Practical Strategies for Preserving Good Cognitive Function into Old Age

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As people age, their cognitive function is threatened by the normal aging process, as well as increasing risk for stroke and a range of inflammatory neurodegenerative conditions, most notably Alzheimer's disease (AD), but also including frontotemporal dementia, Parkinson's disease and others. Our understanding of the origins of these disorders, and of the most definitive ways to prevent, postpone, or treat them is still at a rudimentary stage – which is understandable, in light of the phenomenal complexity of cellular biology and the human brain. Nonetheless, I submit that, based on current evidence, a range of practical prudent strategies can be defined that seem likely to aid preservation of cognitive function during aging and that, in any case, appear consistent with promotion of optimal health:

Prudent Diet and Lifestyle – Epidemiological studies strongly suggest that a diet pattern characterized as "Mediterranean" or plant-based – low in saturated fats, and rich in fruits and vegetables – can slow cognitive decline during aging while reducing risk for AD and other dementing disorders.[1-5] With respect to stroke risk, moderation in dietary salt and a high intake of potassium-rich whole foods appears to be notably protective. Regular exercise training also emerges as globally protective – slowing the rate of age-related cognitive decline, and reducing risk for AD and stroke. And – consistent with the adage "use it or lose it" – some studies point to regular mental exercise as beneficial for cognitive preservation.

The risk for cognitive decline associated with diets high in saturated fats has recently been traced to the fact that these fats, unlike unsaturated fats, can give rise to the pro-inflammatory compound ceramide, which in turn promotes the pro-inflammatory activation of brain glial cells – astrocytes and microglia.[6-11] These cells function in various ways to support healthy brain function. In particular, they protect the brain from invasion by infective agents, for which reason they are capable of generating a wide range pro-inflammatory hormones as well as oxidant chemicals such as peroxynitrite. A notable downside of this is that, in excess, these hormones and oxidants can perturb the proper function of brain neurons; they can impede the efficiency of a process known as "long-term potentiation" required for new memory formation, can amplify the production and potentiate the effects of the amyloid beta protein that is a key driver of neuronal dysfunction and death in AD, and can even kill neurons.[9, 12-16] As people age, there is a natural tendency for brain glial cells to become more pro-inflammatory – either they are chronically active in producing pro-inflammatory hormones (notably interleukin-1), or are on hair-trigger alert, highly sensitive to activating stimuli. This phenomenon is thought to be largely responsible for the modest loss of cognitive function normally associated with "healthy aging", and also has the potential to exacerbate incipient neurodegenerative disorders such as AD or Parkinson's.[14, 17, 18] Hence, aging is associated with chronic low-grade inflammation of the brain – some might call it a "brain on fire" syndrome. Eating a diet rich in saturated fat is like throwing fuel into this fire. As we will see, many of the phytonutrients or drugs discussed below with potential for slowing age-related cognitive decline can suppress the tendency of brain glial cells to become inflamed - and hence have an opposite effect to that of saturated fat.

Dietary intakes of sodium and potassium appear to be a key determinant of cerebrovascular health and stroke risk. Hypertension is of course a major risk factor for both types of stroke – ischemic (triggered by blood clots) and hemorrhagic. In societies that don't salt their food, the most common type of

hypertension – the so-called "essential" form – is virtually non-existent; moreover, there is limited evidence that both stroke and dementia are quite rare in these societies.[19, 20] Few Western studies have examined the association of salt intake with risk for dementia, but one recent study found that relatively low dietary sodium intake in elderly people was associated with a lower rate of cognitive decline over the subsequent three years.[21] Of related interest are reports that memory is superior and risk for dementia is notably lower in hypertensives who use potassium-sparing diuretics; these drugs cause urinary sodium loss while preventing loss of potassium.[22, 23] In societies that do salt their food, many but not all hypertensives are said to be "salt-sensitive", meaning that a reduction in dietary salt can bring their blood pressure down a bit. A high intake of potassium tends to oppose the pro-hypertensive impact of dietary salt, and clinical studies show that an important increase in dietary potassium tends to lower blood pressure.[24] But what is at least as important is that, at any given level of blood pressure, a higher intake of potassium is associated with a lower risk for stroke[25-32] – likely because a modest increase in blood potassium levels has a direct antioxidant/anti-inflammatory impact on the endothelial lining of the cerebrovascular arteries.[33-35] A lower dietary sodium/potassium ratio likewise has a favorable impact on risk for heart attack.[36-38]

In a very impressive recent controlled clinical study, veterans in a Chinese retirement home were randomized to receive either their ordinary diet, or a very similar diet in which a salt substitute (half sodium chloride, half potassium chloride) replaced ordinary salt in cooking and at the table.[39] Use of the salt substitute led to only a modest reduction in salt intake (owing to the use of some pre-salted ingredients), but potassium intake went up by about 76% in this group. During a follow-up of about two and a half years, the death rate from heart attack, stroke, or heart failure was 40% lower in those getting the salt substitute! Moreover, a population-wide reduction of the dietary sodium-potassium ratio in Finland appears to have made an important contribution to the dramatic reduction in heart attack and stroke rates observed in that country over the last two decades.[40] You can notably increase the potassium content of your diet by emphasizing whole foods (added sugars, fats, and distilled liquors are virtually devoid of potassium, and refined grains are a poor source); some fruits, such as bananas, are exceptionally rich in potassium, as are most tubers. When you use salt in cooking or at the table, using a salt substitute in which potassium chloride partially replaces sodium chloride is a shrewd move.

In many epidemiological studies, regular exercise emerges as protective with respect to risk for stroke, age-related cognitive decline, and dementia.[41-48] Part of this protection no doubt stems from the favorable impact of exercise on cerebrovascular function and hypertension.[49] But for reasons that remain unclear, exercise also provokes the brain to produce increased levels of growth factors – so-called neurotrophic factors such as brain-derived neurotrophic factor (BDNF) – that aid the survival and effective function of neurons.[50-53] There is a tendency for the hippocampus – a portion of the brain cortex vital for new memory formation – to shrink a bit during aging; a recent controlled study found that one year of aerobic exercise in adults over over 55 was associated with a modest but significant increase in hippocampal volume.[54] In rodent models of Alzheimer's disease – mice bioengineered to overproduce the amyloid beta protein that drives cognitive dysfunction and neuronal death in this syndrome – voluntary exercise favorably affects their cognitive function and in some instances lowers the deposition of amyloid beta aggregates (plaque) in the brain.[55-60] In normal aging mice, exercise training appears to alter the function of brain microglia so that they are less pro-inflammatory and more supportive of brain health.[61] In short, all signs point to a lifelong habit of exercise as being notably protective for cognitive health during aging, and even suggest that taking up exercise late in life can be beneficial in this regard.[43, 62]

One of the "side effects" of an exercise habit is that it helps you to control your weight; a Mediterranean or plant-based diet emphasizing whole foods can also be quite helpful in this regard.[63] People who are overweight in midlife – particularly if they have a preferential accumulation of body fat in their belly, known as android obesity – are at notably higher risk for AD and age-related cognitive decline in later years.[64] Analogously, the metabolic abnormalities typically associated with android obesity, known as the "metabolic syndrome" (insulin resistance, hypertension, high triglycerides, low HDL) are also mid-life risk factors for late-life dementia.[65-69] These findings serve to emphasize the fact that AD is a chronic disorder that develops gradually over decades, only becoming symptomatic after a number of years. Surprisingly, overweight does not consistently emerge as a risk factor for AD among elderly people, and associations between metabolic syndrome and AD in the elderly are sometimes inconsistent.[64, 70] Conceivably, this may simply reflect the fact that the weight loss which is a typical consequence of AD[62, 71] may often precede diagnosis of the syndrome; if that is the case, then correction of metabolic syndrome or obesity in the elderly might still have utility for diminishing AD risk. In this regard, diabetes, typically associated with overweight, is indeed a major risk factor for cognitive decline and AD in the elderly.[65, 72, 73] Adopting healthful habits that tend to promote a leaner physique – eating a prudent diet and exercising regularly and effectively – is probably a smart idea at any age.

In the context of diet, it may be appropriate to mention coffee and caffeine. The "mental-energizing" effects of caffeine reflect its ability to inhibit certain cellular receptors in the brain which ordinarily are activated by the natural metabolite adenosine. Via interaction with the A2A form of adenosine receptor, caffeine has the potential to exert anti-inflammatory effects on the brain, dampening the activation of microglia, supporting the protective function of astrocytes, decreasing production of beta amyloid, and warding off some of the adverse effects of beta amyloid on neuronal synapses and cognitive function.[74-81] Indeed, most though not all recent epidemiological studies find that people who have made heavy use of coffee for a number of years are at decidedly lower risk for cognitive decline and AD as they age.[82-88] In one provocative Finnish study, people who drank 3-5 cups of coffee daily in midlife were about *two-thirds* less likely to develop dementia as they aged.[85] This one study probably overstates the true benefit of caffeine – some studies find no protection[89, 90] - but the balance of evidence clearly points to a notable protective effect. Whether adopting a caffeine habit at an advanced age can be protective in this regard has not yet been studied. However, one recent prospective study examined blood caffeine levels in elderly subjects with mild cognitive impairment, and found that caffeine level dose-dependently predicted risk for development of dementia over the next 4 years – none of those in the highest bracket of blood caffeine became demented over this time.[91] Other recent epidemiology on coffee points to heavy coffee drinkers as being at reduced risk for mortality from a host of disorders, including heart disease, stroke, diabetes, infections, injuries, and accidents; some of this protection might stem, not just from caffeine, but from the phytochemical antioxidants in coffee.[92] In light of current evidence, it may be smart to drink about as much coffee as you can, consistent with getting appropriate restful sleep and the concurrence of your physician. If drinking coffee in the evening or even afternoon impairs your sleep, you can limit your use to the morning. (Some decades ago, caffeine and coffee developed a reputation as a potential health *risk*, owing to the fact that, in people who are coffee "virgins", a dose of caffeine provokes an increase in heart rate and blood pressure. But if people persist in drinking coffee regularly, this reaction tends to dampen and disappear over several weeks; that's why coffee doesn't harm regular coffee drinkers.)

