CHAPTER 25

COGNITIVE ENHANCERS AND NEUROPROTECTANTS

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SUMMARY

It has taken us twenty-five chapters to finally reach this point: the drugs and supplements that might actually enhance cognition, or, at least, prevent cognitive deterioration. We have already dealt with the psychostimulants, of course, but they are such troublesome drugs, and have so many side effects. They are not drugs one prefers to take, or to prescribe, unless they are absolutely necessary.

One reason we have reserved this issue for an antepenultimate chapter is because the evidence-base to support "cognitive enhancement" is so weak. Clearly, the cholinesterase inhibitors have positive cognitive effects, but only in patients with dementia, and only for a while. They do have stimulant-like effects in brain injury patients. But they are rarely, if ever effective for people with mild learning disabilities or ADHD; this is usually a good test for any drug that proposes to be a general cognitive enhancer.

Nicotine, the neuropeptides and the glycinergic prodrugs have all been proposed as cognitive enhancers. They are all interesting compounds, theoretically, at least, but their clinical utility is marginal. Piracetam and its congeners are also said to be "nootropic drugs." Piracetam has little theoretical support, and even less empirical support.

On several occasions we have raised the issue of free radical generation, oxidative stress, and the utility of antioxidant supplements. This chapter is an opportunity to amplify those remarks, and to examine the wider utility of the antioxidants. If they are protective against age-related cognitive decline and dementia, we all should consider taking them regularly. Brain injury patients, and mentally retarded people, who are more vulnerable to age-related cognitive decline, and more likely to develop dementia, might be well advised to take antioxidant supplements.

For generations, general physicians have recommended B vitamins, especially vitamin B12, for vague and nonspecific neuropsychiatric symptoms. This venerable practice has been criticized in the past, but it does have a theoretical basis, and at least some empirical support as well. We shall venture to propose a defensible regime of "neuroprotective" vitamins and supplements that the reader should entertain for his or her neuropsychiatric patients. The author, at age 57 a *bona fide* neuropsychiatric case, uses this combination himself.

The omega-3 fatty acids (fish oil) have won a good deal of attention recently for their putative effects in depression and bipolar disorder. Less well-appreciated are their role in brain development and recovery from brain injury. When I was a kid, the old people in my neighborhood used to refer to fish as "brain food." How did they know?

Should everyone over forty be taking daily aspirin, ibuprofen, celecoxib, or gingko biloba, to prevent dementia? Should we recommend them to our patients? Read on and see.

COGNITIVE ENHANCERS AND NEUROPROTECTANTS

Psychopharmacology has been concerned almost exclusively with the treatment of mental illness, the alleviation of psychiatric symptoms, the control of untoward and maladaptive behaviors. If improving cognition were at all at issue, it was a by-product, as it were, of improving the patient's overall mental state. The thoughts of a psychotic patient are disorganized and loosely connected, and the patients are highly distractible; "distracted" is a good old English word to describe a patient who is mentally ill. Treating such a patient with an antipsychotic drug usually corrects the patient's cognitive impairment, just as it alleviates the rest of his or her psychotic symptoms. But no one is going to suggest that antipsychotic drugs are "cognitive enhancers."

Patients with depression or anxiety disorders frequently complain of cognitive impairment. Inability to focus or concentrate, distractibility, poor memory, cognitive slowing and mental fatigue are common symptoms of these disorders. When depressed or anxious patients are given neuropsychological tests, the psychologist has to work hard to obtain a valid result; even so, test scores are frequently depressed. After the patient is treated successfully, test scores return to premorbid levels of function. Still, no one would suggest that antidepressants or anxiolytics are "cognitive enhancers."

A **cognitive enhancer** is a neuroactive substance that elevates an individual's cognitive abilities, in a meaningful and sustained way, above and beyond that individual's basal level of performance. Another term that is sometime used, especially in Europe, is nootropic drug. In everyday life, normal people – who don't have psychiatric disorders or cognitive disabilities – seek drugs, herbal remedies or nutritional supplements, to improve their memory, their ability to concentrate, or their clarity of thought. People concerned over the mild memory impairment that occurs in "benign senescence" are especially likely to seek out such "treatments." Ginseng Panax and Gingko Biloba are two popular remedies, so-called nutraceuticals, that are quite popular for just such an effect.

In spite of all the attention given to "cognitive enhancers" in the popular press and the "health-food" industry, in all of medicine, there are only two classes of drug that are proven cognitive enhancers, and even they operate within sharply circumscribed boundaries. They are the psychostimulants and the cholinesterase inhibitors. Their conventional indications, as the reader knows are ADHD and dementia, respectively, but they are also given to patients with cognitive impairments from other causes. Stimulants and cholinergics are often prescribed for BI patients, sometimes to good effect. Stimulants are cognitive enhancers for normal people, at least to a degree, but they are only occasionally helpful to mentally retarded or autistic patients. The cholinergics, on the other hand, do not improve memory performance in normal subjects, but they may have a role for some mentally retarded patients.

A **neuroprotectant** substance is a drug, a nutraceutical, or a dietary supplement that protects nerve cells from damage, either from pathological events, like the excitotoxicity that attends stroke or brain injury, or from normal biological stressors, for example, the generation of free oxygen radicals. There are a host of substances with proven neuroprotectant ability, at least *in vitro*. Deprenyl, for example, is said to retard the progression of Parkinson's disease. Vitamins C and E are protective against oxidant stress.

Research on neuroprotective agents is frequently addressed to the problem of acute ischemic injury in animal models or in humans with stroke. A large number of new compounds have been developed, and are under investigation; a minimum of 800 such trials are currently

underway (1). The pharmacological strategies are diverse and wide-ranging: drugs that inhibit lipid peroxidation or apoptosis, glutamate antagonists, GABA agonists, sodium and calcium channel blockers, and so on (1-4). None, so far, have worked their way into the pharmacopoeia, or have engaged the attention of practitioners. A drug that controlled the neurotoxic events that arise immediately following stroke or brain injury would be welcome, indeed. But it would still be necessary to evaluate its effects over the longer-term, in chronic conditions associated with deterioration over time.

Of course, the best cognitive enhancer is a well-chosen treatment for a specific neuropsychiatric condition. The appropriate treatment of depression, organic affective disorders, anxiety states, psychosis, chronic pain, epilepsy and psychosis is almost invariably associated with a degree of cognitive improvement, simply because these disorders compromise intellectual functions, sometimes to a remarkable degree. And the second best cognitive treatment is withdrawal from an unnecessary or an inappropriate drug. Antidepressants, mood-stabilizers, anxiolytics, antiepileptic drugs, analgesics, antipsychotics and antispasticity drugs all have the potential for cognitive toxicity. Even the newer agents do. "Neuroprotection" is not an established property of any of the current psychotropes, but appropriate treatment of a psychiatric disorder will certainly prevent secondary deterioration. On the other hand, some neuroactive drugs, like phenytoin and neuroleptics, are known to be neurotoxic, at least in certain circumstances, and should be avoided, if at all possible.

Patients with brain injuries or developmental handicaps are obvious candidates for cognitive enhancement. They are good candidates for neuroprotection because they are more vulnerable to mental deterioration and dementia. What, then, do we have for these purposes, beyond optimal psychopharmacology and the measured avoidance of potentially neurotoxic compounds? Is there anything more credible than the exaggerated claims of the "smart drug" set? Not very much, if one is seeking evidence-based recommendations. A good deal, is one is gullible, or optimistic – choose the adjective that you think fits.

