

Some supplements of interest. Not to be a last word or a complete listing.

#### Curcumin :

A derivative of the spice turmeric . When combined with the black pepper extract, bioperine, or micronized, it is a reasonably well absorbed ,fat soluble , highly antioxidant/anti-inflammatory supplement . There are hundreds of studies now attesting to its value in treating and preventing chronic inflammation and its derived degenerative diseases. Animal modeled Alzheimer's pathology is prevented but also ameliorated by turmeric/curcumin , and epidemiological observations and recent early clinical studies and reports are encouraging. It is speculated that the lower incidence of Alzheimer's in India may be significantly related to the universally high, almost daily intake of curry, which contains both turmeric and pepper among its major ingredients.

'Greenmedinfo.com' is a major resource for due diligence on turmeric/curcumin, and many of the other supplements.

#### Vitamin D3:

Vit D3 has been shown to be at low levels [ $< 30$  nanograms/ml] in a majority of patients with all levels of Alzheimer's ,and for that matter ,also Parkinson's disease and Multiple Sclerosis. However it is also deficient to some degree in a large proportion of the general population. ,the result of the skin cancer precautions—avoiding the sun , use of sun screens [many of which paradoxically contain carcinogenic uv blocking chemicals] . Living at higher latitudes with the associated progressively lower UV exposure ,especially during the Fall ,Winter ,and Spring seasons is reflected in lower and lower Vit D3 levels.

This vitamin ,actually a cholesterol derived hormone, which we associate with calcium metabolism and bone health is also a very important immune modulator . It is a key actor in normal self-limited inflammatory processes , an important defense against infectious disease, but also helps protect one from inappropriate chronic inflammation. Its deficiency could well contribute to a susceptibility to many of the chronic degenerative [also autoimmune] diseases including those involving the nervous system, atherosclerosis and cancer, and as is well known ,osteoporosis. Supplementation with 5,000 to 10,000 iu /day is now more and more recommended to bring serum levels up to a healthy 50-90 ng/ml .

Therapeutic doses may need be higher but it is important to note that the major Vit D3 [not the much less effective D2] toxicity is soft tissue calcification which includes pathological arterial involvement [arteriosclerosis] and in particular coronary and also aortic disease.

This can be avoided and calcium /bone health enhanced by supplementation with Vit K2 [not K1, which is an important clotting system cofactor] . Some good evidence now indicates actual reversal of the arterial calcium involvement with K2

supplementation. The long acting fermented soy [natto] derived MK7 form in 100-200 microgram doses best.

Whether improved Vit D levels will prove of therapeutic value for Alzheimer's and other degenerative neurological diseases remains to be seen , but supplementation for those with low levels in the general population will boost one's immune protection systems and this has been associated with lowered incidence ie prophylaxis against many of the degenerative diseases most prevalent in Western nations.

The combination of Vit D3 and probiotics [see below] is a better defense against infection ,including the flu, than vaccinations which are hardly effective and frequently contain brain toxic mercury and aluminum compounds among others.

Vit B 12:

This key vitamin has been shown to be deficient in a significant proportion of our population, especially the elderly. Deficiency is associated with, as a rule , reversible deficits in cognition . Frank dementia is a late effect with some irreversibility even after supplementation.

Decreased stomach acid production as one ages, medicine suppression of acid production eg proton inhibitors- Prilosec etc , and depletion or blocking by some diabetic meds [metformin] ,and dietary insufficiency ,especially in vegans, all are possible etiologies.

Stomach acid and associated intrinsic factor production are necessary for splitting B12 from its bound form in food. Already separated supplements do not need the acid and intrinsic factor. Supplementation with 1000 micrograms /day of the methylcobalamine form appropriate for all elderly folks and all those with predispositions listed above.

Vit B Complex [all the B's]:

B deficiency in general is associated with cognitive decline for a variety of reasons.

Deficiencies in folate [Vit B9] and Vit B6 ,also B12,are associated with a pathological rise in a metabolite of the essential amino acid methionine, homocysteine ,a highly inflammatory substance, which has been considered a predisposition to Alzheimer's disease ,atherosclerosis and some cancers.