Caffeine's particular merit for cognitive health may be its ability to block the adverse impact of amyloid beta – the toxic protein that is a key driver of neuronal death and dysfunction in AD – on cellular uptake

the neurotransmitter glutamate. Glutamate is major neurotransmitter in the brain, including those parts of the brain responsible for memory formation. After its extracellular release at synapses is triggered by a neural impulse, it must be rapidly removed from the extracellular space by cellular uptake; glial cells known as astrocytes are primarily responsible for this uptake. But amyloid beta suppresses the ability of astrocytes to take up glutamate, and there is recent evidence that it does this via stimulation of astrocyte A2A adenosine receptor activity.[93, 94] Failure to rapidly remove glutamate after a neural impulse results in chronic low-grade stimulation of a specific type of neuronal glutamate receptor (so-called extrasynaptic NMDA receptors), and this is now suspected to be a major mechanism whereby amyloid beta impairs neuronal function and ultimately can cause neuronal death.[95-97] By blocking A2A receptors, caffeine negates the adverse impact of amyloid beta on astrocyte glutamate uptake, and hence may strike at the root of a key mechanism whereby amyloid beta damages neurons.

One of the long-chain omega-3 fatty acids found typically in fish oil – docosahexaenoic acid (DHA) – is a prominent structural component of neuronal cell membranes, both in the brain and retina. The process of establishing new memories requires rapid synthesis of new connections between neurons – a process known as synaptogenesis – and this in turn requires efficient production of new neuronal membranes. As DHA is a major component of these membranes, a ready availability of DHA aids the efficiency of this process.[98] Hence, it is not surprising that DHA-enriched diets have shown favorable effects on cognitive function in rodent studies – though not always in AD model mice.[99-106] Epidemiologically, elderly people with relatively high blood levels of DHA or high fish intakes tend to enjoy superior cognitive function and lower risk for dementia, and good DHA status may predict a lower rate of cognitive decline.[1, 99, 107-112] In one recent controlled clinical study, volunteers over 55 performed better on certain tests of learning and memory after they had received 900 mg of supplemental DHA daily.[113] However, supplemental DHA has not been found to slow cognitive decline in AD.[108, 114] You can insure good DHA status if you eat oily fish regularly, or if you take a fish oil supplement rich in omega-3. Krill oil has also been introduced recently as a supplemental source of DHA, and vegans can obtain DHA supplements derived from marine algae (albeit these are currently far more expensive than fish oil per unit DHA). Although humans inefficiently convert the main omega-3 fat found in plant products – alpha-linolenic acid – to DHA, a novel type of soybean oil rich in stearidonic acid, an omega-3 more readily converted to DHA, should soon be on the market.[115]

Another nutrient that is emerging as especially beneficial for cognitive healthy is vitamin D. When microglia become inflamed, their capacity to convert circulating vitamin D to its active hormonal form goes up, and the resulting increase in microglial vitamin D activity acts as a restraint on microglial inflammation.[116-118] As noted, interleukin-1 (IL-1) is a key hormone produced by inflamed microglia that can impair the efficiency of the long-term potentiation required for memory formation in the hippocampus; in aging rats treated with vitamin D, hippocampal levels of IL-1 declined significantly.[119] Recent epidemiological studies are finding that, among aging people, poor vitamin D status tends to correlate with poorer cognitive status, and also is associated with increased risk for cognitive decline and development of dementia.[120-127] Poor vitamin D status is also being linked to increased risk for vascular disease, diabetes, and certain prominent types of cancer and autoimmunity.[128] Although limited amounts of vitamin D can be obtained from food, most people synthesize most of their vitamin D via exposure of their skin to *uv* light; however, the *uv* content of sunlight tends to be quite low at northern latitudes during the winter. Hence, a growing number of health authorities are recommending a daily supplemental intake of vitamin D, in the range of 2,000-8,000 IU daily, as the most practical way to insure good vitamin D

status year- round; this appears to be quite safe, as our own bodies can manufacture over 10,000 IU daily.[129]

Cerebral Antioxidants – There is a growing consensus that cerebral oxidative stress plays a key role in the induction of age-related cognitive decline, AD, Parkinson's disease, Lewy body dementia, and stroke. Cerebral oxidative stress arises primarily from overactivation of an enzyme complex known as NAPDH oxidase, and also from mitochondria (the "power plants" inside our cells that manufacture the energy catalyst ATP) that have been structurally disrupted. Both NADPH oxidase and damaged mitochondria make superoxide, which in turn is converted to downstream compounds – hydrogen peroxide, hydroxyl radical, and peroxynitrite – which are unstable and, if not promptly detoxified by antioxidant enzymes or small molecule antioxidants such as glutathione, can cause severe structural damage to cells and/or activate pro-inflammatory cellular signaling pathways. In microglia, activation of NADPH oxidase is a key driver of pro-inflammatory behavior, and can damage neighboring cells by giving rise to the oxidant compound peroxynitrite.[130, 131] Oxidative damage of neurons by activated microglia is thought to be a prime mediator of Parkinson's disease, and may also contribute to neuronal damage in AD and Lewy body dementia.[132-137] Neurons also can express NADPH oxidase, which can be stimulated by amyloid beta[138, 139] – but activation of mitochondrial superoxide production appears to be a primary way in which toxic amyloid beta promotes neuronal dysfunction and death in AD.[140-143] There is recent evidence that, in mice, chronic activation of NADPH oxidase in a special subset of brain neurons (GABAergic interneurons) promotes the age-related die-off of these neurons, which in turn contributes to age-related cognitive dysfunction.[144, 145] The amyloid beta-driven inflammatory process in AD is often associated with local reductions in blood flow attributable to amyloid beta-mediated activation of NADPH oxidase in the cerebral microvasculature; this process, know as cerebral amyloid angiopathy, is thought to exacerbate cognitive decline in AD.[146, 147] Activation of NAPDH oxidase in the cerebral vasculature may also play a key pathogenic role in the induction of stroke and in the resulting damage to the brain.[148-152] Hence, effective control of cerebral oxidative stress may have potential for stemming age-related cognitive decline, reducing stroke risk, and slowing the onset or progression of dementing neurodegenerative disorders.

Two phytonutrients stand out as having particularly outstanding potential for controlling cerebral oxidative stresss – phycocyanobilin (PhyCB), richly supplied by the food microalga spirulina, and astaxanthin, currently produced for supplemental use from another type of microalga. Bilirubin, a compound produced naturally in our bodies, has remarkable antioxidant activity because it can directly inhibit several forms of the NADPH oxidase complex.[153-155] (Indeed, when cells are under oxidative stress, this provokes the synthesis of an enzyme, heme oxygenase-1, which generates bilirubin within the cell, thereby providing feedback control of the oxidative stress.[156]) Although there are no natural concentrated sources of bilirubin for supplemental use, it is a great stroke of luck that, within our cells, PhyCB can be rapidly converted to a compound almost identical in structure to bilirubin which likewise can potently inhibit NADPH oxidase.[157, 158] This provides a very credible explanation for the fact that, in rodent studies, oral administration of whole spirulina or of protein-bound PhyCB (known as phycocyanin) has shown protective effects in a great many models of inflammation.[158, 159] Indeed, PhyCB may have the potential to provide protection from a vast number of health disorders in which oxidative stress generated via NADPH oxidase plays a mediating or exacerbating role, including vascular diseases, diabetic complications, and autoimmune conditions.[158] Morevover, there is good reason to suspect that orally administered PhyCB has access to the brain, as oral administration of spirulina or of phycocyanin has

been found to be protective in rodent models of Parkinson's disease and epilepsy.[160-162] More pertinently, in SAMP8 mice, a "senescence-accelerated" mouse strain prone to early memory decline and increased brain production of amyloid beta, three months of spirulina feeding prevents loss of memory function in 6-month-old mice, while notably quelling brain oxidative stress.[161] Another recent study shows that spirulina feeding preserves the function of neuronal stem cells (cells capable of generating new neurons) in rats whose brains had been injected with the powerful pro-inflammatory compound lipopolysaccharide.[161] And exposure of microglial cells to phycocyanin opposes their inflammatory activation – as had been predicted.[163, 164] Hence, although clinical assessments of spirulina's cerebroprotective potential are currently lacking, rodent studies and cell culture studies suggest it may have profound potential in this regard. Presuming that humans absorb and metabolize PhyCB in a manner comparable to rodents, it has been estimated that a daily intake of 15-30 g spirulina daily (1-2 tablespoons) could be expected to replicate the protective antioxidant effects observed in rodents.[158] Consuming this much spirulina can be a daunting challenge, as spirulina tastes rather bad and smells even worse, but functional foods in which the flavor of spirulina is masked are being developed, and it should be possible someday for biotechnologists to extract the PhyCB from spirulina and use it in nutraceuticals.