We have already discussed a few candidates: the psychostimulants, the dopamine agonists and the glutamate antagonist amantadine have been discussed in chapter 18; deprenyl, with the antidepressants in chapter 19; "megavitamins" and Vitamin B_6 in the autism chapter (chapter 14). This chapter will round out the discussion: the cholinergics, neuroactive peptides, "nootropics," glycinergic "prodrugs," a few more vitamins, fish oil, NSAID's and gingko biloba.

CHOLINERGIC DRUGS

Drugs that enhance acetylcholine neurotransmission have always been problematic, as far as psychiatrists are concerned, because (a) they may be depressants and (b) they may aggravate parkinsonian symptoms. Those effects are still to be kept in mind, as cholinergic drugs are used more frequently for the treatment of memory disorders, in people with dementia, with stroke or brain injury, or, more recently, with "benign senescence" and ADHD.

The earliest attempt to correlate recovery of cortical function with cholinergic stimulation was made in 1928 when Chavany advocated the use of acetylcholine in the treatment of hemiplegia (5). Positive effects with acetylcholine injections in hemiplegic patients, aphasics, and other neuropathic cases were at first attributed to cerebral vasodilatation. Subsequent research was conducted by Luria (6) and by Ward and Kennard (7) at Yale, during the Fulton era.

This venerable treatment is still current. Indeed, it is central to pharmacological development for dementia in general and for Alzheimer's disease in particular. It is a rational treatment, insofar as it mitigates the deficit in cholinergic neurotransmission that stems from deterioration of cholinergic neurons in the basal forebrain of Meynert (8). Because acetylcholine

is an important neurotransmitter in the physiology of memory and attention, and because deficits in acetylcholine systems are found in amnestic patients and patients with attentional disorders, it was appropriate to explore the potential utility of cholinergic drugs in treatment (9). Because memory impairment is a major element of TBI, cholinergic treatments have been brought to bear in that group as well, with positive effects in at least one study (10).

Luria, the great Russian neuropsychologist, used a cholinergic drug called galanthamine in some of his brain-injured patients (6). Galanthamine is a long-acting acetylcholinesterase inhibitor that was never available in North America until very recently. Clinical scientists who were interested in exploring the clinical utility of cholinergic drugs, for example in Alzheimer's disease, were forced to rely on short-acting parenteral acetylcholinesterase inhibitors, like phisostigmine, acetylcholine precursors (e.g., lecithin), and direct muscarinic receptor agonists. However, "despite several years of clinical attempts to improve geriatric cognition, no *therapeutically* useful results have been demonstrated with cholinergic agents" (11, p. 427). Combined treatment with an ACh precursor and a cholinesterase inhibitor had more utility than treatment with either compound by itself (12,13), but even that approach was more theoretical than practical before the oral acetylcholinesterase inhibitors were available.

Tetrahydro-9-aminoacridine (THA) was the first such drug to be used in North America. THA is a potent central-acting anticholinesterase that can be administered orally. It has a longer duration of action and a more favorable therapeutic index than physostigmine (14). It was the first cholinergic treatment ever to attain clinical utility. Long-term treatment of demented patients with THA led to significant improvement in patients' general clinical status and learning ability. It was a palliative treatment that alleviated some of the symptoms of Alzheimer's disease. It did not, however, alter the ultimate course of the disease (15); none of the cholinergic drugs do. The utility of THA was sharply limited by its expense, the risk of hepatotoxicity and the cost of monitoring, the severe nausea that often occurred, and the time required for titration to a therapeutic dose.

Virtually all of the published THA research was been concerned with demented patients. Its effectiveness for other categories of memory-impaired patients was never tested systematically, but many clinicians (including the author) used it in the occasional stroke or TBI patient. In clinical practise, the results of THA treatment were generally positive, though modest, just as they are for demented patients. Side effects, cost and the time commitment necessary to evaluate the drug were as limiting for TBI patients as they were for demented patients.

When a TBI patient responded to THA the effect resembled that of the psychostimulants. The patient seemed to be more activated and alert, cognitively faster, more attentive and more energetic. There has never been a head-to-head comparison of THA, or of any cholinesterase inhibitor, to a stimulant, in any class of patients, but it would not be surprising if their spectrum of activity overlapped.

THA was an important drug in its day, but it has been eclipsed by the recent development of alternative cholinesterase inhibitors that are just as effective, better tolerated and easier to use. These include donepezil (DNP), rivastigmine, metrifonate and galantamine (16,17). DNP is also a reversible inhibitor of acetyl cholinesterase, with significant advantages over THA. It has a longer half-life, so once-daily dosing is possible. It has no serious toxicity save in extreme overdose. Its effects are manifest within weeks, rather than months, and it is at least as effective as THA (18). DNP may well prove to be the first cholinergic drug to achieve wide use, even among general practitioners. Indeed, the manufacturer has undertaken to market the drug directly to the public.

The newer cholinesterase inhibitors all share these advantages, and they are probably equally effective. They are used, of course, for demented patients, where they are often good for a year or two of stability (i.e., no deterioration), if not a degree of improvement. Some of the

behavioral and emotional problems of demented patients also improve with these drugs. They are also used for stroke, multiple sclerosis and TBI patients, and even for patients with age-related memory decline (19-21). Small, open trials with DNP in Down syndrome have been encouraging.

In the course of his clinical practice, the author has had the opportunity to observe the effects of DNP and rivastigmine for some “off-off-label” indications, like ADHD and refractory depression. They are well-tolerated, even by children, but not particularly impressive. They are not likely to be “broad-spectrum” psychotropics, like valproate, oxcarbazine, lamotrigine and the SSRI’s. Down syndrome and TBI are the most promising new arenas for the cholinesterase inhibitors; for dementia prevention, perhaps, and for improvement in attention and executive functions. The latter effects may prove to be more impressive than their specific effect on memory.

NOOTROPES

“Nootrope” was coined to describe a class of drugs that improve "higher cognitive function." The term was invented by Guirgea, who developed **piracetam**, the alleged "memory drug," described as the first of a new class of nootropic psychoactive drugs. Indeed, there have been a number of related compounds introduced in the subsequent twenty years (e.g., pramiracetam, oxiracetam, aniracetam, nefiracetam). Their mechanism of action, if they have one, is unknown. They were originally thought to enhance “cerebral energy metabolism” and were also referred to as “antihypoxidotics.” It is also possible that they are mildly cholinergic or anti-GABAergic, or protective against excitotoxicity, or that they interact with a “steroid-sensitive memory system” (22-24).

Piracetam has been reported to facilitate learning in animals, to limit the decline in human performance associated with cerebral hypoxia, and to improve cognitive performance, alertness, fatigue, and psychomotor retardation in aged subjects (25). It is said to improve verbal learning in normals (26) and dyslexics (27). It may ameliorate memory deficits in 10-30% of patients with dementia or slow the progression of the disease (22,28,29). Clinical trials of piracetam for dyslexic children were conducted in the United States, and although there were some indications of treatment success, the evidence was not very strong (30).

Pramiracetam is another “cognition activator,” which, in various behavioral models and electroencephalographic studies is found to be "superior" to other drugs marketed for cognitive disorders in the elderly (31). Pharmacologically, it may be cholinergic and also an indirect dopamine agonist. Like all the “nootropics,” it is well tolerated and apparently successful in improving the affective and behavioral symptoms of dementia: learning/memory, motivation, depression, anergia, and the ability to perform activities of daily living (32). *Apparently* successful, it is important to emphasize.

