to “decrease the viscosity of blood.” In fact, health-conscious people who take daily aspirin *and* ginkgo biloba may be given to nosebleeds; one of the components of ginkgo, ginkgolide B, is a potent platelet-activating factor antagonist.

Ginkgo extract is a potent antioxidant and a reversible inhibitor of monoamine oxidase. It tends to reduce glucocorticoid synthesis, which may account for its purported “anti-stress” effect.

There have been a number of studies to support the use of ginkgo extract for a number of neuropsychiatric problems, like neurasthenia (fatigue and tiredness) ; age-associated memory impairment ; “cerebral insufficiency” ; and dementia. In fact, the weight of published studies, including several that meet rigorous criteria, tended to support a small but positive effect for Ginkgo extract in people with various kinds of cognitive problems including AD. A recent study, however, with random assignment of Ginkgo or placebo to elderly patients with cognitive impairment, showed no effect.

There is no apparent toxicity from ginkgo biloba, aside from the interaction with aspirin. In published studies, side effects are no more common than placebo. The evidence that Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is “inconsistent and unconvincing” although controlled studies continue to suggest the possibility of benefit.

Table 00.11. Ginkgo Biloba Extract

EVIDENCE GRADE	<i>B</i>
RISK GRADE	B

Resveratrol

Resveratrol is just one more supplement to prevent cardiovascular disease, cancer and AD. We mentioned it before because it is an important constituent of the Mediterranean diet and red wine. It is a polyphenolic compound found in various plants, including grapes, berries and peanuts, and it has antioxidant and anti-inflammatory effects.

Resveratrol is worth mentioning again because it appears to mimic the physiological effects of calorie restriction (CR). CR is important to mention because it happens to be the only nongenetic intervention that reproducibly extends mean and maximal life span in diverse species. In small animals, CR also delays the onset or slows the progression of many age-related disease processes. The effects of CR have been demonstrated many hundreds of times in laboratory rodents and other short-lived species, such as rotifers, water fleas, fish, spiders, and hamsters, mice and rats. The effects of CR in longer-lived species more closely related to humans are as yet unproven, although ongoing studies in monkeys are encouraging thus far.

CR and resveratrol share a common mechanism. They both activate the SIRT1 protein, a human homologue of yeast silent information regulator (Sir)-2, and a member of the NAD⁺-dependent histone deacetylases. SIRT1 is the mediator of lifespan extension in model organisms. Induction of SIRT1 expression also attenuates neuronal degeneration and death in animal models of AD and Huntington's disease.

In short-lived organisms, including mice and rats, resveratrol produces changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-I) levels, increased AMP-activated protein kinase (AMPK), increased mitochondrial number, and improved motor function.

CoEnzyme Q10

Coenzyme Q10 (CoQ10) is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane. Experimental studies in animal models suggest that CoQ10 may protect against neuronal damage that is produced by ischemia, atherosclerosis and toxic injury. One controlled trial in 80 subjects with mild Parkinson's disease found significant benefits for oral CoQ10 1,200 mg/day to slow functional deterioration.

Curcumin

Turmeric is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Since the time of Ayurveda (1900 BC) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions. Curcumin, which gives the yellow color to turmeric, has been shown to exhibit antioxidant, anti-inflammatory and neuroprotective actions. It has an outstanding safety profile, which may be related to its low systemic bioavailability following oral dosing. However, data from cell cultures and animal models suggest that dietary curcumin is a candidate for use in the prevention or treatment of age-related neurodegenerative diseases. Pilot clinical trials are ongoing.

“CONSERVATIVE” PREVENTION VERSUS “AGGRESSIVE” PREVENTION

Earlier, I said that dementia prevention could be aggressive, or conservative. The former is what you might elect for yourself or a family member, in the face of clear danger; that is, AD risk factors like a strong family history, possession of the ApoE4 allele, a history of severe brain injury, or Down syndrome. Or what you might choose for a patient who had Mild Cognitive Impairment (MCI). In such cases, it might be worthwhile to take a chance on an unproven preventive, even if it carried a small degree of risk.

“Conservative prevention” is what everyone should consider, even people without special AD risk factors, once they reach middle age. This approach includes measures that may be unproven as far as AD is concerned, but seem to have value as health-promoters, and carry no risk at all.

Review the grades I assigned to the various, putative preventives. Here is where they stand with respect to my two categories of preventive treatment:

Table 00.12. Conservative or Aggressive Prevention?