As we have noted, damaged mitochondria are thought to be a major source of pathogenic oxidative stress in AD. Astaxanthin, a fat-soluble membrane antioxidant similar in structure but more potent in antioxidant activity than the carotenoid phytonutrients lutein and zeaxanthin – and many times more active than vitamin E - appears to have considerable potential for protecting cellular membranes, and most particularly the membranes of mitochondria, which are under continual threat from oxidative stress.[165-169] Although healthy mitochondria produce superoxide at a low, tolerable rate, oxidative damage to mitochondrial membranes can turn mitochondria into avid sources of superoxide – which in turn provokes more damage to the mitochondrial membranes. Astaxanthin has the potential to block this vicious cycle by preserving membrane structure. This is likely to be the mechanism whereby astaxanthin is protective in so-called "ischemia-reperfusion" damage, which plays a major role in tissue damage in both heart attack and stroke.[170, 171] Unfortunately, astaxanthin has not yet been tested in rodent models of AD or Parkinson's – but it will be surprising if it doesn't show some protection in these models; one recent review cites its neuroprotective potential and calls it "a potent candidate for brain food".[172] There are however reports that astaxanthin can exert an anti-inflammatory effect on microglial cells in culture.[173, 174] This is perhaps a bit surprising, since NADPH oxidase is the chief source of oxidative stress in these cells – but perhaps this reflects a role for metabolites of oxidatively-damaged membranes in the induction of inflammation in microglia. Although astaxanthin, like spirulina, has so far received little clinical evaluation, initial studies suggest that supplemental intakes of 4-20 mg daily can have a significant antioxidant impact and clinical utility.[175-179] In light of clinical evidence that vitamin E may modestly slow cognitive decline in AD, the utility of astaxanthin in this regard certainly merits evaluation.[180]

An alternative approach to controlling cerebral oxidative stress is to administer natural compounds which can provoke increased synthesis of antioxidant enzymes in the brain cells. Two categories of compounds have this potential – so-called "phase 2 inducers", and the hormone melatonin. The phase 2 inducers include a vast number of phytochemicals, many of which are found in common foods – sulforaphane in cruciferous vegetables, EGCG in green tea, sulfur compounds found in garlic, etc. – and notably the nutritional cofactor lipoic acid, which has shown neuroprotective activity in a number of rodent studies and in human diabetic neuropathy.[181-188] (The cerebroprotective benefits of some of the polyphenols

discussed in the next section may stem in part from phase 2 induction.) Phase 2 inducers, by boosting the level and promoting the nuclear uptake of the intracellular protein nrf2, cause cells to increase their synthesis of a large number of antioxidant enzymes, and to also increase their production of the crucial intracellular antioxidant glutathione.[189-192] None too surprisingly, there is evidence that boosting nrf2 expression in the brains of AD model mice (dementia-prone mice genetically engineered to produce increased levels of amyloid beta) improves their cognitive function.[193] Among the phase 2 inducers, lipoic acid is of particular interest, as it quite clearly has access to the brain; dietary supplementation with lipoic acid is reported to improve cognitive function in AD model mice.[194-196] The daily dose of lipoic acid shown to be effective in treating diabetic nerve damage are in the 600-1800 mg daily range; likely such doses would also provide some protection to the brain.[194] A couple of small pilot clinical studies with lipoic acid suggest that it may indeed slow the onset of dementia in early AD.[197, 198]

Melatonin is a hormone produced by the pineal gland at the base of the brain, and also synthesized by some cells. It is released during the night, and helps to coordinate the body's biorhythms; this secretion tends to diminish with increasing age, which is why supplemental melatonin may be most helpful in the elderly. Melatonin has an impact similar to phase 2 inducers on cellular antioxidant enzymes and glutathione; however, its effects are not dependent on activation of nrf2.[199] Like lipoic acid, melatonin aids cognitive function in AD mouse models; in cell cultures, it protects neurons from amyloid beta-mediated damage, and lessens the proinflammatory impact of amyloid beta on microglia.[200-207] Fortunately, melatonin is absorbed efficiently when administered orally. When used clinically, melatonin is administered at bedtime (to mimic the normal rhythm of its physiological production), usually in a dose of 3-20 mg. Some people may find they are a bit groggy the next morning if they take too high a dose. Initial clinical evalution of melatonin in patients with AD suggests that it may be beneficial for a syndrome known as "sundowning", in which patients become agitated with the onset of evening; this likely reflects its ability to restore normal biorhythms.[208]

As noted, one key way in the phase 2 inducers and melatonin increase the antioxidant defenses of neurons is to boost production of the versatile intracellular antioxidant glutathione; they do this by increasing the expression of the enzyme whose activity is rate-limiting for its production. Glutathione is synthesized within cells from the amino acids cysteine, glutamic acid, and glycine; cysteine is usually the least available of these amino acids, and hence its concentration determines the speed with which glutathione can be synthesized. Hence, supplementation which increases intracellular cysteine levels can increase cellular levels of glutathione. Although high oral doses of cysteine per se cause GI upset, supplementation with the compounds N-acetylcysteine (NAC) or cystine is far better tolerated, and accomplishes the purpose of boosting intracellular cysteine - and hence glutathione.[209-212] Protective benefits of NAC supplementation have been reported in rodent models of Parkinson's disease and AD.[213-220]

Lewy body dementia (DLB), although it so far has received little publicity, is thought to be responsible for 20% or more of clinical dementia. It's origins appear to similar to those of Parkinson's disease (PD), because in each of these disorders intraneuronal aggregates of the protein alpha-synuclein, known as Lewy bodies, are believed to contribute to neuronal dysfunction and death.[137] DLB begins in cortical regions of the brain, whereas PD arises in the substantia nigra, rich in neurons that make the neurotransmitter dopamine. Curiously, patients with DLB often eventually develop Parkinsonian symptoms, whereas PD patients are prone to develop dementia associated with cortical Lewy bodies; it is

reasonable to suspect that these disorders are, from a mechanistic standpoint, very similar, but differing in where they first arise in the brain. Microglial activation and microglial production of the vicious oxidant peroxynitrite appear to be key mediators of the destruction of dopaminergic neurons that charactizes PD; not unlikely, these factors may also drive DLB.[137, 221-225] Peroxynitrite is toxic, in part, because it promotes the aggregation of alpha-synuclein and the formation of Lewy bodies.[226-229] Microglial production of peroxynitrite, which arises from a spontaneous reaction from the compounds superoxide and nitric oxide, can be suppressed by inhibiting microglial superoxide production with PhyCB – likely accounting for the favorable impact of spirulina in rodent models of PD.[160, 162] Furthermore, certain natural antioxidants can provide protection from the pathogenic effects of peroxynitrite – notably the intracellular antioxidant glutathione.[230] Hence, phase 2 inducers, melatonin, and cysteine sources (NAC, cystine) may be useful for controlling PD and DLB – consistent with results in rodent studies.[213-218, 231-234]

But the natural metabolite uric acid (urate) also has important potential for detoxifying peroxynitrite;[235] this may explain why people whose urate levels are naturally high are at significantly decreased risk for PD, or have a slower progression of their disease if they already have this disorder.[236] Unfortunately, the impact of urate on risk for DLB has not yet been studied; however, patients with PD may be at lower risk for subsequent dementia if their urate levels are high[237, 238] – a finding consistent with the possibility that urate provides protection from DLB as well. Supplementation with the purine compound inosine can raise urate levels, and urate supplementation is now being studied in the treatment of multiple sclerosis, another neurodegenerative disorder in which peroxynitrite is suspected to play a key pathogenic role.[239-241] However, supplementation with inosine is not entirely innocuous, because excessive blood and tissue levels of urate can lead to the deposition of uric acid crystals in the body's tissues and kidneys, resulting in the agonizing arthritic disorder gout. Gouty arthritis can be prevented during inosine supplementation if the dose is tritrated such that serum urate levels are kept within the high-normal range 6-9 mg/dL; in the multiple sclerosis clinical trials, physicians start with an intake of 1 g inosine daily, and gradually increase the dose to as much as 3 g daily, in an effort to keep urate in a high but safe target range.[241] However, even if careful dose adjustment succeeds in preventing gouty arthritis, patients supplemented with inosine are at increased risk for uric acid kidney stones.[241] This risk can be minimized if the urine is kept alkaline (as urate tends to crystallize under acidic conditions); a moderate-protein plant-based diet high in potassium helps to maintain an alkaline urine, and supplementation with potassium bicarbonate or potassium citrate can also be employed for this purpose. Because of its logistical difficultly, inosine supplementation can't be recommended for primary prevention of neurodegenerative disorders, but with the supervision of a cooperative physician, it may be worthy of consideration in patients who are developing PD or DLB. Measures which dampen microglial activation (as discussed below), boost neuronal glutathione levels, and protect mitochondrial membranes (such as astaxanthin[242-244]) might also prove useful in these disorders.