Piracetam and its congeners are not available in the USA and there are no plans to market them anytime soon. It has always been the author's opinion that they will not be missed. Yet they remain favorites of the “smart drug” set, people who buy “cognitive enhancers” from pharmacies abroad to improve their day-to-day intellectual performance. And one continues to read of successful trials of piracetam in the wide range of neuropsychiatric conditions, including myoclonus (33), epilepsy (34), aphasia (35) and stroke (36,37). It never seems to go away. Maybe there is something to it.

A recent meta-analysis of piracetam in 1002 stroke patients indicated no benefit whatever (38).

NEUROPEPTIDES

Twenty years ago, there was intense interest in the therapeutic potential of various neuroactive peptides, driven by the discovery that the pituitary peptide hormones **adrenocorticotropin** (ACTH) and melanocyle-stimulating hormone (MSH) exerted a "trophic" influence enhancing the metabolic activity and the viability of their target cells. These effects include enhanced blood flow in the target region and stimulation of macromolecular (RNA/protein) synthesis (39). The brain and behavior effects of the melanocortins (ACTH, MSH) were thought to result from peptide effects on neurons and/or glial cells, similar to the peptide-target cell interactions that are known to occur in peripheral tissues. The idea that the melanocortins might enhance adaptive neural responses to injury was tested, and won at least a measure of support, in preclinical studies employing the following preparations: peripheral nerve damage, hippocampal plasticity, recovery from brain injury, and “behavioral plasticity” (39).

Some neuropeptides, notably ACTH, MSH, and vasopressin, were shown to affect the learning process, particularly in animals (40). Subsequent work demonstrated that the heptapeptide **ACTH 4-10**, a peptide fragment common to both the ACTH and the MSH molecular structures, was responsible for the learning effects of these compounds (41,42). In human volunteers a synthetic fraction of ACTH (ACTH 4-10) seemed to improve visual memory, enhance alertness, and increase motivation -- all without the hormone's usual endocrine effects (43). Yet, in another such study, the effects of ACTH 4-10 were negative (44) and clinical studies have been inconclusive (45-47).

There were also studies of **vasopressin** and other posterior pituitary hormones. The idea was that vasopressin, like ACTH 4-10, might modulate some aspect of the learning/memory process (43,48). The long-term effects of vasopression and **oxytocin**, another posterior pituitary hormone, indicated enhanced learning and memory consolidation in laboratory animals (49). However, it was not possible to extend the results of laboratory research to the clinical arena. Well-constructed clinical studies of neuropsychiatric patients, including TBI cases, have not supported the idea that vasopressin improves memory performance (50). On the other hand, elderly patients treated with vasopressin performed better in tests involving attention, concentration, and motor speech, and better in tests of memory (49). It is possible, however, that vasopressin peptides exercise positive effects on psychological performance, not through any direct nootropic effect, but indirectly, by improving mood, motivation, or alertness (51). Intranasal vasopressin promotes sleep time and improves sleep architecture in elderly patients, too; that alone may explain its (putative) cognitive benefits (52).

The tripeptide **thyrotropin-releasing hormone** (TRH) has been shown to improve long-term neurological outcome following experimental spinal cord injury in cats (53,54). TRH has also been successful in improving recovery from experimental brain injury in animals (55-57). DN-1417, a TRH analogue that is long acting, and not as potent in stimulating the endocrine system, has been shown to promote recovery from concussive head injury in mice (58). In experimental animals, it is anti-amnesic and pro-arousal (59). It has inhibitory and excitatory effects when applied to individual neurons; it interacts with a number of neurotransmitters, including NE, DA, 5HT, Ach, GABA and glutamate (59,60).

In Japan, TRH infusions are sometimes prescribed to enhance recovery in TBI patients. TRH and its analogs have also been used in patients with Alzheimer’s disease (61,62), vascular dementia (63), in cognitively impaired alcoholics (64), in epilepsy (65) and in the post-ECT state (66). But because TRH can only be given as continuous infusion, pharmacological analogues with a longer half-life and the potential for oral administration will be required before clinical trials can be run (67). Indeed, little parenterally administered TRH ever reaches the brain, because of its rapid metabolic clearance, and its limited ability to cross the blood-brain barrier (60). The author’s experience with TRH is limited. But it is safe to try, with virtually no side effects, and it

may conceivably exercise a degree of benefit. It may, for example, reverse glutamate-induced excitotoxicity (68); it may also stimulate nerve growth factor (69).

Nerve growth factor (NGF) is a protein of known sequence and structure, a neurotrophic factor for central cholinergic neurons (but not for central catecholaminergic neurons). In animal studies NGF "preserves" cholinergic neurons from lesion-induced degeneration, and improves learning in rats with cholinergic septohippocampal lesions (70). NGF is hard to test in human patients with brain disorders associated with cholinergic deficits, such as Alzheimer's disease, because the protein cannot cross the blood-brain barrier, but intraventricular infusions have been done, "with potentially beneficial effects" (71). The side effects outweighed whatever small benefit accrued, however. It is possible that compounds exercising NGF-like effects may at some point be a rational treatment, but their time has not yet arrived.

The neuro-active peptides are included in this chapter largely out of historical interest. Research on their neuropsychiatric effects has largely faded from the scene. Not because their effects are meaningless, or that the preclinical studies are irrelevant; but probably because the technology does not yet exist to harness their effects in a clinically meaningful way.

GLYCINERGIC PRODRUGS

Vitamin B_{15}, or pangamic acid, is something that was isolated from apricot kernels and other natural sources – a mixture of substances, its exact composition never precisely defined, yet effective nevertheless for a host of diseases of the skin, respiratory tract, nerves and joints. Or, at least, the people who sold it said that it was, and some credulous journalists did, too. In fact, it was first extracted by Ernst Krebs, the physician who gave us laetrile. Two of the constituents of this ersatz vitamin, though, are glycine and N,N-dimethyl glycine (DMG)(72), and they deserve a measure of attention here.

The amino acid glycine is an important inhibitory neurotransmitter in the brain. For example, it potentiates NMDA receptor neurotransmission, and thus inhibits dopaminergic neurons in the substantia nigra, and modulates DA release (73). In contrast, phencyclidine ("angel dust") is an NMDA antagonist, and a drug that causes psychosis. It is necessary to mention phencyclidine because a theoretical model has been based on its psychotomimetic effect, and that inspired a series of NMDA augmentation strategies for the treatment of schizophrenia. This new avenue for treatment research is still quite active. Glycine, DMG and D-cycloserine (a glycinergic agonist) have all been explored as potential treatments for schizophrenia because they are NMDA augmenters. The results have been mixed, thus far.

Glycine exerts a profound inhibitory effect on non-dopaminergic cells in the substantia nigra, possibly on interneurons that control the diffusion of generalized seizures (74). In fact, DMG, an analog of glycine that is probably better able to penetrate the blood-brain barrier, was once claimed to be an effective treatment in refractory epilepsy (75). Subsequent studies, however, have been disappointing (75,76).

DMG is widely available in "health-food" stores. It is supposed to stimulate the immune system and to improve athletic endurance (77,78). The autism community has embraced it, for reducing behavior problems and enhancing communication in autistic children. The author has not been impressed with the results he has seen.

D-cycloserine is thought to be a "nootropic" drug, a cognitive enhancer, on the basis of preclinical studies and clinical studies in patients with Alzheimer's disease (79-82). It may also have anti-seizure potential (83-85). D-cycloserine was found to enhance recovery from

experimental TBI in rats (86). A multi-center, controlled study of gavestinel, a selective glycine agonist, had no more effect than placebo in 1367 patients with ischemic stroke (87).