Treatment	Evidence Grade	Risk Grade	Category
Aspirin	B	C	Conservative
Coenzyme Q 10	C	A	Conservative
Curcumin	C	A	Conservative
Estrogen	C	C	Not recommended
Folate	B	A	Conservative
Gingko Biloba	B	B	Conservative
NSAID's	C	C	Aggressive
Omega-3FA	B	A	Conservative
Pyridoxine	C	A	Conservative
Resveratrol	B	A	Conservative
Statins	B	C	Aggressive
Thiamine	C	A	Conservative
Vitamin B ₁₂	B	A	Conservative
Vitamin C	B	A	Conservative
Vitamin E	B	C	Conservative

To simplify matters, this is what I propose: everyone older than 50 who is planning to live a long time ought to take Fish Oil, 1000 gm bid, and aspirin in low doses (80-100 mgm/d). Resveratrol and B complex are defensible, and so is Gingko, if one doesn't take aspirin.

The recommendation of supplemental micronutrients is not intended to diminish the importance of diet, especially a diet that is rich in fresh fruit and vegetables, especially garlic, green tea and red wine.

Aggressive prevention is a term I apply to the higher doses of ASA (600 mgm/d) or an alternative NSAID and a statin. They have a low risk profile, but not a negligible one, and they cannot be recommended to everyone. On the other hand, any older person who is at all physically active is likely to have a lot of aches and pains, at least from time to time; he or she will probably be using anti-inflammatory drugs as mild analgetics, and fairly frequently at that. So, one NSAID or another is likely to be part of his or her diet. And as far as the statins are concerned, it does seem that the bar to getting one prescribed is getting lower every day. No primary care physician is likely to consider a statin to be "aggressive" treatment of anything.

We used to recommend high doses of Vitamins C (1000 mgm bid) and E (1000 mgm bid), until the bubble burst a couple of years ago. Is it necessary to take these antioxidant supplements if one is already taking resveratrol and Gingko? I don't think so, but no one really knows.

Inevitable questions arise: how much protection is enough, is any amount ever too much, how many pills can a normal person stand to take every day, what is the optimal dose of all this stuff and, most important, how "aggressive" can a physician be in recommending treatments that are, as yet, unproven? Are there untoward interactions among these various "neuroprotectants" over the long term? Does anybody believe that the mavens of "evidence-based medicine" are likely to have answers to these questions anytime soon?

ACTIVE TREATMENT

“Active treatment” for dementias like AD is a contradiction in terms. There are no treatments available now that are likely to reverse the pathology and make the patient well, although there are some, including anti-amyloid drugs, on the near horizon, and they will be interesting, indeed. Nevertheless, some treatments available today can be expected to slow the course of the disease or to delay, at least, the disability associated with it. There are likely to be more such treatments before long.

The only “active treatments” currently available for demented patients are acetylcholinesterase inhibitors (ACI); competitive NMDA antagonists, like amantadine and memantine; and psychostimulants, antidepressants and nicotine.

ACETYLCHOLINESTERASE INHIBITORS (ACI)

Practice guidelines, published papers and drug manufacturers advise beginning treatment with an ACI as soon as the diagnosis of AD is made. They are, in fact, safe, though some people find them hard to tolerate. They are effective, to a degree. For many patients, dementia symptoms improve – cognitive impairments as well as behavioral and emotional problems. The benefit may be sustained for some time, perhaps a year or two, perhaps longer. Maybe it depends on how far the disease has progressed at the time treatment commences. Younger patients (i.e., <65 years old) seem to respond more favorably to treatment than older patients do.

The ACI are, strictly speaking, a dementia treatment, tried and approved for patients with “mild to moderate” AD. But the effectiveness of ACI, limited though it is, raises a number of questions pertinent to our discussion. If physicians were able to diagnose presymptomatic AD, should they begin treatment at that point? Should patients with MCI take an ACI? Should patients with late life depression take an ACI as an antidepressant augmenter? Should people with a genetic proclivity take an ACI as a preventive? What “genetic proclivity,” exactly, is pertinent? We know that ACI’s are effective for patients with non-Alzheimer’s dementia, and for cognitive disorders caused by other conditions, like brain injury. But is treatment just symptomatic, or does it mitigate the course of the disease? If so, which disease? If treatment were started early, would it be more effective over the long run? Should people at special risk, like Down syndrome patients, take an ACI and, if so, when should they begin?