Acetyl-L-carnitine (ALC) is often thought of as a brain antioxidant, as it does exert antioxidant effects on the brain in certain circumstances, but the basis of its antioxidant activity remains rather obscure.[245-247] Speculation centers on the possibility that it may reduce oxidant production by damaged mitochondria. Dr. Bruce Ames and colleagues have shown that, in aging rodents, supplementing with the combination of lipoic acid and ALC aids the production of new mitochondria in various tissues, including the brain.[247-250] Since new mitochondria are less prone to generate oxidative stress than damaged old mitochondria, perhaps this helps to explain how ALC acts as an antioxidant. The ability of lipoic acid/ALC to boost brain production of mitochondria is of particular interest in light of the fact that amyloid beta provokes

mitochondrial damage in AD. ALC also has the potential to promote production of the neurotransmitter acetylcholine, as discussed below.[251-253] Regardless of how ALC influences brain function, a great many clinical trials have conclusively demonstrated that, in daily doses of 2-3 grams, ALC has a beneficial impact on cognitive function in elderly people with minimal cognitive impairment or early AD.[254] Despite this, there appear to be few published studies evaluating its impact in mouse AD models.

Taurine is a vitamin-like cofactor that has a special antioxidant function (quenching the hypochlorous acid produced by activated macrophages), but it also regulates membrane function and calcium metabolism in a range of tissues. Neurons are among the cells that accumulate taurine. As you will recall, there is recent evidence that age-related loss of GABAergic interneurons plays a role in normal cognitive aging. A New York research group has recently reported that, when mice were supplemented with taurine for 8 months beginning at 8 months of age, the cognitive decline typically seen in 16-month-old mice was prevented; this effect was thought to reflect protection of a subset of GABAergic interneurons.[255, 256] Aside from this provocative report, researchers have so far shown little interest in exploring the long-term effects of taurine on cognitive function. In any case, taurine is inexpensive and quite safe, and there is considerable reason to believe that optimal taurine status may be protective for vascular health. Supplemental intakes in the range of 1-6 g daily are feasible, as taurine is highly soluble in fluid and has no flavor (in fact, it is a key ingredient of Red Bull™!)

Controlling hypertension is of course well known to be beneficial for stroke prevention, and this often entails use of anti-hypertensive drugs. There is recent evidence that brain-permeable drugs which antagonize the function of the pro-hypertensive factor angiotensin II (drugs known as ACE inhibitors and type 1 angiotensin receptor antagonists) can exert an anti-inflammatory/antioxidant effect on the brain, and moreover have a beneficial impact on mouse AD models.[257-262] This likely is pertinent to humans as well.[263-265] In one recent epidemiological study, in which the age-related cognitive decline of treated hypertensives was assessed, those treated with ACE inhibitors capable of entering the brain showed a 65% lesser decline over 6 years than the group as a whole – whereas those receiving ACE inhibitors that did not have access to the brain declined at a slightly higher rate than the whole group.[266] Other recent epidemiology points to lower risk for dementia in users of angiotensin receptor antagonists.[267] In salt-sensitive rats, a high-salt diet has recently been shown to boost hippocampal levels of angiotensin II and impair cognitive function; concurrent treatment with an angiotensin receptor antagonist alleviated the cognitive impairment.[268] This may be germane to previously cited evidence that a relatively low dietary salt intake is associated with lesser risk for cognitive decline. ACE inhibitors with the ability to cross the blood-brain barrier include captopril, fosinopril, lisinopril, perindopril, ramipril, and trandolapril.[266] Angiotensin receptor antagonist drugs have access to the brain, and seem likely to be comparably protective for brain function.

Anti-inflammatory Polyphenols – A vast and growing research literature focuses on the potential of dietary polyphenols for aiding preservation of cognitive function during aging . Polyphenols, found in a wide range of plant foods and herbs, come in tens of thousands of different forms, traditionally categorized as flavonoids, tannins, and stilbenes. Major categories of flavonoids include flavonols and flavones (notably quercetin, fisetin, and luteolin), catechins (prominent in green tea and grape seed extract), and anthocyanins (richly supplied by berries and their juices). Tannins, which derive their name from the fact that some have been used in the tanning of leather, are found in pomegranate, raspberries,

strawberries, and gall nuts. Stilbenes include the much ballyhooed resveratrol, as well as the up-and-coming pterostilbene, which may have much greater promise for health promotion.

In rodents and cell culture studies, a number of polyphenols have demonstrated positive effects on cognitive function and on the integrity of cultured neurons. These effects include:

- Suppression of microglial inflammation, as reported for anthocyanins from blueberries or acai, the chief catechin in green tea (epigallocatechingallate, or EGCG), fisetin, luteolin, and pterostilbene;[269-276]
- Improved cognitive function in aging normal mice, seen with green tea, blueberries, and luteolin;[274, 277-280]
- Improved cognitive function in AD model mice, as demonstrated with green tea catechins, anthocyanins from blueberry or mulberry, grape seed extract, tannic acid, pomegranate juice, and pterostilbene;[281-288]
- Protection of neurons from the toxic effects of amyloid beta in cell culture, as seen with quercetin, EGCG, blueberry extract, and the prominent anthocyanin cyanidin-3-glucoside;[289-294]
- Improved cognitive function in healthy young rodents, as reported for fisetin, epicatechin, and blueberry anthocyanins.[295-297]

With respect to AD, there is evidence that some polyphenols have the potential to suppress production of the dangerous amyloid beta proteins. Amyloid beta is generated by processing of the large membrane protein amyloid precursor protein (APP), produced by most cells, including those in the brain. Amyloid beta arises when APP is successively cleaved by the membrane-associated enzymes beta-secretase and gamma-secretase; the resulting small peptides, 40-42 amino acids in length, have a tendency to bind to each other, forming small complexes known as oligomers. These oligomers of amyloid beta appear to be the truly dangerous actors in AD.[298] They act on neurons, directly or indirectly, to induce oxidative stress, pro-inflammatory signaling, and neuronal dysfunction. In particular, they disrupt the complex intraneuronal mechanisms required for long term potentiation (LTP), a process crucial to memory formation. In higher concentrations, they can directly kill neurons, and may contribute to the die-off of neurons seen in late-stage AD. Amyloid beta oligomers can also perturb the function of the brain's glial cells, promoting inflammation in microglia and limiting the ability of astrocytes to take up the excitatory neurotransmitter glutamate. This latter effect is important, because excessive extracellular levels of glutamate can lead to a phenomenon known as excitotoxicity which can induce neuronal dysfunction and death. Hence, via their impact on brain glial cells, amyloid beta oligomers can act *indirectly* to threaten the function and survival of neurons. As noted, amyloid beta oligomers also perturb the cerebral vascular system, impairing the delivery of oxygen and nutrients to affected regions of the brain; this lapse of blood flow, in turn, is believed to contribute to the inflammatory syndrome in AD, possibly boosted amyloid beta production. It is thought that, as AD progresses, all of these effects interact to induce a catastrophic deterioration of brain structure and function. Although amyloid beta oligomers are now believed to be the chief mediators of amyloid beta's pathogenic impact, amyloid beta can also coalesce into large extracellular aggregates known as plaques; the accumulation of these insoluble plaques can be observed via microscopy, and is a hallmark of AD.

Fortunately, the APP protein can have a benign, alternative fate. If cleaved by the membrane enzyme alpha-secretase before beta-secretase can act on it, APP cannot give rise to amyloid beta. The rate at

which amyloid beta is produced is therefore dependent on the the balance between alpha-secretase and beta-secretase activity directed toward APP. One of the most intriguing discoveries about the EGCG found in green tea is that, in concentrations which appear to be physiologically feasible, EGCG selectively increases the brain's alpha-secretase activity, such that APP tends to be more preferentially cleaved by alpha-secretase, and that the production of amyloid beta oligomers is suppressed.[281, 299-303] This effect has been observed both in neuronal cell cultures and in the brains of mice fed EGCG. Conversely, there is recent evidence that tannins, including tannic acid and the punicalagin that is a prominent component of pomegranate juice, can decrease amyloid beta production by direct inhibition of beta secretase activity.[286, 304, 305] Potentially, green tea and pomegranate juice (or supplementary tannic acid) could collaborate in suppressing brain amyloid beta production by altering the balance between alpha- and beta-secretase activities; this possibility has not yet been tested in AD mice.

As noted, some flavonoids have shown the ability to boost cognitive function *in healthy young rodents*. Prominent in this regard is fisetin, which, in concentrations which appear to be physiologically relevant, can amplify the sensitivity of the LTP process in neurons from the brain's hippocampus; this likely explains why feeding fisetin to young rats acutely enhances their performance on standard tests of hippocampus-dependent memory formation.[295, 306, 307] Other studies have found that chronic feeding of epicatechin or blueberry anthocyanins can have a favorable impact on memory function in young rodents.[296, 297]

A key reason we can be relatively confident that these remarkable findings in rodents and in cell culture studies are pertinent to humans is the growing epidemiology focusing on green tea. The Tsurugaya Project evaluated cognitive function in over 1,000 Japanese subjects aged 70 or above, using a standard test called the Mini-Mental State Examination.[308] Using a score under 26 as a cutoff point for cognitive impairment, those who drank at least 2 cups of green tea daily *were less than half a likely to be cognitively impaired* than those who drank no more than 3 cups a week – a finding that had extremely high statistical significance. Those drinking an intermediate amount of green tea showed an intermediate level of protection. Green tea may also provide cognitive protection by lessening risk for stroke; a number studies from Japanese or China find lower risk for stroke in people who are heavy regular users of green tea.[309-313] (This protection from stroke may reflect a favorable effect of EGCG on the endothelial lining of the cerebral arteries, as discussed below.) But perhaps the most impressive recent Japanese epidemiology dealing with green tea derives from the Ohsaki Cohort 2006 Study, which enrolled nearly 14,000 Japanese subjects 65 years old or older, and determined their characteristic consumption of green tea at the time of enrollment.[314] The researchers then followed these subjects for the next 3 years to determine which of them became functionally disabled during this time, and correlated this information with their green tea drinking habits. (Functional disability was defined objectively as application for Long Term Care Insurance, a government program that provides daily living assistance for the elderly; disability could result from such common causes as stroke, onset of dementia and severe bone fractures.) As compared to those drinking less than one cup of green tea daily, those drinking 1-2 cups daily were 10% less likely, those drinking 3-4 cups daily were 25% less likely, and those drinking 5 or more cups daily were 33% less likely to become functionally disabled during the 3 years of follow-up. It would be hard to make a stronger case for use of green tea by the elderly!