Vitamin B3 [the niacinamide form] has been shown in the last few years to prevent and reverse the mouse Alzheimer's model. Human studies are in progress.

Vit B1 [thiamine] deficiency is especially prevalent in chronic malnourished alcoholics, who have many reasons, acute and chronic, for cognitive decline, at least in part irreversible. The fat soluble form of B1, benfotiamine , is able to more easily gain access to neuronal tissue and has been shown also to be especially useful in improving diabetic associated peripheral neuropathy.

Aging is associated with decreased intake and absorption of the B vitamins so it is reasonable to supplement with a B Complex such as a B50 capsule which contains a goodly amount of all the B's, is cheap and without risk. Chronic heavy alcohol users and diabetics should add fat soluble thiamine [benfotiamine]. The multivitamin source of B1 is water soluble, making adequate therapeutic access to the brain and peripheral nerves more difficult.

Vit E [mixed tocopherol form and tocotrienols]:

Free radicals, the product of oxidation, cause an inflammatory response which as discussed, when chronic, is destructive to all tissues, the brain included. Vitamin E is a popular antioxidant and readily available.

Although the standard Vit E supplement, the alpha-tocopherol form has not been clearly shown to be of use for preventing or treating Alzheimer's disease, the mixed form including all the tocopherols and also tocotrienols, has been shown to be neuroprotective. A high gamma tocopherol form plus a tocotrienol supplement might be useful, although increasing intake of whole grains, nuts and seeds a good, if not better alternative. Palm oil [highest concentration of tocotrienols], coconut oil and oats are healthy sources of tocotrienols, and wheat germ oil [highest concentration of tocopherols], and coconut and grapeseed oils have good concentrations of tocopherols.

Vitamin A [Beta-carotene]:

Low levels of beta carotene [and also Vit C] have been found in early cases of presumed Alzheimer's disease and supplementation or dietary improvements have been recommended as possible prophylaxis. However, prospective clinical studies are necessary to confirm the observations and support the recommendation, and it is not clear that the lower levels were not developed after the onset of dementia and subsequent dietary deterioration.

Nevertheless, supplementation or dietary additions useful in general as these are both significant antioxidant/anti-inflammatory substances readily available in fresh produce and inexpensive supplements. Clinical studies of these vitamins have been well shown to bolster the immune system and modulate acute and chronic inflammation.

Fresh vegetables and whole fruit the best sources for both beta carotene and Vit C. Fruit juices a problem because of their high fructose content in the absence of whole fruit fiber.

Alpha Lipoic Acid:

This is a potent antioxidant and antioxidant regenerator and readily crosses into the brain. It has been shown on supplementation to significantly slow the progression of Alzheimer's disability in prospective, blinded studies. Supplementation by the healthy elderly could prove prophylactic.

It is a chelator of heavy metals [mercury, lead, cadmium and arsenic] and also elemental iron [when present in excessive amounts], all of which are all highly oxidative/inflammatory and toxic in many tissues including the nervous system.

### Magnesium:

Magnesium has been shown to be necessary in 350+ metabolic processes throughout the body. Tissue deficiency [99% of magnesium is in tissue --bones, soft tissue, while 1% is present in serum] is not reflected in the usual serum tests---magnesium serum levels are kept intact by leaching the magnesium from tissue so that depletion progresses slowly and is symptomatically undetected until functionally significant tissue deficits have occurred. Low serum levels when finally reached will be reflected by major and damaging magnesium deficits in brain, heart, arteries, and bones among others.

It has been confirmed that 50% or more of aged individuals have tissue magnesium deficiencies though only a small fraction will reflect this in their serum. This deficit is due to poor dietary intake caused by the Western proclivity for nutrition devoid of magnesium ---processed/junk food and also the increasingly scarce magnesium in produce raised in non replenished soil. It has been estimated that today only 30% of Americans have an adequate intake of magnesium.

High dietary intake of magnesium has been associated with a lower risk for dementia, while lower tissue levels have been associated with cognitive decline. A recent study at M.I.T. showed a clear cut improvement in basic memory parameters in aging laboratory rats fed chow supplemented with magnesium, suggesting a reasonably possible improvement would also be expected in the elderly with delayed recall problems or worse deficits.