Just as “active treatment” for AD is a new idea, the ACI are relatively new drugs, and it is not possible to answer all of these questions. The ACI have a pedigree, though, in the study of brain injury. In fact, the earliest attempt to correlate recovery of cortical function with cholinergic stimulation was made in 1928 when Chavany advocated the use of acetylcholine in the treatment of hemiplegia. Positive effects with acetylcholine injections in hemiplegic patients, aphasics, and other neuropathic cases were at first attributed to cerebral vasodilatation. Subsequent research was conducted by Luria and by Ward and Kennard at Yale, during the Fulton era. That was two generations ago.

Advances in understanding the actions of acetylcholine in the CNS led to an appreciation of its role in the consolidation of long-term memory. For many years, physicians appreciated that anticholinergic drugs can cause memory impairment. Researchers have used physostigmine and acetylcholine precursors like lecithin to improve memory performance in brain injury patients. The problem for cholinergic therapeutics, though, was the lack of an effective drug that could be administered orally, that could cross the blood-brain barrier and that had a long duration of action. Luria, the Russian neuropsychologist, used gallanthamine, an ACI that met exactly those specifications, during the 1940’s.

(The drug has come available in North America recently, with a slightly different spelling.) Cholinergic drugs improve memory and other cognitive functions in brain injury patients.

Cholinergic treatment has been central to pharmacological development for dementia in general and for AD in particular. It is a rational treatment, because it mitigates the deficit in cholinergic neurotransmission that stems from deterioration of neurons in the basal forebrain of Meynert. Because acetylcholine is an important neurotransmitter in the physiology of memory and attention, and because deficits in acetylcholine systems are found in amnesic patients and patients with attentional disorders, it was appropriate to explore the potential utility of cholinergic drugs in treatment.

Tetrahydro-9-aminoacridine (THA) was the first cholinergic treatment to attain clinical utility. Long-term treatment of demented patients with THA led to significant improvement in patients' general clinical status and learning ability. It was an effective palliative treatment. Patients' cognitive state tended to improve for a few months, some could return to premorbid activities, and often their psychiatric symptoms would get better, too. It might delay the need for nursing home care, but it did not increase patients' lifespan. It did not, in other words, alter the outcome of the disease.

The newer ACI (donepezil [DNP], rivastigmine, metrifonate and galantamine) have proven to be just as effective, better tolerated and easier to use. DNP is the first cholinergic drug to achieve wide use, and not just by specialists. The new ACI are used not only for demented patients but also for stroke, multiple sclerosis and brain-injury patients, and even for patients with age-related memory decline. Small trials with DNP in Down syndrome patients have been encouraging.

Now, back to those difficult questions.

ACI seem to be clinically useful for non-Alzheimer's dementia and for cognitive disorders associated with vascular events or brain injury ; they seem to be effective in patients with Lewy body dementia and Parkinson's dementia but not necessarily for fronto-temporal dementia. It is not necessary to have a specific diagnosis of AD to consider a trial of ACI.

As they are currently used, then, the ACI are symptomatic treatments, helpful for a while, palliatives, as it were, but not much in the way of disease-modifying drugs. The fact that ACI are effective for cognitive disorders in general suggests a "downstream" effect on a common pathway by which dementing disorders are manifest, rather than on a primary event in AD pathophysiology. The fact that ACI do not alter the course of AD reinforces that belief.

Suppose, though, it were possible to identify AD patients at a very early, presymptomatic stage? Could the ACI, in those circumstances, be useful in modifying the course of the disease? And if they did, would it be safe to use them for years and years? Would it be safe to use them along with the other "treatments" and preventives we have discussed above? And if so, would their effects be additive, or synergistic, or something else?

Studies are underway, at the present time, to address at least some of these questions, although the results of ACI studies in patients with MCI have been disappointing so far. There is evidence that early initiation of treatment offers sustained benefits and that early treatment may have "disease-modifying effects", but it is entirely preliminary.

There is suggestive evidence, from preclinical studies, that ACI may be neuroprotective, by one mechanism or another, depending on the drug. Possible mechanisms include an anti-inflammatory effect and a protective effect against glutamate neurotoxicity. Of course, we have seen that many other drugs and supplements have similar effects in animal models and cell cultures absent clinically important effects. To put matters in perspective, in one of the few comparative studies that has been published, DNP was equally effective to *Ginkgo biloba*.