Unfortunately, it is not possible to find comparable epidemiology addressing other types of dietary polyphenols with protective potential, as consumption of blueberry or pomegranate juice, or of

polyphenol supplements, has never (or at least not yet!) achieved the fetishistic intensity of green tea consumption. Nonetheless, a handful of epidemiological surveys from Western countries suggest that even the modest levels of food polyphenols provided by ordinary self-selected diets may have a meaningful impact on cognitive function in the elderly. Researchers in France estimated daily dietary intake of total flavonoids in over 1600 volunteers aged 65 years or older; they then examined the cognitive function of these subjects during ten years of follow-up, using the Mini-Mental State Examination.[315] They found that cognitive loss tended to be significantly greater in those whose flavonoid intake was in the bottom fourth of the distribution (average loss of 2.1 points on the test), as compared to those whose flavonoid intake was in the top fourth (average loss of 1.2 points). A more recent U.S study focused on berry consumption (the chief determinant of dietary anthocyanin intake) in over 16,000 participants in the Nurses' Health Study, and correlated this with subsequent performance on standardized tests of cognitive performance.[316] With respect to both blueberries and strawberries, relatively high consumption correlated with a slower rate of cognitive decline; indeed, cognitive decline appeared to be decelerated by about 2.5 years in those with high berry intake. Arguably, those who choose to include ample amount of flavonoid-rich foods in their diets may have other dietary and health habits that are partially responsible for the protection observed in these studies; nonetheless, in the light of the favorable impacts of flavonoids on cognitive function in rodents, these findings are provocative and quite possibly meaningful.

Polyphenols with cognitive-protective potential are found in a wide variety of plant foods, and a range of nutraceuticals featuring such polyphenols are also becoming available. Among flavonoid sources, green tea and green tea polyphenol supplements should take pride of place, in light of the rather astounding epidemiology now coming from Japan. A traditional Japanese teacup is said to contain about 80 mg of catechins (primarily EGCG), and optimal protection is seen in those taking 5-6 cups daily, so a daily catechin intake of about 500 mg, preferably dispersed throughout the day (to mimic the typical ingestion pattern of green tea) would seem to be a prudent target. For anthocyanins, frequent consumption of blueberry juice (also available as blueberry juice concentrate, that can be blended with other fluids) is a feasible strategy. Flavonoids can also be obtained from Concord grape juice (which cuts the tartness of blueberry juice a bit if you blend them), and from nutraceuticals featuring fisetin, quercetin, and grape seed extract. For tannins, pomegranate juice is the best practical source, albeit supplements of tannic acid may become available in the future. With respect to the stilbenes, resveratrol unfortunately is metabolized too rapidly by humans to be of much practical benefit, but its close relative pterostilbene can achieve far higher concentrations in the blood, and is now being studied as a nutraceutical in pilot clinical studies.[317, 318] A smart policy may be to "think cognitive" when consuming fluids – get most of your fluid throughout the day from coffee, green tea, and grape or berry juices, and complement this intake with nutraceutical supplements featuring high-potency polyphenols.

Amplify Nitric Oxide Bioactivity – Nitric oxide is a gas produced by one of three forms of an enzyme known as nitric oxide synthase (NOS). The endothelial form of this enzyme, eNOS, is found in the endothelial cells that line the cerebral arteries, and the NO it produces promotes appropriate blood flow to the brain by exerting a vasodilatory effect, while also suppressing arterial inflammation and helping to prevent blood clots; effective eNOS activity appears to be crucial for stroke prevention.[20] Neurons contain their own form of NOS, neuronal NOS (nNOS), whose activity is crucial for the LTP process required for memory formation.[319] A third form of NOS, so –called inducible NOS (iNOS), is found in inflammatory cells such as activated microglia; as opposed to eNOS and nNOS, which produce low, non-

toxic concentrations of NO, iNOS has the potential to produce high concentrations of NO that can react with the oxidant molecular superoxide to generate the highly toxic compound peroxynitrite; this is capable of killing or damaging neurons and may contribute to the neuronal damage seen in Parkinson's disease and AD.[320]

Remarkably, there is recent evidence that the NO produced by eNOS in the cerebral vasculature may act directly on the brain to suppress brain production of amyloid beta; in mice that have been genetically altered to lack eNOS activity, their brains express higher levels of both APP and beta-secretase, and they make higher levels of amyloid beta.[321] Conceivably, this helps to rationalize evidence that risk factors for stroke – which often compromise cerebrovascular eNOS activity – also tend to be risk factors for AD.[20, 321, 322]

The vital biological activities of the low concentrations of NO produced by eNOS and nNOS are mediated largely by activation of an enzyme that produces the compound cyclic GMP (cGMP). cGMP plays a key role in maintaining effective cerebral blood flow, warding off stroke, and supporting effective memory formation via the process of LTP.[319, 323] cGMP is also produced in inflamed microglia expressing iNOS; this cGMP acts as a negative feedback signal, suppressing some of the pro-inflammatory activities of microglia, while supporting their protective activity as phagocytes.[324, 325] Evidently, effective cGMP activity is beneficial for brain health in many respects. The concentration of cGMP is regulated by phosphodiesterase enzymes which break it down. One of these enzymes, PDE5, is inhibited by Viagra (sildenafil) and related drugs prescribed for treatment of erectile dysfunction; these drugs function to boost tissue levels of cGMP, a key mediator of erections. Intriguingly, the Chinese medicinal herb epimedium (a.k.a. horny goat weed) contains a compound, icariin, that can also inhibit PDE5, albeit less potently.[326-328] When ingested in feasible amounts, icariin does not have the acute impact on PDE5 that one sees with Viagra or Cialis, but rodent studies suggest that chronic consumption over days can indeed promote erectile function and boost cGMP levels; the data suggest that decreased expression of PDE5 and/or increased expression of nNOS may play a role in this effect. Whether icariin can be effective for boosting cGMP in humans has not yet been established, albeit icariin nutraceuticals are now available, and anecdotal comments suggest that high-dose icariin may indeed be bioactive in humans; evidently, controlled clinical studies are required to assess this.

One of the adverse effects of amyloid beta on neuronal function is to interfere with the production of cGMP – this is one of the ways in which amyloid beta disrupts LTP.[329-331] PDE5 helps to regulate cGMP in regions of the brain vital for cognition, and both sildenafil and icariin, unlike some drugs, have access to the brain. In light of the foregoing discussion, it isn't surprising that both of these compounds have been reported to aid cognitive function in AD model or senescence-accelerated mice.[332-338] Both sildenafil and icariin can also suppress the activation of microglia in cell cultures.[339, 340] How these agents influence early cognitive dysfunction in humans remains to be assessed. Those who wish to try icariin should be aware that the highest potency (and hence most credible) icariin supplements currently available provide 180 mg icariin per capsule, and the recommended dose is 3 capsules daily.

As noted, optimal eNOS activity in the cerebral vasculature helps to maintain effective cerebral blood flow and is crucial for stroke prevention.[20] One key to maintaining this activity is to control oxidative stress in cerebrovascular endothelial cells, as oxidants can inhibit the activity of eNOS – turning it into an enzyme that generates superoxide rather than protective NO – and superoxide can react directly with NO,

destroying its activity and producing dangerous peroxynitrite in the process.[341] Owing to its ability to inhibit NADPH oxidase, the PhyCB in spirulina is likely to have particular merit for protecting eNOS bioactivity.[20]

But there are also some flavonoids which can act directly on vascular endothelium to stimulate eNOS activity, boosting NO production. These include epicatechin, the key compound in raw cocoa powder which mediates its ability to acutely increase brain blood flow, and thought to be largely responsible for the absence of hypertension and the superior vascular health enjoyed by the Kuna Indians of Panama, whose traditional diet incorporates about 4 cups of raw cocoa daily.[342-344] Quercetin, the most common flavonol in the American diet, has a direct activating effect on eNOS comparable to that of epicatechin.[345] Although the EGCG in green tea does not acutely stimulate eNOS, its consumption somehow makes vascular eNOS function more effective – likely accounting for the diminished stroke risk of green tea drinkers.[346-348] Quercetin and green tea polyphenols are of course available as nutraceutical supplements, and specially processed cocoa powder that retains its native epicatechin content is also now available commercially. (Contrary to much current hype, most dark chocolate products on the market today are poor sources of epicatechin.)