D-cycloserine is a prescription drug, but glycine and DMG are freely available over-the-counter. Physicians, then, are likely to encounter patients who are taking DMG, or giving it to their children, in hopes that it will correct a cognitive or a developmental weakness. It is probably a harmless drug, if one can call it a drug, and it is not an outlandish thing to try, but there is little scientific evidence to support its use. It is a good idea to pursue investigations of NMDA activators like the glycinergic "prodrugs," but there is no basis for recommending them to patients at this time.

THE THEORY OF OXIDANT STRESS

The uncontrolled production of free radicals is a primary cause of many pathophysiological reactions, but since oxyradicals are difficult to study, their role as etiological agents was viewed with a certain amount of skepticism (88). However, the development of new experimental methods has generated evidence that oxidative damage does occur to tissue in the development of a number of pathological states, like stroke (88), Parkinson's disease (89), brain injury (90), Alzheimer's disease and aging (91). Lipid peroxidation by free radical reactions is now thought to be a basic deteriorative process in a variety of pathological conditions, such as atheroschlerosis, degenerative arthritis, cataracts, irradiation syndrome and trauma (92).

There is agreement that oxidative stress is associated with neuronal degeneration under acute pathological conditions, like stroke and brain injury, and also in brain aging. It is an intuitive concept, since life span in animals is inversely proportional to the basal metabolic rate, i.e., the rate of oxygen consumption, and is directly related to the extent of oxygen radical scavenging systems (93). Tissue damage due to oxidative stress accumulates with age (94). Since oxidation is a ubiquitous phenomenon in the aerobic environment of biological systems, and since the damage it may cause at a molecular level is so fundamental, there is no apparent limit to its potential relevance. And because oxidative stress may be attenuated, the theory opens avenues for pharmacologic manipulation.

The theory of oxidative stress has been related to the phenomenon of aging, and to the pathophysiologic conditions that are associated with aging, like atheroschlerosis, dementia, parkinson's disease, senile cataracts, degenerative arthritis; and to catastrophic events that are more likely to occur in older people, like cancer, stroke and, coronary artery disease. Relationships are usually drawn from preclinical studies, that demonstrate oxidative events as a component of the pathological process, or that suggest oxidative stress *may* be a component. Epidemiological studies indicate the favorable effects of a diet that is rich in antioxidant micronutrients. Treatment studies support the utility of antioxidant drugs or supplements in the prevention, treatment or attenuation of the disorder. Oxidative stress, however, remains no more than a theory. Preclinical studies are only suggestive, and epidemiological studies are never more than correlative. The treatment studies have never been conclusive. So, no one can say that antioxidants are, in fact, therapeutic (or preventative) for anything. At least, no one can say that *now*.

Oxidative stress is a threshold reaction that occurs when antioxidant defenses are overwhelmed. The chain reactions that characterize oxidative stress stop when two free radicals react with each other or when they are quenched by reacting with an antioxidant. The major antioxidant defense systems include enzymes like superoxide dismutase, catalase and glutathione peroxidase; and chemical reductants like ascorbate (Vitamin C) which is water soluble and present in the cytosol, and α-tocopherol (Vitamin E), which is lipid soluble, and localized to lipid membranes (94). The chemical antioxidants act by donating a hydrogen atom to

the radical, and simultaneously a stable tocopherol or ascorbate radical is formed (89). They are referred to as "free radical scavengers," and Vitamin E is the major chain-breaking lipid antioxidant.

Naturally, therapeutic attention has been directed to pharmacologic agents that also seem to function as "free radical scavengers" or that are integral to the function of antioxidant enzymes. These include Vitamins C and E, retinoic acid (Vitamin A, beta-carotene), deprenyl or selegiline, an MAO-B inihibitor, and gingko biloba extract (95), selenium, zinc and riboflavin (96). Regular intake of antioxidant vitamins and minerals is often recommended to ward off illnesses like cancer, cardiovascular disease, and neurological conditions associated with aging. For example, a scientific advisory group in the USA that works to advance medical research on human aging (but is not connected with the FDA or the NIH) has already advised healthy adults to sharply increase their intake of selected antioxidant nutrients, suggesting daily intake of 250-1000 mg of Vitamin C, 100-400 IU of Vitamin E, and 10-30 mg of beta-carotene (provitamin A) -- four to sixteen times higher than current RDA's (97).

Brain Trauma & Ischemia

What happens to the brain after stroke or brain injury may be influenced by prooxidant-antioxidant status. Lipid peroxidation by free radical chain reactions has been implicated in the pathophysiology of brain damage following ischemic stroke and brain trauma (98). When the flow of blood to brain tissue is interrupted, injury ensues from lack of oxygenation and then from subsequent re-oxygenation (ischemia-reperfusion). It is during the reperfusion stage, however, that the bulk of tissue injury seems to occur, and this is believed to be a function of the generation of oxygen free radicals, especially in the presence of low molecular weight iron (88). The re-introduction of oxygen to ischemic tissue has been demonstrated to result in the explosive generation of oxygen radicals (90,99).

The primary injury to brain tissue following trauma is mechanical in nature, of course, but subsequent events amplify the pathological process and lead to the death of additional tissue originally spared from the primary injury. Although not every aspect of this secondary process is understood, it is increasingly appreciated that a primary component is ischemia. Traumatic injury to the CNS rapidly evolves into an ischemic insult.

Within brain, oxygen free radicals impair capillary endothelium that maintain water and electrolyte homeostasis, alter membrane fluidity characteristics and contribute to synaptic damage. Because brain has a high concentration of polyunsaturated fatty acids, it is very susceptible to injury by lipid peroxidation, and once peroxidative reactions have been set in motion, they are chain propagating in the presence of sufficient concentrations of oxygen (99).

Following injury, astrocytes appear to exercise a neuroprotective effect by expressing antioxidant enzymes and recycling vitamin C (100). Intrinsic defense mechanisms may not be sufficient, however, to meet the acute demands of oxidant stress induced by ischemia/reperfusion. The idea, then, is to mitigate the process of secondary injury by raising the availability of free radical scavengers (101). In experimental models, pre-treatment with α-tocopherol has been shown to attenuate lipid peroxidation during reperfusion. Another strategy has been to administer antioxidant enzymes like superoxide dismutase or catalase, usually in modified forms (99). Novel free radical scavengers and peroxidation antagonists have been developed, like the so-called "lazaroids" (102).

Parkinson's Disease

In 1979, Stanley Fahn, a neurologist at Columbia who specialized in the treatment of Parkinson's disease (PD), began to recommend antioxidant vitamins to his patients. He was impressed with the antioxidant stress ("endogenous toxin") theory of the disease. He recommended 3 grams of Vitamin C and 3200 IU of α-tocopherol per day, in divided doses. In 1992, he reported that his patients were able to delay the need for dopaminergic therapy by 2-3 years, compared to a another group of patients, treated similarly by another neurologist, but without the antioxidant vitamins (89). His contention that antioxidants might delay the progression of PD, led to the DATATOP study in 28 medical centers in the USA and Canada.

PD is the prototypic age-related neurodegenerative disease. It is especially attractive to the study of oxidative stress, because the basal ganglia, of all the anatomic regions of the nervous system, may be particularly vulnerable to reactive oxygen species. For example, the catabolism of dopamine by monoamine oxidase is productive of hydroxyl radicals, especially in the presence of iron, and the basal ganglia contain the highest concentration of iron in the nervous system. Activity of monoamine oxidase is known to increase with age 103).

The results of DATATOP were not supportive of the idea, though. End-point analysis (time to introduction of L-DOPA treatment) indicated a positive effect for deprenyl but not for Vitamin E (104). Neither treatment influenced mortality (105). Of course, the DATATOP study used a lower dose of Vitamin E (2000 IU/d) and no Vitamin C at all. Along the way, other investigations have questioned the oxidant stress theory of PD (106), and epidemiologic studies of dietary antioxidants have had mixed results (eg, 107-109).