N M D A A N T A G O N I S T S : A M A N T A D I N E A N D M E M A N T I N E

The only other class of drugs specifically addressed to the problem of dementia are the glutamate receptor antagonists, or to be more specific, non-competitive antagonist of the NMDA receptor-ion channel. One is amantadine (AMT) and another is memantine (MMT). The former has been around since the 1960's; the latter was approved for dementia treatment, in Germany, many years ago, and was approved in North America recently. Both drugs, at one time, were thought to be dopamine agonists. AMT was used for Parkinson's disease and MMT was used as an antispasmodic. Occasionally, they would be prescribed to patients with "senile dementia of the Alzheimer type." In both conditions, they were helpful, sometimes. Now we know that AMT and MMT are NMDA antagonists. Their clinical effects are believed to be mediated by mitigating the excitotoxic damage of glutamatergic hyperactivity.

Glutamate is the principle excitatory neurotransmitter in the brain. It is released at the majority of excitatory synapses in the mammalian CNS, and responsible for functions like cognition, memory, movement, sensation and neuronal plasticity. Excessive activation of glutamate receptors causes neuronal injury or death, and there is only a small gradient between physiological levels of glutamate and levels that may be toxic. Excitotoxicity is clearly manifest in pathological conditions, like PD, stroke and TBI, and it may also be an active participant in the insidious degeneration that accompanies normal aging. In neurodegenerative conditions like PD, Huntington's disease and AD, excitotoxic damage may be the consequence of a pathological chain of events that includes the generation of free radicals. In various animal models of focal brain hypoxia/ischemia, NMDA antagonists have neuroprotective effects.

The early reports of AMT and MMT in patients with dementia, during the 1970's and 80's, were encouraging, although the results of subsequent clinical trials have been mixed. There were occasional reports of reduced agitation and improved alertness in demented patients treated with AMT but therapeutic effects were compromised by the frequent occurrence of behavioral toxicity or seizures. Nevertheless, MMT (but not AMT) continued to be used in Germany, at least, as an anti-dementia drug. It could alleviate dementia symptoms, like anergia and withdrawal, or agitation and screaming.

There were also suggestions that NMDA antagonists might have disease-modifying effects. In 1996, for example, Uitti et al suggested that AMT might be neuroprotective. They also reported that it prolonged survival in patients with PD. There is evidence that MMT also is a neuroprotectant.

Recent publication of large and well-controlled studies indicates that MMT can improve cognition and activities of daily living in patients with moderate-to-severe AD. MMT can be used safely with ACI, and if it is added to a stable ACI regime, patients seem to improve a little bit more. This sequence is entirely accidental, because, in North America at least, ACI were available well before MMT was. The efficacy of MMT and AMT in MCI has not been proven, but neither have the ACI. If one elects to treat an MCI patient, should one choose NMDA antagonist, an ACI, or both, or neither? Or should one choose AMT, because it is the only generic in this crowd? MMT studies employ placebo comparisons. That is appropriate, but it would be nice to know how MMT compares to AMT.

S T I M U L A N T S A N D A N T I D E P R E S S A N T S

The conventional psychostimulants have long been used for symptomatic improvement in patients with mild-to-moderate dementia. They have been prescribed for many years, although there is not a robust literature, by any means; nicotine is a stimulant, as well, albeit a different kind of stimulant. We mention it because the pharmaceutical industry is very active these days trying to develop nicotine-like drugs for cognitive disorders.

That psychostimulants are beneficial for symptoms of inattention, depression, abulia and anergia in elderly patients, with or without dementia, is hardly controversial. One would be surprised if such were not the case. They are beneficial, for these problems, in a wide range of patients with static or degenerative conditions, like brain injury, stroke, PD, multiple sclerosis, etc. It is less well appreciated that stimulants can, in some circumstances, improve cortical recovery.

For example, in patients who have had brain injuries, clinical reports and small trials have shown reduction of untoward behaviors, cognitive improvement, and subjective improvement. In stroke patients, studies have addressed the problem of post-stroke depression, where methylphenidate (MPH) is found to be useful, by itself, or in conjunction with an antidepressant. There are also reports in stroke patients, of beneficial stimulant effects on recovery. Positive effects on recovery from aphasia were reported in 6 stroke patients treated with amphetamine (AMP) by Walker-Batson et al. Positive effects on motor recovery were reported when AMP is combined with physical therapy.