Histone Deacetylase Inhibitors – Histone deacetylases (HDACs) are enzymes which work in the nucleus of cells to modulate gene expression by regulating transcription of DNA; by removing acetyl groups from a family of DNA-associated proteins known as histones, they tend to repress the synthesis of messenger RNAs required for new protein synthesis. The late phase of LTP required for long-term memory formation is dependent on induced production of a number of proteins that effectively strengthen the synaptic connections between neurons.[349] There is exciting recent evidence that the enzyme HDAC2 functions to antagonize the production of a number of these proteins and that, in addition, the adverse effect of amyloid beta and AD on LTP is largely traceable to increased activity of HDAC2.[350-353]

HDAC2 is one of the so-called type 1 HDACs that are susceptible to inhibition by certain drugs or metabolites that are currently available.[354] The expensive cancer drug vorinostat has this activity, as do the anti-epileptic drugs valproate, the orphan drug phenylbutyrate (used to treat a rare metabolic disorder), and the natural metabolite butyrate. Recent studies have concluded that type1 HDAC inhibitors can markedly aid memory function in AD model mice, and may even boost memory function in healthy young mice.[349, 354-359] It is also possible that this strategy might slow the neuronal die-off characteristic of late-stage AD, as one of the proteins whose synthesis is induced by LTP is BDNF, the hormone evoked by exercise training that promotes neuronal survival.[352, 360]

So far, there have been no clinical trials to determine whether type 1 HDAC inhibitors can improve memory formation in patients with early-stage cognitive dysfunction. And there are logistical difficulties with current HDAC inhibitors. Vorinostat and phenylbutyrate are extremely expensive – too expensive for off-label use by people who aren't wealthy, and valproate induces tiredness. Butyrate, a safe natural metabolite, has a blood half life of only about 6 minutes, as it is rapidly burned as fuel by the body's tissues; hence, unless ingested constantly, it presumably would be of limited value. A ray of hope is offered by the fact that tributyrin (glyceryl-tributyrate) is an approved food additive that is broken down gradually in the body to act as a time-release source of butyrate.[361-364] A decade or so ago, tributyrin was tested in cancer patients, as HDAC inhibitors have some potential in cancer therapy (witness the recently approved drug vorinostat).[362] But tributyrin would need to be administered in very high daily doses to be

effective – perhaps several tablespoons daily - and in these clinical studies it was administered in capsules, entailing the ingestion of 60 or more capsules daily! This obviously would be a non-starter from a compliance standpoint. Hence, tributyrin will not be clinically practical until and unless nutraceutical entrepreneurs find a feasible way to incorporate high doses in functional foods.

In any case, let's hope that phenylbutyrate is soon evaluated in patients with early-stage cognitive dysfunction sometime, so we can learn whether this avenue of therapy is worth pursuing; this agent is currently being tested clinically in several other neurodegenerative disorders, and is well tolerated in doses of 9-15 grams daily.[365, 366]

Targeting Tau - Thus far, little has been said in this essay about tau protein, whose excessive phosphorylation in AD and certain other dementing neurodegenerative conditions disrupts its function and leads to the formation of abnormal intraneuronal structure known as neurofibrillar tangles. Amyloid beta drives the hyperphosphorylation of tau, and this phosphorylation of tau is believed to play a key mediating role in AD neurodegeneration; indeed, AD model mice which are also bioengineered to produce lesser amounts of tau are protected from cognitive decline.[367-369] Moreover, hyperphosphorylation of tau plays a pathogenic role in other types of dementing neurodegeneration not linked to amyloid beta excess, such as frontotemporal dementia (these are known as "tauopathies"). Hence, measures which can prevent or reverse the phosphorylation of tau are being sought as therapeutic options.

One of the key enzymes which phosphorylates tau in AD is glycogen kinase synthase-3beta (GSK-3β). It has long been suspected that the therapeutic efficacy of lithium in manic-depressive illness hinges on its ability to inhibit this enzyme;[370] it is therefore reasonable to suspect that therapeutic doses of lithium might lessen tau phosphorylation in AD or other neurodegenerative conditions. Moreover, lithium may also have the potential to decrease amyloid beta production, since phosphorylation of APP by GSK-3β increases its propensity to be converted to amyloid beta.[371, 372] Indeed, several epidemiological studies have found that, in patients with manic-depressive disorder, those receiving lithium are at much lower risk for AD than those not receiving this drug.[373-375] This has been followed up with a controlled 12-month pilot study in which, while both groups experienced further cognitive decline, this was of lesser magnitude in the lithium-treated group.[376] Lithium has also shown a favorable effect on cognitive function in some, but not all,[377, 378] studies in AD model mice, and has reduced the adverse impact of amyloid beta in neuronal cell cultures.[371, 379, 380] And a very recent report suggests that "mini-doses" of lithium (300 mcg daily) may also be useful in early cognitive decline;[381] standard dosing with lithium is potentially toxic and must be carefully monitored by a physician to insure that blood levels do not exceed the safe range.

An enzyme which de-phosphorylates tau (and hence potentially mitigates the problem) is protein phosphatase 2A (PP2A). Remarkably, it has recently been discovered that the compound sodium selenate – long employed as a supplemental source of selenium – can interact with PP2A in a way that boosts its ability to dephosphorylate tau.[382, 383] In a strain of mouse bioengineered to overexpress a mutant human form of tau that gives rise to neurofibrillary tangles, simply giving selenate in drinking water (12 mg per liter) was associated with a marked reduction in tau phosphorylation, a complete prevention of neurofibrillary tangles, and an improvement in memory. While the mice appeared to tolerate this treatment well, selenium is potentially toxic, and, though selenate is the best tolerated form of

supplemental selenium, it remains to be established that prolonged administration of selenate doses sufficient to reduce tau phosphorylation can be tolerated well by humans. Fortunately, a recent phase I clinical study, in which sodium selenate supplementation was assessed in prostate cancer patients, has reported a maximum tolerated daily dose of 60 mg, which is likely more than would be required to modulate PP2A activity.[384] Hence, selenate may ultimately emerge as a useful option in the management of AD and other neurodegenerative conditions associated with tau hyperphosphorylation. And lithium plus selenate might supply a "one-two punch" in that regard. Arguably, such a strategy would have the best chance for important clinical benefit if allied with additional measures that more directly address amyloid beta toxicity.[377]

Inhibiting 5-Lipoxygenase – The omega-6 fatty acid arachidonic acid can be enzymatically converted to a number of pro-inflammatory factors, known as prostanoids and leukotrienes. The cyclooxygenase enyzmes give risk to the prostanoids, and NSAID drugs commonly used to treat inflammation – agents such as aspirin, ibuprofen, and Celebrex – are potent inhibitors of these enzymes. Some epidemiological studies have found that people who have been chronic users of NSAID drugs (people with rheumatoid arthritis, for example) are at markedly lower subsequent risk for AD.[385-387] This encouraged clinical trials of NSAIDS in patients suffering the early stages of AD; unfortunately, no benefit for cognitive function was seen, and the patients receiving the NSAIDS were at higher risk for side effects and cardiovascular mortality.[388] It seems that brain prostanoids can help to trigger an inflammatory process that, once florid, has its own self-sustaining momentum. NSAIDS may therefore have some utility for the prevention of AD, but cannot be recommended for its treatment. And unfortunately, the side effects and increased cardiovascular risk associated with NSAID therapy (especially with the putatively less toxic cyclooxygenase-2-specific inhibitors) makes it imprudent to recommend these agents for AD prevention.

However, there is now evidence which suggests that another pro-inflammatory enzyme, 5-lipoxygenase, may also contribute to the progression of AD. 5-lipoxygenase (5-LOX) produces pro-inflammatory factors known as leukotrienes. 5-LOX expression has been found to be increased in the brain (specifically in the hippocampus, the key target of AD inflammation) of people with AD, possibly owing to induction by stress hormones.[389, 390] In mouse models of AD, measures which increase the expression of 5-LOX within the brain exacerbate memory deficits, boost the production of amyloid beta, and increase the phosphorylation of tau.[390, 391] This increased production of amyloid beta has been traced to increased brain expression of gamma-secretase, which plays an essential catalytic role in this production; and increased tau phosphorylation reflects increased activity of the enzyme CDK5, whose activation in neurons is a common feature of AD. In cell culture studies, increased 5-LOX activity makes neuron-like cells more vulnerable to the toxic impact of amyloid beta.[392] Conversely, drugs which inhibit 5-LOX activity, or genetic measures which prevent 5-LOX expression in the brain, tend to ameliorate the memory decline, suppress amyloid beta production, and lessen tau phosphorylation in AD model mice.[393-397]

Since 5-LOX plays a key role in asthma, drugs which inhibit it – notably zileuton – are currently available, and, in notable contrast to cyclooxygenase inhihitors, seem to be safe and relatively well tolerated.[398] Natural compounds known as boswellic acids – richly supplied by a traditional Ayurvedic herbal remedy, salai guggal – also can serve as 5-LOX inhibitors, and boswellic acid-enriched extracts are now available as nutraceuticals.[399-401] (There is however some question as to whether the clinical anti-inflammatory activity of these nutraceuticals reflects 5-LOX inhibition.) Since the evidence relating AD

to 5-LOX activity is very recent, there aren't yet any clinical trials that have assessed the impact of zileuton or boswellic acids on early AD; such studies now appear to be warranted. It has been suggested that a possible reason why NSAIDS haven't proven useful in treating AD is that these drugs tend to make arachidonic acid more available to 5-LOX, potentiating production of leukotrienes.[402] Intriguingly, joint administration of a boswellic acid inhibitor of 5-LOX and a cyclooxygenase-2 inhibitory drug for 15 days was reported to reverse age-related cognitive impairments in mice.[403] It should be noted that diets with a very high ratio of omega-3 to omega-6 can suppress production of pro-inflammatory leukotrienes by lessening arachidonic acid availability.[404]