Most magnesium supplements are poorly absorbed, especially the most available commercial form, magnesium oxide [2-4% absorbed] while other forms --magnesium malate, citrate, sulfate, taurate and glycinate are better absorbed. Magnesium threonate has been shown to most easily enter the brain, and was the form used in the above mentioned laboratory memory studies. It is readily available commercially.

Considering the widespread deficiency, supplementation with magnesium, especially the threonate form, is reasonable and there are few caveats. Too high a

dose will be heralded by GI upset, in particular diarrhea. A huge 20 gm dose of magnesium citrate in soda pop form is used to flush the bowel in prep for sigmoid and colonoscopies. For supplementation, doses in the range of 1 gm /day reasonable.

Tissue magnesium can be approximated with red cell levels while serum levels ,as mentioned , not as a rule helpful.

Resveratrol :

This is a potent polyphenol antioxidant/anti-inflammatory found in red grape skins [ red wine included],Japanese Knotweed ,blueberries, pomegranate ,peanuts, and raw cacao. It may be one of the reasons, when included with the overall Mediterranean diet, for the French Paradox, healthful longevity in spite of a diet high in fat [ turns out it is good fat as outlined above] ,and a fair amount of processed wheat --and a higher prevalence of smoking!!

Resveratrol supplementation has been shown to modify Alzheimer's beta amyloid pathology in the lab model ,and in preliminary human studies was associated with slowed progression of mental decline.

Its antioxidant/anti-inflammatory properties are likely the reason it is associated with decreased vascular disease and cancer. Also in the lab ,it has been shown to have the same life extending associated cellular mitochondrial effects as calorie restriction .

Resveratrol as also garlic, curcumin and coconut oil have been shown to have broad spectrum antibiotic effects, likely related to boosting immune defenses and some direct natural antibiotic effects.

It takes a lot of red wine, way too much, to get a significant dose of resveratrol ,but seeded grapes [the seeds in addition to the skins, have higher concentrations of resveratrol and other antioxidants] eg Concord grapes [also 100 % Concord grape juice] and seeded Muscadine [Scuppernong] and seedless red grapes reasonable sources as also other berries ,and raw cacao [less so processed cacao] which can be added to coffee which itself has antioxidant effects .

Supplements containing approximately 20 mg of grape seed and skin extracted resveratrol appear to be reasonable .

The best advice today re red wine [white wine with much lower antioxidant potency] is one glass /day for women, who have on average half the alcohol detox capability of men whose livers can handle two glasses.

Pure pomegranate juice a reasonable source , and its benefits likely outweigh the potential problem of high fructose which is not counterbalanced by fructose binding whole fruit fiber.

Ubiquinol , the reduced active form of Ubiquinone [CoQ 10] :

This is another multipurpose antioxidant which is important in the mitochondrial energy[ATP] production ,and not just in the brain but all cells in the body . It is particularly important in highly active , energy consuming tissues such as the brain and heart.

It is not surprising that deficits are associated with memory problems ,and also congestive heart failure.

All cells produce ubiquinol but as the years go by our ability decreases . Unfortunately, major factors today causing depletion of ubiquinol are the liver toxic statin drugs which block the synthesis of mevalonate , ubiquinol's precursor, in addition to blocking the formation of cholesterol , a maligned fat necessary for cell wall integrity in all body tissues including the brain---and cholesterol is also a building block for most hormones ,including the hormone Vit D3, and virtually all enzymes.

Almost one in three adults from middle age up ,in spite of the very modest if any prophylactic effect ,are taking one statin or another and very few are advised to supplement the depleted ubiquinol.

A very important observation on the basis of epidemiological observations is that the elderly with the highest cholesterol levels have greater longevity. Lowering cholesterol is not synonymous with health maintenance. Cholesterol ,in addition to its many other functions is actually an anti-inflammatory substance. Statins have a modest anti-inflammatory effect probably the reason for some of their very modest prophylactic effects. These effects do not come close to justifying the high incidence of damaging effects caused by depleting the extraordinarily important substances, cholesterol and ubiquinol.

There are many , many natural anti-inflammatory substances ,some of which we are discussing in this handout ,which have few or no downsides.