The clinical literature is interesting, but somewhat sparse. The preclinical literature, however, is more salient and to the point. Enduring recovery of function has been demonstrated in cats subjected to bilateral cortical ablations. Treatment with AMP, combined with visual experience, results in recovery of binocular depth perception. In rats, unilateral cortical ablation causes a motor deficit that is apparent when the animal has to traverse a narrow elevated beam. A single dose of AMP administered 24 hours following cortical ablation accelerates the rate of cortical recovery, as long as the drug is coupled with beam-walking experience. Post-lesion treatment with AMP also enhances motor recovery in cats with unilateral or bilateral frontal cortex ablation.

The element that is common to both the clinical and the preclinical studies of AMP-induced recovery is the requirement for co-training. That is, drug combined with experience (training, therapy) exercises a positive effect when drug alone does not. Brain plasticity, therefore, in a variety of paradigms in developing and adult animals, seems to require an optimal monoamine environment; conversely, the monoaminergic stimulants seem to require an optimal experiential environment. This suggests that the drug itself serves as a facilitator of the learning experience, an agent that renders the organism capable of capturing an experiential phenomenon in a meaningful way.

One candidate mechanism to explain the effect of stimulants on cortical recovery is long term potentiation (LTP). LTP is one of the substrates for brain plasticity and memory formation in normal development and neuropsychiatric disorders. Although the mechanisms responsible for the development and persistence of LTP is unknown, consideration is usually given to changes in synaptic strength, neosynaptogenesis and use-dependent sprouting.

Changes in synaptic strength are believed to be the basis for learning and memory. Neocortical neurons, for example, can display sustained increase in synaptic efficacy following conditioning stimulation. In LTP, a brief tetanic stimulus to specific neural pathways produces an increase in synaptic responses that can last for days or weeks. The development of LTP is triggered by brief physiological events, appears to be strengthened by repetition, and can persist indefinitely. LTP appears to require an optimal monoamine environment. The process is impeded when monoamines are depleted, and is enhanced when monoaminergic drugs, like the stimulants, are administered. Kindling, a potentially destructive variant of LTP, is enhanced in a suboptimal monoamine environment.

Antidepressants

The most common clinical condition that current understanding attributes to a "sub-optimal monoamine environment" is depression, and we have discussed the intimate association between mood disorders and dementia in Chapter X. If, in fact, mood disorders represent a risk factor for the

subsequent development of dementia, then it is appropriate to ask if optimal treatment might, in the long run, lower the risk.

We know that antidepressants are widely used in patients with dementia – as many as 43%, in one study. We also know that antidepressant treatment for depression in patients with AD is efficacious, although it does not necessarily improve cognition. But neither does it cause cognition to decline, as the antipsychotic and the sedative drugs often do.

We also know that antidepressants promote hippocampal neurogenesis and that selected antidepressants may have additional effects to slow the development of AD pathology. But we do not know whether antidepressant treatment, optimal or otherwise, is protective against dementia. The fact of “pseudodementia,” discussed in Chapter X, strongly suggests that depression accelerates the clinical expression of dementia, so it is reasonable to suspect that the converse may also be true.

Deprenyl or Selegiline

Selegiline (formerly L-deprenyl or Deprenyl) is a selective and irreversible inhibitor of MAO-B. There have been reports to suggest that it may delay the initiation of L-DOPA treatment in patients with beginning symptoms of Parkinson's disease (PD) and prolong the life of PD patients. Theoretically, it can delay the death of striatal dopaminergic neurons. These reports, however, have not been supported by later studies.

Selegiline is thought to be prophylactic in PD because it prevents the oxidation of dopamine by MAO-B, which results in the formation of oxygen-derived species that are toxic to dopaminergic neurons. As neurons die, turnover of dopamine is increased in the neurons that remain, and there is even more production of neurotoxic oxygen radicals. This may have some importance on the physiology of normal aging, a process that is associated with an inexorable depletion of dopaminergic neurons even in the absence of PD. Indeed, deprenyl has been discovered to prolong the life span of laboratory rats and elderly dogs who do not have PD.