AGING, DEMENTIA

The larger issue, going beyond the over-simplified view of PD as a disease of dopamine in the basal ganglia, is the fact of neurodegeneration itself, in aging, and in dementia. If oxidant stress is relevant to PD, then it may also be relevant to Alzheimer's disease.

The proposition that free radicals are an important factor in aging remains to be rigorously proven. But we do know that the damage caused by oxidative stress accumulates with age (94). We also know that aging systems have increased concentrations of oxidized proteins (110). And we know that relatively longer life expectancy within and between species is associated with a correspondingly lower accrual of oxidative damage. Aging itself is normally associated with an increase in the rate of generation of oxygen free radicals, a decline in the antioxidant defenses, and a decline in the efficiency of repair or removal of damaged molecules (111)

The brain is particularly vulnerable to oxidative stress due to a relatively high rate of ROS generation without commensurate levels of antioxidant defenses. In fact, there is a progressive increase in the steady-state concentration of oxidatively modified DNA and proteins in the brain during aging (112). So, it is not surprising that preclinical studies as well as clinical studies show positive effects for various free radical scavenger therapies, for example, against age-related memory impairment (113-116).

Alzheimer's disease is more than an exaggeration of the normal aging process, but oxidative stress is thought to play a role in both conditions. Perhaps it is only a secondary effect of the disease process, but it has opened new avenues for treatment. Direct and indirect indicators of free radical injury in the Alzheimer's disease patient include: increased iron, aluminum and mercury, which stimulate free radical generation; increased lipid peroxidation and decreased polyunsaturated fatty acids; increased protein and DNA oxidation in the AD brain; diminished energy metabolism in the AD brain; increased concentration of oxidation by-products in neurofibrillary tangles and senile plaques; and evidence that amyloid itself is capable of

generating free radicals (117). The overall peroxidation activity of brain tissue from people with AD is elevated, and the levels of antioxidant enzymes are substantially reduced (118).

More to the point, treatment of AD patients with 2000 IU/d of Vitamin E was found to retard the course of deterioration to a significant degree (119).

TREATMENT WITH ANTIOXIDANT SUPPLEMENTS

There is a substantial body of evidence, therefore, to support the theory that oxidative stress is a component of the aging process, in general, and of neurodegeneration, in particular. There is evidence – of varying degrees of cogency, but not to be ignored – that antioxidant supplementation in normal people reduces the incidence of cardiovascular events, cancer, cataracts and degenerative joint disease. It may be recommended, then, to virtually any middle-aged person who is otherwise in good health, but who wishes to attenuate physical and mental deterioration. It is, arguably, a universal cell protectant. Neuroprotection, then, would be a special case within that general rule. Granted, the evidence-base for neuroprotection is shallow, but the theory-base is deep.

Neuroprotectants are necessary and appropriate to consider as potential treatments during the acute stage of brain injury, be it stroke or traumatic injury or perinatal injury. They are appropriate for any middle-aged person to use, if he or she is convinced that the oxidant stress theory of aging has merit. But do they have a specific role to play in the long-term management of people with brain injuries or mental handicap? Oxidant stress, as we know, is implicated in the cascade of destructive events that follow acute stroke or brain injury, but is it a factor in the long-term, ongoing pathology that sometimes ensues?

With the exception of Down syndrome, the evidence base is empty. One simply has nothing to go on, at least in terms of direct address to the question. Nothing but this syllogism:

1. Brain injury and mental handicap are neuropathic conditions characterized by significant reduction in the cerebral reserve.
2. That alone renders them more vulnerable to the normal biological stressors that accompany aging, and is sufficient to explain the substantial increase in the incidence of mental deterioration over time.
3. Other, specific mechanisms are at play in the development of post-traumatic or Down syndrome dementia, for example; but oxidant stress is implicated in at least some of the purported mechanisms.
4. Antioxidant supplements, especially vitamins C and E, are efficient free radical scavengers; they are cheap, safe and well-tolerated.
5. They are clearly neuroprotective in laboratory paradigms; in some clinical circumstances, they *may* be neuroprotective.
6. It is unlikely that definitive answers to the questions raised herein, on the basis of long-term clinical trials, will be forthcoming, anytime soon.
7. Therefore, and as an interim measure, it is not unreasonable for physicians to recommend antioxidant supplements to patients at risk of cognitive deterioration or dementia, because they are *clearly safe* and *possibly effective*.

Or, to pose the question in a different way, is it not the physician's responsibility to set before the patient all of the data that he or she needs to make an informed choice about a treatment that is clearly safe and possibly effective?

(Is antioxidant therapy "clearly safe"? Consider the massive population studies done by our colleagues in cardiovascular medicine, where seemingly innocent drugs, that are cardioprotective in the short-term are, in fact, associated with increased mortality over the long-term. Could such a thing happen is this arena? Should we say, *clearly* safe, or *probably* safe?)

Psychiatrists have to contend with the possible value of antioxidant supplements when they care for patients who need long-term antipsychotic drug therapy. There is evidence that antioxidant supplements prevent the development of tardive dyskinesia, a particularly noxious side effect of those drugs. The evidence is not definitive, however. The physician is, once again, dealing with a treatment that is probably safe and possibly effective.

VITAMIN E

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

The neurological problems associated with Vitamin E deficiency respond to oral doses of 1600 mg of synthetic α-tocopherol (120). Children with cystic fibrosis are advised to take 100 mg/d. The RDA is 4 mg/d and the average diet contains about 8 mg/d (121).

The Alliance for Aging Research recommends 250-1,000 mg/d of α-tocopherol. Fahn used 3200 IU/d in his Parkinson's patients (along with 3 gms of Vitamin C). His treatment worked, he says. According to DATATOP, it didn't, but they used 2,000 mg/d of α-tocopherol and no Vitamin C at all. One the other hand, the Alzheimer's Disease Cooperative Study found substantial benefit from 2000 IU/d, *sans* C. A dose of 800 mg/d may prevent tardive dyskinesia.

An ordinary multivitamin contains about 30 mg of Vitamin E, and an ordinary "antioxidant formula" contains 200 mg. What dose should one take, for the purpose of "neuroprotection"? Should a brain-injury patient, or a young person with Down syndrome, take more than a healthy 50 year old? Probably, but how much more? No one can say**.** 400-2000 mg/d of tocopherol is not unreasonable.

VITAMIN C

Vitamin C is synergistic with Vitamin E (122). One of its primary roles in vivo is the regeneration of oxidized tocopherols, recycling them to the reduced state that is essential for an antioxidant effect. This is one reason why DATATOP was not a fair test of Fahn's proposal that Vitamin E (*cum* Vitamin C) delayed the progression of PD.

Linus Pauling's name is indelibly associated with the birth of "megavitaminism" since he proposed that high doses of Vitamin C could prevent the common cold. The assumption was that the vitamin enhanced immune response, and there is ample evidence to support that idea. For example, the concentration of Vitamin C in leucocytes is quite high and decreases rapidly during phagocytosis and infection. Nevertheless, the metabolic function of vitamin C is not entirely understood, and its effect on human immunity continues to be a cause for debate. There have been innumerable studies on its effects against upper respiratory infections. The balance of the evidence is in favor of a small effect in reducing the severity and duration of the common cold (123).

