

# Natural Support for Neurologic Health: A Multiple Pathway Approach

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**ABSTRACT:** *As more people than ever before reach their "golden years," there is growing concern about maintaining neurologic health and brain function. Diseases and disorders that affect neurologic functioning more often in older adults, including the dementias, cerebrovascular disease, and progressive disorders like Alzheimer's or peripheral neuropathies, are significant health concerns for aging patients. While some progressive decline in neurologic functioning during the aging process is normal, progression to actual neurologic*

*disease does not represent the inevitable in many cases. Some of these disorders may very well be the cumulative effect of imbalanced biochemical pathways that propagate premature neurologic senescence. Four major biochemical pathways that may underlie neurologic cellular decline are identified and the appropriate nutritional support discussed. By addressing optimal function in these systems, the healthcare professional may be able to help their patients live out their lives with optimal neurologic health and brain function.*

With advances in hygiene, science, and medicine, modern man has become the longest-lived in human history and life expectancy continues to lengthen. Diseases and disorders that specifically affect the nervous system more often in aging persons are being diagnosed in record numbers in the United States: 4 to 6.8 million suffer from dementia; approximately 4 million have Alzheimer's disease (AD), a number expected to jump to 14 million by the year 2050; up to 1.5 million may suffer from Parkinson's disease (PD), with 50,000 newly diagnosed each year; amyotrophic lateral sclerosis (ALS), while affecting all age groups, is seen in increasing numbers of aging Americans and over 5,000 new cases are diagnosed each year.<sup>1,2</sup> Though peripheral neuropathies are too heterogeneous to access accurate epidemiological data, there is clear evidence that loss in specific peripheral functions occurs as humans age. Furthermore, the cumulative changes that occur in the aging brain related to vascular structures and brain tissue likely contribute to the increased risk of stroke and multi-infarct (stroke related) dementia, which are disorders more frequently seen in aging persons.

Dysfunction in older patients should not be assumed to be secondary to normal aging; disease processes should be considered. Furthermore, within normal aging, there are individuals who show very little decline in function with age whereas others exhibit "age-related" decline. In this context, it becomes important to not only separate disease from aging, but "usual" from "successful" aging. It is relevant to consider all factors which might optimize cellular and tissue function and hence each person's potential for healthier and "successful" aging. There is mounting evidence that a cumulative effect of imbalanced biochemical pathways can and does impact the progression of neurologic diseases, as well as affecting the natural progression of aging.<sup>3,9</sup>

As there are a wide variety of neurologic disorders that can affect patients in their older years, and because there are many symptoms and signs that can be determined prior to precise diagnosis of a disorder, it is important to screen for early warning signs of neurologic deterioration (Table 1). Interventions begun in the initial stages of the disease process may prevent or possibly delay the course of deterioration in these disorders. Early intervention may also result in more successful improvement, rather than simply treating the symptoms once a diagnosis is made.<sup>10-14</sup>

**Table 1. Early Warning Signs of Neurologic Degeneration<sup>2</sup>**

- Impaired expression or comprehension of written or spoken language.
- Difficulty in decision making and problem-solving.
- Agitation—a state of hyperarousal, increased tension, and irritability.
- Disturbances in or loss of memory, especially for recent events.
- Difficulty in carrying out tasks with multiple steps.
- Impaired judgement.
- Intellectual decline.
- Confusion or disorientation, hyperactivity, and overt hostility.
- Depression.
- Anxiety.
- Poor hygiene and appearance.
- Loss of balance and coordination.
- Impaired motor function.
- Rhythmic tremors in a hand or foot, particularly when at rest.

## THE GENETIC COMPONENT OF AGE-RELATED DISEASES

It is tempting to assume that the loss of certain physiological functions in humans is specifically related to genetic factors. However, recent scientific breakthroughs suggest that many characteristics we associate with aging can be modified by nutritional, behavioral, and environmental influences. In fact, research indicates that nutrition and other environmental factors can modify the *phenotype*—the way our genes are expressed.<sup>14,15</sup> Nutritional modification of gene expression contributes to how we look and feel and impacts our health and disease patterns. By supporting the healthy balance and function of underlying biochemical pathways it may be possible to enhance genomic potential and prevent the expression of "aging" phenotypes, as well as the progression of neurologic diseases including the dementias, neuropathies, and other progressive neurologic diseases like Parkinson's or ALS.<sup>14,15,17</sup>

Over the years, the cumulative effect of environmental factors such as poor diet, micronutrient insufficiency, oxidative stress, toxins, psychosocial stress, and a sedentary lifestyle, compounded by genetic predisposition toward disease, can stress biochemical pathways within the body, propagating the biological aging of tissues.<sup>14,15</sup> The biochemical pathways underlying neurologic disease are multiple and overlapping—a failure or imbalance of one affects the function of others. Therefore, protection against one pathway may not be enough and multimodal therapy may be needed for a significant clinical benefit.<sup>14,18,19</sup> By simultaneously addressing four major pathways that can lead to neurodegeneration, a significant impact on the occurrence and/or progression of premature aging and neurologic disease may be made.