Selegiline is one of several “anti-aging” drugs that have been prescribed in many countries, including piracetam, gamma-aminobutyric acid (GABA), Ginkgo biloba, pentoxifylline, cerebrolysin, solcoseryl, ergoloid, vinpocetin, sertraline, and estrogens. Because the increase in human life expectancy at birth over the second half of the last century was mostly caused by the better survival among the old and “oldest old,” gerontologists have actually suggested that consumption of antiaging properties is the cause.

If true, the event has not been manifest in clinical studies. We have already referred to the study of selegiline and vitamin E, which indicated delayed progression of AD as a result of both treatments (but not a stronger effect for the combination). In a recent analysis of 16 subsequent studies evaluating selegiline treatment for patients with AD, however, “there were very few significant treatment effects” and the authors concluded that “there is no evidence of a clinically meaningful benefit for AD sufferers.” In fairness, however, what effects there were favored the drug.

Patients are warned against using selegiline in combination with pseudophedrine or dextrometorphan, and antidepressants, although the actual incidence of adverse effects is probably low. This risk is not so much sympathetic crisis, but serotonin syndrome, which is equally dangerous.

Nicotine

In experimental animals, decreased nicotinic activity in the hippocampus and amygdala impairs memory. Nicotinic interactions with dopaminergic and glutaminergic systems are also important components of cognitive function. One of the major neurochemical features of AD is the marked

reduction of nicotinic acetylcholine receptors in disease-relevant brain regions such as the cerebral cortex and hippocampus. Neocortical nicotinic receptor binding is lost during the transition from MCI to AD.

Nicotine has been shown to improve cognitive function in a variety of studies in humans and experimental animals. Nicotine and agonists of the alpha4beta2 and alpha7 nicotinic receptors improve working memory function, learning, and attention in normal volunteers. Transdermal nicotine has been found to improve attentional function in people with AD and a variety of other neuropsychiatric disorders, and a number of novel nicotinic agonists are in clinical trials.

In different ways, the psychostimulants, nicotinic agonists and antidepressants improve the monoamine environment of the brain. They counter the depletion of the governing neurotransmitters that is an inexorable accompaniment of normal ageing. They certainly provide symptomatic relief for many of the problems that beset old people and patients with MCI or early dementia. Is it possible that an "optimal monoamine environment" can influence the onset or the progression of dementia?

PREVENTION & TREATMENT: SUMMARY

Dementia treatment is largely a primary care responsibility. Elderly patients are attached to their primary physicians, and prefer to confine their care to one doc, if they can. Many of them don't have the resources to pursue specialty care – even if they have the money, driving to a far-off clinic, walking two or three blocks from the parking deck, and waiting for two hours to see a specialist is not something they are likely to do very often.

As I have had the opportunity to discuss the problem of dementia screening with primary care physicians, I noticed that a natural experiment in dementia prevention is occurring right now. Through the assiduity of pharmaceutical representatives and the lack of any alternative, at least some primary care doctors seem to be prescribing ACI's to virtually any old patient who complains of memory difficulties, most of the time without a work-up. How we are ever going to assess the impact of this practice is beyond me.

The point is that dementia prevention and treatment is likely to remain a primary care responsibility, and simply throwing an ACI at any old patient who comes in the door complaining of memory problems is not the best approach. I have tried to summarize the pros and cons of various approaches, and I shall end by summarizing the approach we recommend at our clinics. It is not an especially complicated system, for primary care docs or for their patients. It isn't too expensive, either. But before I give my own suggestions, let us review the opinions of two expert panels recently convened on opposite sides of the Atlantic.

In 2006, the British Association for Psychopharmacology convened a panel to review the evidence on drug treatment for dementia. The panel felt the scientific evidence was strongest for the following contentions:

- ACI for mild to moderate Alzheimer's disease, Lewy body dementia and cognitive impairment associated with vascular dementia; but that
- Neither ACI nor vitamin E reduced the risk of developing AD in people with MCI.
- MMT was effective for moderate to severe AD, for cognitive impairment associated with vascular dementia and that
- MMT added to an ACI was sometimes beneficial.
- Gingko biloba produced a modest benefit on cognitive function.

This same panel also felt that there was good evidence in support of bright light therapy, aromatherapy and metal chelating agents (sic) but no effect at all for anti-inflammatory drugs or statins and “no evidence that there is any intervention that can prevent the onset of dementia.”