The association between vitamin C intake and protection from cancer, heart disease, cataracts and arthritis is based, almost entirely, on epidemiological studies. On the basis of this research, it is virtually impossible to discern whether the protective effect is due to vitamin C, to vitamin E, or carotene, to the combination thereof, or to some unmeasured constituent, like the bioflavonoids. Nevertheless, the epidemiologic evidence does suggest a protective role for vitamin C (124).

Specific mental changes that occur in Vitamin C deficiency (scurvy) include lassitude, depression and personality change (125). Excluding scurvy, the health consequences of inadequate vitamin C are not well characterized (124).

Brain has the highest concentration of vitamin C in the body. Ascorbate in the CNS influences the actions and the metabolism of dopamine, norepinephrine, serotonin, acetylcholine, NMDA and glutamate (126). The clinical importance of these actions is not known. High doses of vitamin C have not been demonstrated to alter the course of neuropsychiatric disorders or the effects of neuroactive drugs.

Treatment of scurvy in adults requires 1 g/d of Vitamin C for about a week, which is usually sufficient to replenish body stores of 2-3 gms. The RDA for adults is 60 mg/d, and the average diet contains about 80 mg/d (121). Pauling recommended 1-5 g/d for prevention of colds. The Alliance for Aging Research recommends daily intake of 250-1,000 mg/d. The ordinary multivitamin has about 60 mg and the "antioxidant formula" has 250 mg.

You can probably take as much Vitamin C as you can stand to swallow. After all, a lot of people have been taking megadoses of Vitamin C since the 1970's, and there is no fallout yet. One or two grams per day is not an outlandish dose.

THE B VITAMINS

VITAMIN B_{12}

Folic acid and vitamin B_{12} (cobalamin) are essential in several metabolic pathways in the CNS and a close relationship exists between them. Both are involved in single carbon transfer reactions necessary for the production of monoamine transmitters, phospholipids, and nucleotides. Deficiencies of either vitamin produce characteristic hematological abnormalities and neuropsychiatric symptoms.

The RDA for B_{12} is 6 µg/d, and the average diet contains about 20 µg/d. Because the vitamin is tightly conserved through the enterohepatic circulation, it takes two to five years to develop overt deficiency from malabsorbtion and 10-20 years from strict vegetarianism ("vegans," who don't eat eggs or dairy products)(127). Treatment of pernicious anemia usually begins with intramuscular injections of 100-1000 µg of B_{12} for five days, and monthly thereafter (127). There is a prejudice against oral B_{12} among American physicians, because it is poorly absorbed in the absence of gastric acid and Intrinsic Factor (IF). In fact, a daily dose of 1000 µg by mouth will allow absorption by passive diffusion (absent HCl or IF) of 10 µg, which exceeds the RDA (128). The ordinary "B Complex" one buys at the health food store, or a "high-potency" multivitamin ordinarily contains only 25-75 µg of B_{12}.

Cobalamin, pyridoxine and folate are co-factors in the synthesis of methionine from homocysteine, which is why homocysteinemia is indicative of a B_{12}/B_6/folate deficiency. In the mitochondria, cobalamin catalyzes the conversion of methylmalonyl CoA to succinyl CoA which is why elevated levels of methylmalonic acid are indicative of B_{12} deficiency.

Changes in mood and cognition may accompany low levels of B_{12} or folate, even in the absence of hematological abnormalities. Such patients may present to neuropsychiatry clinics with undiagnosed deficiencies, and their conditions may improve dramatically with replacement therapy (129,130). Psychiatric abnormalities associated with cobalamin deficiency include depression, paranoia, organic psychosis, obsessive-compulsive disorder, personality and mood changes (131). B_{12} deficiency is, of course, a reversible cause of dementia, and it is a subcortical dementia with processing speed deficits, memory and visuospatial impairment. But not all of the neurocognitive deficits improve after replacement therapy (132).

The common view is that the neurological manifestations of cobalamin deficiency are a late manifestation that occurs only after the deficiency and its hematological abnormalities are well established. In fact, neuropsychiatric abnormalities may occur even in the absence of low serum cobalamin levels, anemia and macrocytosis (133). Neuropsychiatric symptoms in the absence of anemia "should not be considered rare" (129, p1727). Since the alleged neuropsychiatric manifestations of subclinical B_{12} may be nonspecific (weakness, fatigue, memory loss, irritability, mood and personality disorders) and extremely common in the general population of clinic attenders, the issue of diagnosis is problematic. One can measure serum levels of the cobalamin metabolites methylmalonic acid and homocysteine (129), but the test is expensive; considerably more expensive than a therapeutic trial of weekly B_{12} injections.

FOLATE

Folate is a water-soluble vitamin of the vitamin B complex and its function is intimately related to Vitamins B_{12} and B_6. It functions as an enzyme cosubstrate in the metabolism of amino acids and nucleotides. Nutritional deficiency results in impaired biosynthesis of DNA and RNA, and thus in reduced cell division, which is manifested clinically as anemia, dermatologic lesions and poor growth. Its status at the level of subclinical deficiency is difficult to assess (72,121).

Experimental folate deficiency has been shown to cause elevated plasma homocysteine concentrations, and the use of folate-containing multivitamin supplements is associated with low mean plasma homocysteine levels. Folate-responsive homocysteinemia can be demonstrated in people who are apparently healthy, suggesting the prevalence of undiagnosed suboptimal vitamin status (72,134). Hyperhomocysteinemia is especially prevalent in the elderly (as high as 29%)(135). This is important, because homocysteinemia is a risk factor for occlusive vascular disease, cancer and birth defects. In fact, the FDA has recommended adding folate to foods, in order to achieve a daily intake of 0.4-1.0 mgm, and thus reduce the occurrence of affected pregnancies. Fortification of the food supply may also reduce the occurrence of cardiovascular disease (136). Mandatory fortification of grain products with folate began in the USA in 1999.

Folate levels are often found to be low in psychiatric patients, for example, in depression, dementia, schizophrenia, alcoholism and anorexia. Experimentally-induced folate deficiency in normal volunteers can cause sleeplessness, irritability and memory deficits. The commonest neuropsychiatric complication of severe folate deficiency is depression (137). Dietary intake may play a role, but the cause of folate deficiency in psychiatric patients, compared to normal controls, is unknown. The relation of folate deficiency to neuropsychiatric disorders may be mediated by the metabolism of serotonin, by phospholipid methylation in the neuronal membrane (138) or by the neurotoxicity of homocysteine (139). Folate and B_{12} are both required for the methylation of homocysteine to methionine and in the synthesis of s-adenosylmethionine, which is, in turn, involved in numerous methylation reactions involving proteins, phospholipids, DNA and various neurotransmitters. S-adenosylmethionine (SAMe), by itself, is said to have antidepressant properties (137,139).

Folate therapy, however, does not always lead to clinical improvement, although patients with low baseline folic acid levels tend to respond less well to antidepressants (130,140), antipsychotic drugs (141,142), lithium (143) and anticonvulsants (144,145).

THE RATIONALE FOR TREATMENT WITH ANTIOXIDANTS AND B VITAMINS

Simply because a vitamin is essential to some aspect of metabolism in the CNS does not mean that supplemental vitamins will improve CNS function. Vitamins are taken up into the CNS by an active transport system that gives priority to the requirements of brain metabolism, and the synthetic steps in which the B vitamins participate are not usually rate-limiting bottlenecks. Nevertheless, it is arguable that some of the B vitamins, notably folate, enhance the response of patients to psychoactive drugs and it does appear that a course of cobalamin may lead to nonspecific improvement in patients with a variety of neuropsychiatric conditions. The science is not well-developed, and the controversies are not likely to be settled anytime soon. But it is not outlandish to offer brain injury patients a course of B_{12} by injection, or to advise the patient on chronic psychotropic drug therapy to take a supplemental B complex tablet every day.