Fresh produce, preferably organic when possible, and many of the discussed supplements are far more effective anti-inflammatory choices than the broadly toxic statins ,and even the other cholesterol lowering medications.

If chronic inflammation is suppressed, cholesterol will drop because there will be less demand for it as an anti-inflammatory substance.

Omega 3 fatty acids :

In particular, docosahexaenoic acid [DHA] as contained in fish, calamari [squid] and krill,and some algae is important for brain development and integrity. It is a major component of neuronal cell walls. Epidemiological studies have linked high intake of omega 3 fatty acids, especially DHA, with Alzheimer's disease prevention.

Supplementation in mice bred to have Alzheimer's pathology has shown prevention and also reduction of the beta-amyloid plaques.

DHA and the other common Omega 3, eicosapentaenoic acid [EPA] have been shown to be cardio-protective, in particular against arrhythmias ---A recent highly publicized negative study claimed that fish oil is no better a prophylactic than placebo---the placebo was extra virgin olive oil, a proven cardio-protectant !!! Not surprising, the underwriter was a Big Pharma company.

If you do not supplement with one of these oils, eat lots of fatty fish, preferably wild caught, and the smaller ones are best eg sardines, herring, anchovies and mackerel, because they contain fewer heavy metals and PCBs. This is a bigger problem in the large, long lived pelagic fish such as swordfish, tuna species, marlin species, king mackerel, tile fish and shark. Wild caught salmon is a better choice and also contains natural astaxanthin[see below]. Most farm raised salmon and also tilapia are fed a diet deficient in Omega 3s, and also contain higher levels of other toxins including dioxins, PCBs, and antibiotics. The benefits of occasional farmed fish meals probably outweigh the risks, but regular use not advised.

Calamari oil has the highest DHA /EPA ratio and is readily available. High potency DHA containing fish oils are also available. Pure DHA from algae also available and is now an additive in most baby food formulae.

#### Astaxanthin:

This is the powerful antioxidant/anti-inflammatory which colors the flesh of salmon, krill and other shrimp, crabs and lobsters, and makes Flamingo's feathers pink. An artificial form is used to color farm salmon which do not have access to the natural algae-formed astaxanthin.

Laboratory studies have revealed improvement in memory tasks in aged mouse models and preliminary, clinical placebo controlled studies have shown improved memory functions at high [12 mg] doses. It has also been shown to reduce blood pressure in hypertension models, and reduces stroke damage when experimental subjects are pre-medicated.

These latter observations emphasize that the effects on brain structure and function of apparently useful substances are direct and indirect, and multiple.

Antioxidant/anti-inflammatory effects include prevention and amelioration of vascular [ischemic =decreased blood flow] disease and its downstream tissue damage effects[stroke], in addition to protection from other externally and internally caused direct nerve cell damage.

Also, it is difficult to separate primary Alzheimer's pathology and dysfunction from that caused by frequently co-existent small and large vessel, arterial insufficiency.

A major per cent of Alzheimer's involved brains also have diffuse amyloid infiltration of small arteries.

Interventions which prevent and improve arterial disease[atherosclerosis] overlap with those modalities useful for protection and amelioration of chronic brain degenerative disorders---not surprising as the major common denominator for both is chronic inflammation ,which is also involved in cancer susceptibility. It is not clear that interventions prevent or reverse the amyloid infiltration of brain small vessels but it would not be surprising.

#### Taurine [2-aminoethanesulfonic acid]:

This is an organic acid present in many tissues and is synthesized internally but predominantly sourced from foods ,especially eggs ,cheese, milk, red meat ,and seafood . Taurine deficiency is unusual, but possible in vegans as there is no taurine in the vegan diet. However, vegans may compensate by ramping up internal taurine synthesis when it is not supplied in their diet.

Taurine has been shown to have multiple prophylactic cardio-vascular disease uses, and has recently been shown to stimulate germ cell activity in the nervous system when supplemented, and is also associated with recovered learning and memory functions in Alzheimer's model mice . Clinical studies are not yet supportive. Among other attributes , it is a powerful antioxidant/anti-inflammatory. It also protects against toxic nerve cell calcium overload , a characteristic of brain blood/oxygen deprivation [stroke], but also degenerative diseases.