In 2005, an American expert panel presented their “best practice” recommendations, which included:

- Control of hypertension and diabetes for patients at risk for dementia, in patients with mild/moderate/severe vascular or mixed AD/vascular dementia.
- Aspirin and possibly a lipid-lowering agent in patients at risk for vascular dementia and in patients with mild/moderate vascular or mixed AD/vascular dementia,
- ACI for patients with MCI and for mild/moderate mixed AD/vascular dementia.
- To slow cognitive impairment in mild/moderate AD, an ACI alone or combined with vitamin E.
- Combining an ACI with an NMDA antagonist in patients with mild/moderate dementia who respond only partially to monotherapy, and for moderate/severe AD or mixed AD/vascular dementia.
- Selective serotonin reuptake inhibitors were recommended for the treatment of depression or anxiety in patients with dementia.

I don't know about aromatherapy or metal chelating agents, but most of these recommendations are quite sound. They reveal, however, a powerful and troubling bias: they are about *dementia*. That is, they are based almost entirely on evidence that was generated by studying patients who had already developed dementia. That is, to me, the equivalent of studying treatments for cancer that has already spread to bone. When that happens, nothing works very well, except for palliative relief.

It is true that the evidence base now includes numerous studies of conversion from MCI to dementia. In the crucible of the randomized, placebo-controlled clinical trial few if any of the “preventives” have proven effective. So it is true, though painful to admit that there is “no evidence that any intervention can prevent the onset of dementia.” On the other hand, many such trials reported that patients who responded best to an intervention were younger, or had the mildest symptoms.

I am always dubious about the naysayer, who faced with hard evidence to the contrary, maintains that the trial wasn't done quite right. If a slightly different formulation had been used, then... But I do believe that it likelier that treatments would be effective if they were begun earlier in the course of the condition. There is an incontrovertible body of evidence that the pathology of AD and other forms of dementia begins decades before the disease itself is clinically manifest, and we have reviewed that evidence at length in earlier chapters. I think what we have to do is identify patients at the very earliest sign that something might be going wrong.

In our clinical practice, we regularly meet with patients in their fifties who have subjective complaints of cognitive weakness, or lingering depressions, or subtle personality change, and who have subtle findings on computerized tests. They always perform perfectly well on screening tests like the MMSE, and they usually do well enough on conventionally administered neuropsychological tests as well, because those tests are not paced quite so fast as the computerized tests. Very few of these patients would meet entry criteria for an MCI trial. Many have cardiovascular risk factors and/or a family history of dementia.

The risk that any American will have dementia by age 80 is about 40%. If dementia pathology begins, say, thirty years before the disease is manifest, then 40% of 50 year-olds are in the process of developing dementia. That is almost certainly an underestimate, because people who die between the age of 50 and 80 often have diseases like diabetes and atherosclerosis that are aggressive participants in the dementing process. In comparison, the 80-year-olds are the healthy ones, the survivors. But 40% of these *survivors* have dementia.

It is not unreasonable to think that the patients I described in the last paragraph but one are *more likely than not* in the process of an evolving dementia. Such patients, I believe, deserve consideration for aggressive prevention and active treatment.

Here is the system that I propose:

- Computerized neurocognitive testing should be routine for all patients, on an annual basis, beginning in their 40's, when most people start getting annual physical examinations. This gives every patient a baseline against which future changes can be measured. It also will identify MCI at the earliest possible moment.
- Conservative protectives for every patient over 50: fish oil, low dose aspirin or ginkgo and B complex.
- Identify patients at the earliest stage of MCI by using computerized tests, and by recognizing these factors: family history of dementia, cardiovascular risk including homocysteine and other inflammatory markers, depression, anxiety, rigidity, personality change.
- Consider aggressive prevention for patients at risk: anti-inflammatory doses of aspirin or other NSAIDs, a statin, perhaps also a "cocktail" of antioxidants.
- A low threshold to use stimulants and antidepressants for mild problems with energy or depression in elderly patients. A vigorous approach to antidepressant treatment if the patient has residual depression.
- ACI and/or AMT/MMT, certainly as soon as there is evidence that a patient at risk is beginning to decline, but preferably earlier
- Lifestyle modification and optimal cardiovascular health for everyone. A Mediterranean diet, red wine, green tea, a lot of fruit and vegetables, vigorous physical and mental exercise. Stay active, stay connected, play a meaningful role in the lives of others. Don't retire, don't watch TV and never stop making love. Contemplate the enormity of Creation, your own deep and abiding connection to it, and the everyday miracle that you are here. Try to stay with us as long as you can.