The science behind the theories of oxidative stress, on the other hand, is well-developed. The brain injury patient should be particularly interested in antioxidant supplementation, even if she or he is young and healthy, and has made a good recovery from the trauma. Even mild brain injuries seem to be associated with at least a degree of compromise of the "cerebral reserve"; the young brain injury patient has, for all practical purposes, a middle-aged brain. It is our custom to present this argument to patients who have sustained brain injuries, as we do to all of our middle-aged patients, and to invite them to participate in a theoretical treatment that carries little risk, if any, and that may exercise at least a degree of benefit over the long-term.

We do so with the *caveat* that large doses of vitamin supplements may induce a *relative deficiency* of other vitamins/minerals. Patients who choose to take high doses of C, E or B complex should also take a good multivitamin tablet as well.

OMEGA-3 FATTY ACIDS

That fish are good for you first came to the attention of the medical world in 1980, when Bang, Dyerberg & Sinclair suggested that the low rate of coronary artery disease in Greenland Eskimos might be due to their high consumption of seafood. Five years later, Kromhout and his coworkers showed that eating just one or two portions of fish very week was associated with a 50% reduction in coronary heart disease mortality (146). Since that time, more than 15 cohort studies have been done to address the topic, and the majority supported a cardioprotective role from the consumption of a small amount of fish (147).

Fish are high in n-3 fatty acids (omega-3 polyunsaturated fatty acids, n-3 PUFA) which experiments have indicated have antiarrhythmic properties. That may not be the only cardioprotective mechanism they have; they are also antihypertensive, decrease platelet aggregation and sometimes lower serum triglycerides (148,149). In other areas, they also have been demonstrated to have anti-inflammatory effects, and to be beneficial for ulcerative colitis, rheumatoid arthritis, asthma and certain types of cancer (150). Low levels of Omega-3 fatty acids are associated with neuropathy and impairment of the immune system (151). So, it's important to eat your fish. But is it *brain food*?

Let us begin with mother's milk. The lipid fraction of human milk is the main energy source for the newborn infant, and supplies essential nutrients, including the polyunsaturated fatty acids. The essential fatty acids in milk, linoleic and linolenic acid, have been known to be necessary for normal growth and development since 1930 (151). There is substantial transfer of Omega-3 PUFA from mothers to infants during pregnancy and during lactation. In fact, mothers are found to have relative deficiencies of Omega-3 fatty acids (152), something that may influence the development of post-partum depression, as we shall see.

Linoleic and linolenic acid are precursors of the long-chain polyunsaturated fatty acids, such as arachidonic acid (an Omega-6 PUFA) and **docosahexaenoic acid** (DHA, an Omega-3 PUFA). The long-chain PUFA are indispensable structural components of all cellular membranes, and they are incorporated in relatively large amounts during early growth of the brain. Some long chain-PUFA are precursors of **eicosapentanoic acid** (EPA), an Omega-3 PUFA with potent biological activity (153). DHA and EPA together are referred to a Omega-3 Fatty Acids, or "Fish Oil," since they are found in high concentrations in fish, especially fatty fish like salmon, tuna and mackerel.

Several sources of information suggest that man evolved on a diet with a ration of Omega-6 to Omega-3 fatty acids of approximately 1:1, whereas today the ratio is 10:1 or 20:1. It would appear, then, that the conventional Western diet is deficient in Omega-3 fatty acids compared to the diet on which humans evolved (149). In natural populations, there is a wide range of Omega-6:Omega-3 proportions; some individuals are high in one and low in the other, and vice-versa. The two are not interconvertible and their levels are inversely related, in individuals, as well as populations (149,151). It is tempting to think that the chronic diseases of modern man are related to unnaturally low levels of Omega-3 fatty acids in their diets; the composition of cell membranes is to great extent dependent on dietary intake. In animals, for example, dietary restriction that decreases omega-3 fatty acids and raises levels of omega-6 fatty acids tends to accelerate age-related changes of dopamine and serotonin in the frontal cortex and the brain stem (154,155).

Omega-3 fatty acids are necessary for the normal growth and development of brain, and are also required for maintenance of normal brain function in adults. The turnover of DHA in brain is very fast. Deficiencies of DHA are associated with learning deficits in infants and children, while inclusion of plentiful DHA in the diet improves learning ability. It is troubling to think that most infant formula diets lack omega-3 fatty acids (156).

Learning deficits are demonstrated in animals deficient in omega-3 fatty acids (157), and, in preliminary reports, in children with dyslexia (158), ADHD and behavior problems (159-162).

Studies of dementia are equally intriguing, though preliminary. Animal studies indicate a therapeutic role for DHA in rats subjected to transient forebrain ischemia (163) and in humans with dementia from cerebrovascular disease (164). Low serum DHA is said to be a "significant" risk factor for Alzheimer's disease (165). There are lower levels of omega-3 fatty acids in the parahippocampal cortex of patients with AD (117,166). Dietary fatty acids may attenuate the neurotoxic effects of alcohol (167,168). On the other hand, oxidative transformation of n-6 and n-3 fatty acids in brain by free radical species may adversely affect neuronal function (169). Oxidative products of essential fatty acids ("isoprostanes" or "neuroprostanes") seem to be elevated in demented patients (170). For this reason, if a patient elects to take Omega-3 supplements, he or she ought to take Vitamins C and E as well.

The clinical relevance of long-chain fatty acids can be investigated by examining dietary intake, lipid fractions in serum, or the constitution of membrane phospholipids in tissue samples like erythrocytes or fibroblasts; or by measuring light sensitivity, since DHA is found in high concentrations in the photoreceptor cells of the retina; or, by measuring clinical response to

dietary supplements of omega-3 fatty acids. This is a particularly fertile avenue for psychiatric investigation because even a modest abnormality in cell membrane metabolism would be greatly amplified in brain, which requires the coordinated sequential and parallel activities of billions of neurons. The idea that schizophrenia, for example, may be a disorder of cell membrane phospholipid metabolism has been investigated, and with interesting results (171-173).

More pertinent to this discussion is the relation between omega-3 fatty acids and affective disorders. There are a few reports of reduction in depressed patients (174-177); and one controlled study of omega-3 fatty acids for the treatment of bipolar patients (178). People who eat fish two or three times a week are less likely to be depressed or suicidal (178).

Low levels of serotonin and dopamine metabolites are inversely related to plasma DHA in violent patients (179). Omega-3 supplements are found to reduce stress-induced aggression in young adults (180). These observations may reflect on the problem of depression associated with low serum cholesterol. Serum cholesterol may simply be a surrogate marker for the long-chain polyunsaturated fatty acids (181).

Dietary supplements of the two omega-3 fatty acids, DHA and EHA, are widely available and relatively inexpensive. Supplemental omega-3 is attractive to consumers who are aware of its benefits as a putative cardioprotective. It is sometimes promoted as an arthritis remedy. Neither “indication” is medically proven, of course. Physicians are more likely to recommend a weekly serving, or two, of fish. It is possible that omega-3’s will be more interesting to psychiatrists, for the adjunctive treatment of affective disorders and other mental conditions, and for the prevention of cognitive deterioration in the elderly. By the same token, they may be included as part of a “defensible” neuroprotectant regime for brain injury patients (Table 25.1). Paradoxically, patients on Omega-3’s may *become* depressed or irritable. If this happens, stop the supplement immediately.