Supporting Synaptogenesis – As we noted above, one of the key roles of DHA is to support the efficient production of new synaptic membranes required for memory formation. But DHA is not the only nutrient that can be rate-limiting in this regard. Richard Wurtman and colleagues, working with gerbils, have shown that brain availability of cytidine – a key cofactor required for the production of the phospholipids that constitute the bulk of neuronal membranes – can also be rate-limiting for synaptogenesis. Although the brain does not take up cytidine efficiently from this blood, it does efficiently take up uridine, which the brain rapidly converts to cytidine.[405] Wurtman's studies show that supplementing gerbils with uridine (as uridine monophosphate, an approved food additive) improves their performance in memory tests; this benefit is potentiated if DHA is administered concurrently.[98, 406, 407] Moreover, this strategy is associated with an increased level of dendritic spines – the receptive component of a synapse - in the hippocampus of these animals. Bioavailable sources of choline (see below) can also be beneficial in this regard, as choline is also a precursor for phospholipid synthesis. Hence, Wurtman recommends DHA, uridine monophosphate, and bioavailable choline as a strategy for improving memory function; clinical studies to evaluate this are underway.[408]

The compound orotate is of related interest. Orotate is a natural metabolite that, when ingested orally, is rapidly taken up by the liver and converted primarily to uridine, most of which is then returned to the bloodstream.[409, 410] Hence, orotate might function as an alternative to uridine monophosphate. Intriguingly, in a number of studies dating back to the 1970s and 1980s, European researchers reported that various complexes of orotate had favorable effects on memory in rodent models of cognitive dysfunction.[411-414] Magnesium orotate is of particular interest, as it appears to be clinically useful in congestive heart failure and in angina, common conditions in the elderly; uridine is likely to be the primary mediator of this benefit.[415-417] The dose of magnesium orotate which appears to benefit congestive failure is 3-6 g daily; if this dose produces enough uridine to benefit the heart, it likely also would produce enough to influence brain function.

Intriguingly, there are recent reports that supplementation which boosts brain levels of magnesium may also aid synaptogenesis. The compound threonate (a metabolite of vitamin C) may aid transport of magnesium across the blood brain barrier and increase the concentration of magnesium in cerebrospinal fluid.[418, 419] This effect has been associated with increased synaptogenesis and improved learning in rats. Whether threonate is unique in this respect remains to be seen; orotate, which has traditionally been viewed as a "mineral transporter", has not been evaluated in this regard.

Boosting Cholinergic Activity – The progression of AD tends to selectively kill and damage "cholinergic" neurons which function to release the neurotransmitter acetylcholine; loss of acetylcholine activity is responsible for much of the cognitive dysfunction in AD. Two compensatory strategies are

feasible – providing more choline to the brain, so that the remaining viable cholinergic neurons can make acetylcholine more efficiently, and inhibiting the acetylcholinesterase enzyme that terminates acetylcholine's bioactivity by degrading it. Each of these strategies has been avidly pursued clinically.

Taking straight choline is not a viable way increase brain choline levels, as free choline is inefficiently absorbed, and the unabsorbed choline is degraded by gut bacteria to generate a "dead fish" odor. The nutraceutical delivery vehicles for choline that have shown the most promise are glycerylphophorylcholine (a.k.a. GPC or choline alfoscerate) and CDP-choline (a.k.a. citicoline).[420] The former has received more clinical evaluation from the standpoint of cognitive impairment, whereas citicoline has been studied primarily from the standpoint of its ability to restore brain phospholipid levels following a stroke.[421] An overview of clinical trials with GPC suggests that it is indeed modestly beneficial for improving cognitive function in early-stage cognitive impairment, in a dose of 1200 mg daily.[422]

While choline is obviously required for acetylcholine synthesis, so is an acetyl group. Acetyl groups are generated in profusion by mitochondrial metabolism, but these need to be shuttled to the cell cytoplasm if they are to be used for acetylcholine synthesis. Carnitine is the carrier for this shuttle system, and this likely explains why acetyl-L-carnitine has been shown to boost the efficiency of acetylcholine synthesis in neurons.[251-253] This effect no doubt contributes to the improvement of cognitive function achieved with supplemental acetyl-L-carnitine in elderly people with eatly AD.

The first drug approved for treating AD, donepezil (a.k.a. Aricept), is an acetylcholinesterase inhibitor; other agents of this type that have been approved are tacrine, rivastigmine, and galantamine. Subsequently, scientists discovered that huperzine A, the active component of the herb Huperzia serrata long used to treat age-related cognitive dysfunction in China, likewise can inhibit acetylcholinesterase, and that its pharmacological properties are superior to those of donepezil.[423] An overview of numerous controlled Chinese clinical trial with huperzine A concludes that, in doses averaging 200 mcg twice daily, it is indeed effective for improving diminished cognitive function, and appears to be at least as effective as donepezil in this regard.[424] Furthermore, studies in neuronal cell cultures and in AD model mice suggest that huperzine A may have some neuroprotective properties not related to its abilities to inhibit acetylcholinesterase.[425-427] Huperzine A is now available as an affordable nutraceutical in the U.S. Acetylcholinesterase inhibitors are usually well tolerated in recommended doses, albeit an associated increase in the cholinergic activity of the GI tract occasionally induces symptoms such as nausea and vomiting.

The downside of choline-boosting strategies for cognitive dysfunction is that they do not affect the implacable underlying inflammatory process associated with AD, and they gradually lose their efficacy as the die-off of the cholinergic neurons becomes so extensive that the remaining viable neurons can generate too little acetylcholine to be worthwhile. Also, there does not appear to be any evidence that selective loss of cholinergic neurons is part of the normal aging process, so these agents may be primarily useful in early AD.[428] However, the possibility that huperzine A may confer neuroprotection indendent of its impact on acetylcholine merits further evaluation.

Decreasing Excitotoxicity – As noted above, the chronic stimulation of certain neuronal receptors (extrasynaptic NMDA receptors) by inappropriately elevated extracellular levels of the neurotransmitter glutamate is now suspected to be a major way in which amyloid beta perturbs the function and

jeopardizes the survival of neurons; this phenomenon is known as excitotoxicity and, in a starker and more acute way, also contributes to the brain damage inflicted by stroke. Caffeine may be beneficial in this regard by aiding control of extracellular glutamate.[429] However, the drug memantine, via suppressive interaction with NMDA receptors, can also aid in control of excitotoxicity, and has been demonstrated to slow cognitive decline in patients with mid-stage AD.[430] Indeed, aside from a group of cholinesterase inhibitor drugs of which donepezil is the prototype, memantine is the only other drug currently approved for use in AD treatment. Although it is only modestly beneficial for cognition, it does appear to slow subsequent atrophy of the hippocampus, and hence may be a quite worthwhile option as a follow up to cholinesterase treatment.[431, 432] It does not seem to be beneficial in early-stage AD, possibly because memantine only blocks NMDA receptors when they are very strongly activated.[433, 434] (Indeed, activation of synaptic NMDA receptors is crucial for LTP and memory formation, so memantine would be expected to worsen cognition if its inhibitory activity were non-selective.)

A key mediator of intracellular signaling by extracellular NMDA receptors is activation of the proteolytic enzyme calpain.[95, 435] Recently a drug inhibitor of calpain has shown remarkable benefit in AD moue models, without overt toxicity.[436-438] Perhaps this, or some analogous drug, will become available for clinical use in the future.

Neuronal Growth Factor Mimics – A particularly interesting recent development is the discovery by Emory University scientists that the flavonoid 7,8-dihydroxyflavone – which is said to occur naturally in tiny amounts – can directly activate a key neuronal receptor for BDNF, TrkB.[439] Activation of this receptor plays a key role in support of LTP, and also aids neuronal survival; thus, 7,8-dihydroxyflavone might be expected to have potential for promoting effective cognitive function and staving off neurodegeneration.[440] Another group soon showed that administration of this molecule reversed memory failure and suppressed expression of beta-secretase and of amyloid beta in an AD mouse model; and this molecule likewise is beneficial for normal age-related cognitive decline in rats.[441, 442] The Emory group has also identified another natural molecule, deoxygedunin from the neem tree, that can directly activate the TrkB receptor.[443] These discoveries are particularly exciting in light of the fact that direct administration of the BDNF neural growth factor is impractical, in that it does not penetrate the brain after intravenous administration, and also has a limited half-life.

Meanwhile, other researchers have discovered that sominone, a natural metabolite of withanoside IV found in the ayurvedic herb ashwagandha, can directly activate another neural growth factor receptor, RET.[444] 60 minutes after sominone was injected into normal mice, their memory performance was improved. These researchers soon followed up with evidence that sominone improved memory in AD model mice.[445] Unfortunately, withanoside IV per se is not currently available as a supplement, and the amount of ashwagandha extract required to provide an effective dose of this compound would likely be quite high.