Regeneration of brain neurons has been traditionally considered unlikely, but this has been proven wrong ,and studies have now shown that modalities such as interval and resistance exercise increase germ cell activity, particularly in the temporal lobes ,an important part of the memory system. Taurine may now be added to a hopefully growing list of stem cell stimulators and regenerators [see nitric oxide reference below].

To 'an[organic] apple a day ' should be added 'one to two eggs a day' , cheese , plenty of seafood, and a modicum of grass fed red meat ,not overcooked ie rare. Dietary sourcing for taurine is best. Otherwise ,taurine supplements are widely available and cheap and might be tried therapeutically for folks with pathological memory and cognition problems.

#### Phosphatidylcholine [PC] :

This is the predominant phospholipid in the cell membranes of our neurons and also incorporates the important omega 3, DHA [see above]. It is also a source for acetylcholine ,one of the key neurotransmitters involved in memory functions.

Prospective clinical studies have shown that elderly individuals with lower initial levels of PC/DHA appear to have a greater chance of developing Alzheimer's disease over a twelve year observation. The study numbers have been too small to reach statistical significance. The separate DHA data are statistically more substantial.

Liver, eggs , peanuts and whole grains are good sources for PC and supplements are available and inexpensive ,but the clinical support for supplementation is not yet adequate.

#### Phosphatidylserine [PS]:

PS is also a significant component of neuronal cell membranes in the brain.

When supplemented some prospective studies have shown it to improve memory functions in the elderly and also Alzheimer's patients.

Originally PS was derived from cow brain, but the fear of Mad Cow Disease delayed further development and studies .

PS used in studies is now derived from soy and has no known downsides when supplemented.

Food sources of PS are fish and meat, especially organ meats and brain products, and high concentrations are present in eggs and soy beans [edamame]. Soy derived supplements are readily available.

#### L-Arginine/Citrulline:

L-Arginine and also its precursor citrulline are amino acid sources for nitric oxide .

Nitric oxide has a number of critical functions, the most studied being its function as a major micro-vascular vasodilator. But it is also has antioxidant/anti-inflammatory and other properties including stem cell activation and muscle growth generating creatine formation. Not surprisingly , arginine has been shown to be useful in treating and preventing vascular disease.

A role in preventing or ameliorating Alzheimer's pathology with supplemental doses of L-Arginine has been supported by laboratory models and also preliminary clinical studies. These are encouraging observations which need to be further supported and may be the result of the vascular , also antioxidant/anti-inflammatory properties of L-Arginine.

Athletes have been supplementing with L-Arginine for some time now. It is involved in the synthesis of creatine which is considered a muscle builder when supplemented; L-Arginine increases growth hormone release ; it is a vasodilator[nitric oxide]; has antioxidant functions which may help quench the free radicals formed during vigorous exercise.

L-Arginine also has been used with some success in erectile dysfunction [ED] presumably related to the nitric oxide vasodilation effect, also the presumed basis for the sildenafil [Viagra etc] lift.

Arginine deficiencies are rare. The body can make some arginine ,and it is a component amino acid in many foods including nuts, whole grains , seeds, chocolate ,meat and dairy products.

Forced deficiency diets have been important in delineating the functional properties of arginine and its semi-essential need ie there needs to be some supply from diet.

The salutary effects cited above are based on supplemented therapeutic doses ie up to several grams/day. Similar doses of L-citrulline might be more effective than L-arginine because of citrulline's longer time curve of action.

#### Acetyl-L- Carnitine:

L-Carnitine is a molecule important for fat derived cell energy and has been shown to be especially useful in treating congestive heart failure. It does not easily get into the brain , however the Acetyl-L-Carnitine form does.

Intuitively one would predict it to be useful in improving or preserving cognitive function, possibly slowing down Alzheimer's deterioration. Some clinical studies have been positive, and old rats supplemented with Acetyl-L-Carnitine and added lipoic acid [see above] had significant memory improvements and histological evidence for increased synapse formation [neuronal connectivity in the brain].

Sources other than supplements are eggs, beans , especially kidney beans, and dairy products.