ANTI-INFLAMMATORY DRUGS AND DEMENTIA

An interesting contribution of anti-inflammatory drugs, including dapsone, indomethacin, nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors may be to inhibit the course of Alzheimer's disease. (Aspirin, an antithrombotic drug and a selective COX-1 inhibitor, may not share this effect(182)) The idea originated with the pathologic demonstration of acute phase reactants and other markers of immune processes, absent or present at very low levels in normal brain, in the post-mortem brains of AD patients. It was buttressed by a series of epidemiologic studies that consistently demonstrated lower rates of dementia in patients who take anti-inflammatory drugs for the usually medical indications (183-186). A number of controlled studies have also demonstrated that AD occurs at a lower rate in patients who have been treated longterm with NSAIDs, for example, people with rheumatoid arthritis or osteoarthritis, and that a course of treatment with anti-inflammatory drugs may slow the progression of dementia in patients with AD. In the Rotterdam study of about 8,000 elderly people, the relative risk of AD among users of ASA or NSAID's was 0.38 (187,188).

The weight of the evidence, therefore, is that drugs that limit inflammatory reactivity might reduce the risk of AD or slow its progression. How, precisely, does that happen, and how may it be relevant to the treatment of patients with brain injury?

The major mechanism of action of NSAID’s is the inhibition of cyclooxygenase activity and thus the synthesis of prostaglandins (189). Prostaglandins are potent mediators of the inflammatory response, and are generated from arachidonic acid via the action of two distinct but related enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Both enzymes contribute to the inflammatory process, but COX-2 is of greater therapeutic interest, as it is

inducible (as opposed to constitutive). That is, its activity is induced by pro-inflammatory stimuli in migratory cells and inflamed tissues. This results in enhanced formation of prostaglandins (or prostanoids) during acute as well as chronic inflammation. The traditional NSAIDs are non-selective cyclooxygenase inhibitors, while the new ones, celecoxib and rofecoxib are 100-1000 times for selective for COX-2 than COX-1. Since COX-1 is mainly present in the gastric mucosa and kidney, the conventional NSAIDs are far more prone to gastro-intestinal and renal side effects than the selective COX-2 inhibitors. Drugs with more COX-2 effect and less COX-1 effect have potent anti-inflammatory activity with fewer side effects (190,191).

The idea that inflammatory responses may be a component of the development of AD began with observation, in 1987, that plaques in brains from AD patients were filled with reactive microglial cells. The activity of micoglial cells is not an innocent event, a form of neuronal housekeeping, as it were, but potentially toxic in its own right. Microglial cells are prone to secrete complement proteins and other biochemical weapons, like COX-2, that are, by themselves, potentially neurotoxic. In various experimental models, ischemia, for example, and neurotoxic injection, microglial cells can be induced to generate COX-2 and pro-inflammatory prostanoids. COX-2 induction is also a component of the cascade of events that surround neuronal excitotoxicity (192-195). Brain injury, itself, induces the expression of several genes, including the gene for COX-2 (196).

Drugs that inhibit the activity of COX-2 are thus expected to interrupt, or at least, to attenuate a series of inflammatory processes that are potentially neurotoxic in their own right, and that aggravate the impact of the original pathogenic event, be it *tau* protein, ischemia or traumatic injury. Thus, theories of pathogenesis complement the results of epidemiological studies, and the COX-2 inhibitors find themselves on a unique pedestal, along with the antioxidants and the Omega-3 fatty acids, as practical and potentially useful neuroprotectants. (The COX-2 inhibitors are also believed to prevent the development of certain gastro-intestinal cancers (197))

Now, a familiar question arises: to what degree is a neuroprotectant NSAID useful for patients with brain injury or mental retardation? Yes, they are *possibly effective*, to prevent certain forms of late degeneration, but they are not inexpensive, and neither are they entirely free of toxic effects.

High doses of NSAIDS interfere with other biological processes not dependent on prostaglandins, the activity of various enzymes and transmembrane ion fluxes (189). Nor is the inhibition of Cox-2 inevitably beneficial for the health of one's brain; the expression of COX-2 is a normal component of brain development, and the basal production of prostaglandins through COX-2 may "participate in neuronal homeostasis" (182). Patients taking traditional NSAID's, especially elderly patients, have had a variety of mental problems, including depression, forgetfulness, difficulty concentrating, paranoia, mania and frank psychosis; the COX-2 inhibitors are no different in this regard (198,199). Even young, healthy patients of NSAID's may experience mental slowing or "fuzziness" at high doses. Celecoxib has clinically significant interactions with fluconazole and lithium, as do other NSAID's, and it is metabolized by CYP2C9 (200).

Just as one feels safe in encouraging patients pursue an antioxidant/fish oil strategy to protect the health of his or her brain, one is hesitant to recommend routine daily dosing with a COX-2 inhibitor. Patients who are at high risk for dementia, on the other hand, should be considered for prophylactic treatment. This, at least, is an area where definitive studies will be done.

GINGKO BILOBA

Extracts from the leaves of the Gingko tree (maidenhair tree) have been used for hundreds of years in Chinese medicine. Gingko biloba is now the most commonly prescribed drug (sic) in France and Germany. In the USA, it is not deemed a "drug," but rather a "dietary supplement," and it is one of the most popular herbal remedies.

In Europe it is used for "cerebral insufficiency," a term that covers a wide range of problems including absent-mindedness, difficulties with concentration and memory, confusion, lack of energy, fatigue, impaired physical performance, depression and anxiety, usually associated with aging. It is also used for intermittent claudication, because it is said to "decrease the viscosity of blood" (201). In fact, health-conscious people who take daily aspirin *and* gingko biloba may be given to nosebleeds; one of the components of gingko, ginkgolide B, is a potent platelet-activating factor antagonist (202).

There have been a number of controlled studies, published in respectable journals, that support the use of gingko extract for a number of neuropsychiatric problems, like neurasthenia (fatigue and tiredness) (201); age-associated memory impairment (203); "cerebral insufficiency" (204); and dementia (205). There are also preclinical studies that demonstrate a positive recovery effect for gingko in brain trauma and spinal cord injury (95,206,207).

Gingko extract is a potent antioxidant (208-210) and a reversible inhibitor of monoamine oxidase (211) It tends to reduce glucocorticoid synthesis, which may account for its purported "anti-stress" effect (212).

There is no apparent toxicity from gingko biloba, aside from the interaction with ASA, but there are no long-term safety/efficacy studies, either.

One might say this: patients deserve the opportunity to decide for themselves, whether to take Gingko, just as they have to decide about the antioxidants, B vitamins and Omega-3's. On the other hand, most people don't like to take a lot of pills, and the effects of these putative "neuroprotectants" is not something the patient is likely to experience as immediately reinforcing (except, possibly, for the Omega-3's). Even if every substance we have mentioned is, in fact, "neuroprotective," we have no way of knowing whether, if they are taken together, their effects are additive, synergistic, or, in some way, subtractive, or even dangerous.

I suppose it falls to physicians to come to terms with this promising but woefully underdeveloped area as best he or she can do. Physicians have to decide whether to recommend this approach to long-term "neuroprotection," how to educate patients about its pro's and con's, and then how to keep after patients, who must commit to a lifetime of treatment. The author, in his practice, tends to recommend the supplements listed in **Table 25.1**. As far as Gingko is concerned, the author is neutral, but don't take it with aspirin.

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Table 25.1. A defensible regime of neuroprotective supplements

Vitamin E	400 – 800 units *bid*
Vitamin C	1 000 – 2 000 mg *bid*
B Complex	1 tablet/d
Multivitamins	1 tablet/d
Omega-3 fatty acids	300 – 600 mg *bid*