Another feasible way to increase neuron-supportive growth factor activity in the brain is via intranasal administration of insulin.[446] In the many neurons which express insulin receptors, increased insulin activity could be expected to decrease phosphorylation of tau, and also increase the survival of stressed neurons.[447] Two recent pilot clinical trials have evaluated intranasal insulin (20 to 40 IU daily, for 3 weeks or 4 months) in patients with mild cognitive impairment or early AD; both doses were found to aid preservation of cognitive function and functional ability.[448, 449] These doses of insulin were well tolerated;

they did not detectibly influence blood insulin levels and hence caused no side effects related to low blood sugar. Further studies evaluating this intriguingly simple strategy are in progress.

Clearing Amyloid Beta from the Brain - Ashwagandha figures in another provocative recent study. Although much attention has been devoted to strategies to suppress amyloid beta synthesis, there is evidence that the accumulation of amyloid beta in the brains of AD patients may be more attributable to inefficient disposal of amyloid beta than to increased synthesis.[450] The brain has mechanisms both for degrading amyloid beta, and for expelling it into the blood stream. One of these latter mechanisms is dependent on expression of the protein LRP1, which is also expressed in the liver and enables uptake and degradation of amyloid beta from the blood.[451, 452] In a recent study, Indian researchers discovered that massive oral doses of a withanolide-rich ashwagandha extract markedly induced LRP1 levels in the liver of AD model mice, such that blood as well as brain levels of amyloid beta markedly declined.[453] This effect was associated with behavioral improvements in the mice. Sadly, the amount of ashwagandha extract employed in this study would be rather ruinously expensive if translated into a human dose, so it is not clear that this discovery has any practical import. Nonetheless, it does suggest that a more practical means of inducing LRP1 might help prevent and possibly control AD. A recent report suggested that the drug rifampin could induce increased LRP1 expression in cerebral blood vessels[454] – in nice concordance with a previous clinical study suggesting that it might be useful in early AD[455] - but unfortunately this drug failed to improve cognitive function in AD patients in a more substantial recent controlled trial.[456]

The uptake and degradation of amyloid beta fibrils by microglia, which contribute importantly to amyloid beta disposal, is dependent on the production of the apoE protein by astroglia.[457-459] Impairment of this mechanism may explain why people who inherit the variant apoE4 form of this protein are at greatly increased risk for AD.[460] Drugs which activate the LXR receptor, being evaluated as potential treatments for atherosclerosis, promote apoE production in the brain, and in AD mice decrease brain amyloid beta levels while improving cognitive function; these drugs are not currently approved for clinical use, however.[458, 460-463] Fortuitously, there is a report that the antioxidant nutrient taurine has the potential to at least mildly activate a form of the LXR receptor expressed by astrocytes; it therefore potentially might influence brain amyloid beta metabolism.[464] Taurine has not yet been tested in AD model mice, so this possibility remains hypothetical. The LXR receptor partners with the RXR receptor in inducing apoE, and a cancer drug which activates the RXR receptor, bexarotene, has also been reported to boost apoE expression and reduce amyloid beta levels in AD model mice.[465] Moreover, the diabetes drugs Actos (pioglitazone) and Avandia (rosiglitazone), via activation of the PPARgamma receptor, can increase expression of the LXR receptor, and hence may act indirectly to increase production of apoE.[466] These drugs have shown favorable effects on cognitive function and amyloid beta levels in mouse AD models, and hence may have some potential for AD control.[466-470] Pilot clinical trials evaluating their impact in patients with cognitive impairment have so far yielded mixed results.[471] In any case, this ongoing research bears watching. In light of evidence that rosiglitazone can increase heart attack risk in diabetics, pioglitazone would likely be the superior choice.[472, 473]

Overview and Provisional Recommendations

Every now and then we hear about the clinical results with another new drug-in-development intended to treat AD; more often than not, the results are equivocal if not downright disappointing.[474, 475] The fact is that AD is an extremely complex and still rather poorly understood disorder, for which mouse models are

a very imperfect replica, and it may be quite unrealistic to expect any single drug, new or old, to offer definitive and lasting benefit. More likely, effective prevention and treatment of this disorder will require a complex regimen of drug, nutraceutical, and lifestyle measures that address in a complementary manner a range of the dysfunctions that promote and sustain it. And it is increasingly recognized that attempting to control AD when it is already floridly symptomatic may be a losing proposition – AD is likely to be a disorder that it more readily prevented (or at least markedly postponed) than cured.[476] Proactive measures are also required for stroke prevention, and for optimal prevention of age-related cognitive dysfunction.

The foregoing discussion provides evidence that quite a number of measures, many of them reasonably practical, have credible potential for warding off cognitive decline and AD during aging. But it clearly would be impractical and quite likely inadvisable to implement all of these measures simultaneously – a triage strategy is evidently needed. I suggest that we classify these measures as first-line – recommended for use by healthy people before symptoms of cognitive dysfunction manifest; second-line – relatively practical measures which can be introduced when signs of cognitive decline first appear (or, in the future, when a doctor can detect incipient AD by novel diagnostic techniques); and third-line – measures which are less inherently practical or affordable, but which can be considered as options if cognitive dysfunction continues to worsen. First-line measures are intended to slow onset of age-related cognitive decline and AD, while decreasing stroke risk; they should also be expected to have a favorable impact on overall health. Provisionally (as no one truly has "the answer" to this vexing health conundrum), I suggest the following:

First-Line Measures – for primary prevention

- Mediterranean or plant-based diet, low in saturated fat, high in fruits and vegetables, moderate in salt and high in potassium;
- Aerobic exercise training
- Avoidance of obesity and diabetes (which should be aided greatly by the previous two measures);
- Anti-hypertensive therapy as needed (brain-permeable angiotensin anatagonists preferred);
- Effective antioxidant supplementation, including: spirulina – 15 g/day; astaxanthin – 4-20 mg/d; lipoic acid – 600-1200 mg/d; NAC or cystine – 600-1800 mg/d; taurine – 2-4 g/d
- Caffeinated coffee – as much and as often as you can without impairing effective sleep or inducing other unacceptable side effects
- Green tea and green tea polyphenols –several cups daily and/or several caps of green tea polyphenol extract (at least 500 mg of green tea catechins daily)
- Blueberry, pomegranate, and Concord grape juices, multiple servings daily (you may blend them if desired);
- DHA, 500-1,000 mg daily (from supplements or frequent ingestion of oily fish)
- Quercetin or cocoa flavanols, several times daily

Second-Line Measures – To be added to first-line measures when cognitive dysfunction first appears

- Acetyl-L-Carnitine – 2-3 g daily
- Melatonin – 3-10 mg at bedtime
- Fisetin – 200-300 mg twice daily
- Icariin – 180 mg, 3 times daily

- Magnesium Orotate – 2-4 g daily
- Glycerylphosphorylcholine (GPC) 400 mg – 3 caps daily; and/or Huperzine A – 200 mcg twice daily
- Zileuton – 1200 mg, twice daily; or Boswellic acid nutraceuticals
- Inosine – 1-3 g daily (for incipient PD or DLB – does to be titrated with physician supervision to insure that serum urate does not exceed 9 mg/dL; alkalinizing diet advisable)

Third-Line Measures – Options to consider as cognitive dysfunction continues to progress, with the cooperation and supervision of your physician

- Memantine – gradually tritrated up to 20 mg daily
- Lithium – dosage intended to maintain blood level of 0.25- 0.5 mM, as determined by your doctor (or recently described 300 mcg/d mini-dose regimen)
- Sodium selenate – 20-30 mg daily (note – potential for side effects)
- Tributyrin – 10 g 3 times daily (when and if available)
- Pioglitazone – 30 mg (may cause fluid retention; contraindicated in congestive heart failure)
- Intranasal Insulin – 20 IU once daily

This list is not exhaustive, and is admittedly somewhat subjective – no doubt other competent analysts would provide recommendations that differed in some particulars. The roster of phytochemicals which have been assessed in rodent models of cognition is very long and getting longer; it wouldn't be logistically feasible to take meaningful doses of all of the phytochemicals which have shown promise in these studies. (Those who would like to add grape seed extract, ginseng, ginkgo, ashwagandha, bacopa, etc. to their neuroprotective regimens are welcome to do so.[477-480]) It also should be acknowledged that many of the recommended measures might not be notably effective if tested as monotherapies in AD; rather, the hope is that, by addressing a number of different aspects of the AD syndrome simultaneously, the combination of these measures will provide worthwhile benefit. **In aggregate, these measures are intended to dampen microglial activation, provide comprehensive antioxidant support for healthful brain function, boost protective NO/cGMP function, block A2A adenosine receptors, inhibit leukotriene production, suppress amyloid beta synthesis, promote microglial disposal of amyloid beta, inhibit HDAC2 activity, inhibit tau phosphorylation, suppress the production and pathogenic impact of peroxynitrite, potentiate LTP, support acetylcholine activity, support efficient synaptogenesis, decrease excitotoxicity, promote efficient cerebral blood flow, and lessen stroke risk.**

It is greatly to be hoped that within the next few years one or more promising new drugs (or possibly 7,8-dihydroxyflavone?) will become available for AD treatment. But it would be rash to sit back complacently and expect that some future new drug will be "the answer" to AD. The smart thing to do is to start taking steps to protect your aging brain when you are still relatively young – or at least before frank cognitive dysfunction manifests. It bears re-emphasis that AD is a disease better prevented than treated. And that's obviously true of stroke as well.

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