#### Coconut oil :

This is the latest 'miracle' food substance with a massive supportive literature related to its health benefits [lots of references worth researching on line]. It is predominantly a medium chain saturated fat ,and has been vilified by the medical establishment for at least three decades- huge mistake and scam. Saturated fat intake hardly, if at all, increases cholesterol and cholesterol itself is not a demon, but a substance without which we cannot survive [see discussion above].

Alzheimer's deterioration is associated with insulin resistance in the brain and therefore defective ability to utilize glucose which is the major energy source for brain neurons. For this reason Alzheimer's is now called Diabetes type 3 by some. Nasal insulin spray application, with its quick access to the brain, has been shown in preliminary studies to improve memory functions in Alzheimer's patients.

Another approach would be to increase the presence of ketones derived from fats. Ketones are another and efficient energy source for brain neurons and can replace glucose and are not dependent upon insulin for entry into neurons. A ketogenic high saturated fat intake-eg coconut oil - has been anecdotally associated with some dramatic improvements in cognitive function in Alzheimer's patients.

Further studies are needed and in progress , but an increased intake of good oils is highly recommended for general health including coconut and palm oils, extra virgin olive oil, nut oils and Omega 3s [especially seafood derived]. Unfortunately, the essential omega 6s are a markedly excessive part of the modern Western diet and ,as discussed , are inflammatory .

#### Probiotics:

Approximately 100 trillion microbes, mostly bacteria [1,000 plus different species] inhabit the normal human bowel. This is an impressive three times the estimated human body cell count.

Recent studies are revealing the major contribution to health made by these fellow travelers. It is estimated that these microbes and their interactions with the bowel represent 70-90% of our immune system. This is another example of the evolutionary importance of bacteria in our development and maintenance as a species ---Even our mitochondria ,the cell organelles in the center of energy production are thought to have been developed from cohabiting bacterial forebears.

The health of this so called bowel microbiome is now considered an important issue. A reflection of this is the now well accepted advice to replenish healthy bacteria with probiotics [live bacterial supplements] during and beyond antibiotic therapy which depletes ,if not destroys both normal and less healthy bacteria. The

latter may become predominant without supplementation, and lead to significant immune system weakening and subsequent problems throughout the body.

A nervous system/bowel biome interconnection is becoming recognized. A recent study by researchers at UCLA showed a salutary effect of live culture yogurt on brain activity during emotional challenges.

It has been suggested that bad species of bacteria ,possibly also gluten[see 'Grain Brain' text by neurologist David Perlmutter MD] in some , can break down the normal gut permeability causing a generalized inflammatory response , then immune reactions to normally excluded substances which may have molecular characteristics similar to normal tissues ,including the nervous system among many others. A multitude of symptomatic pathologies are possible. Brain effects might well contribute to or trigger degenerative changes such as Alzheimer's pathology and Parkinson's disease among others.

A study, also at UCLA ,of a small number of subjects [10] with various stages of dementia showed partial or complete reversal of symptoms in 9 of the 10 subjects after a few months.

A combination of probiotics , Vit D, DHA [OMEGA 3] supplementation was the experimental regimen which adds support for the value of a normal bowel flora for helping to maintain cognition.

Whether or not of major prophylactic and therapeutic value for use in cognitive decline , it is now clear that maintenance of a normal gut microbiome is important for the maintenance of bowel integrity and health in general. A daily probiotic supplement is advisable and best taken with water prior to eating to avoid the bacteria destructive effects of stomach acid formation. Otherwise fermented foods - eg sourcroust ,kimchi, live culture plain [non sweetened] yogurt and kefir - are heavily concentrated and excellent sources of normal bacteria. Also, a good intake of fiber rich foods is beneficial for the health of the microbiome.

### Epilogue:

It is apparent and suggested by the dramatic UCLA study that one should not look for a silver bullet to prevent or treat cognitive decline. If chronic and inappropriate oxidation/inflammation ,which as we have seen is triggered and maintained by many preventable influences, is present, a broad approach to health maintenance and longevity is appropriate .

The life style changes recommened are a good starter, and before launching into added supplements, further due diligence is a must. The Greenmedinfo.com site is a good takeoff point . It is an excellent well referenced resource. There are many other useful sites. Keep in mind that some of them recommend and sell various supplements and this can be a conflicting influence.