### THE FOUR PATHWAYS

Discussion of four major biochemical pathways recognized as possible pathophysiological mediators of both aging and neurodegenerative processes are outlined below. These include I.) chronic inflammation, II.) mitochondrial dysfunction, III.) endocrine imbalance, and IV.) hypomethylation. Though these pathways are critical in all cellular function, because of the differences in potential for cellular regeneration in the nervous system, these systems may play a more important role in maintaining normal function within the nervous system. Two other critical differences between the nervous system and other body tissues are the mechanism for segregation of brain tissue by the blood brain barrier (BBB) and the metabolic dependency on consistent access to oxygen and glucose. The BBB is a physiological mechanism that alters the permeability of brain capillaries, so that some substances, such as certain drugs, are prevented from entering brain tissue, while other substances are allowed to enter freely, specifically certain lipophilic molecules.

It should be noted that while the concept of oxidative stress and free radical damage could comprise a fifth pathway, its impact on the other pathways is instead discussed. A large body of evidence suggests that oxidative injury either causes or exacerbates neuronal injury and leads to primary or secondary pathophysiological mechanisms underlying many neurologic disorders.<sup>20-24</sup> The brain may be particularly vulnerable to oxidative damage due to the fact that it has a high energy requirement and a high oxygen consumption rate, is rich in peroxidizable fatty acids, contains high levels of metals (e.g., iron), and has a relative deficit of antioxidant defenses compared to other organs.<sup>21,24</sup> Boosting antioxidant defenses may be an effective means of preventing or stopping the progression of many neurologic diseases. Different antioxidants have affinities for nucleic acids, proteins, or lipids in neurologic tissue. Thus, combination therapy using a variety of potentially synergistic antioxidants may be superior to supplementing with single antioxidants.<sup>24</sup> Furthermore, antioxidants that readily pass through the BBB make the best candidates for neurologic disorders.

### I. CHRONIC INFLAMMATION

Though inflammation as a mechanism is usually protective, downstream effects of this process when it is maintained beyond its usefulness in defense can be harmful to all tissues. Chronic inflammation has long been recognized as a possible pathophysiological mechanism in aging-associated neurodegeneration.<sup>25-28</sup> Furthermore, epidemiological evidence indicates that populations taking anti-inflammatory drugs for other conditions have a sharply reduced risk of neurodegenerative disease.<sup>16</sup> Inflammation and oxidation are intimately linked. A rise in the body's free radical load, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), accompanied by decreased antioxidant defenses, is a hallmark of aging. Oxidants serve as signaling agents for pro-inflammatory mediators and are capable of changing patterns of gene expression by activating transcription factors such as nuclear factor kappaB (NF- $\kappa$ B), which give rise to both aging and inflammation pheno-

types.<sup>25,27,28</sup> Because non-neuronal cells of the nervous system (e.g., microglia, endothelium, and astrocytes) are known to secrete a wide variety of molecules involved in inflammation, optimizing the function of anti-inflammatory cytokines as opposed to perpetuation of pro-inflammatory and potentially harmful substances is important.<sup>29-31</sup>

Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme that is activated by DNA strand breaks and involved in the repair of DNA, as well as genome stability. Chronic cellular insults resulting from such things as oxidative stress (especially peroxynitrite) or inflammation may lead to increased genetic damage and hence increased PARP activation. PARP activity appears to increase with age and is prominent in vascular stroke and other neurodegenerative processes, including AD.<sup>32-35</sup> Overactivation of PARP results in mitochondrial nicotinamide adenine dinucleotide (NAD) depletion, causing ATP production to be diminished. This not only reduces cellular energy, but eventually leads to cell necrosis.<sup>33,35</sup> When a neuron dies via necrosis, its internal contents, including chemicals and enzymes, spill out into the extracellular space, damaging surrounding neurons.<sup>36</sup> Furthermore, research indicates that cell necrosis is a potent inflammatory stimulus.<sup>37</sup>

Multiple factors related to the inflammatory pathway are capable of propagating premature brain aging and neuronal cell death by:

- encouraging the expression of genetic characteristics associated with neurologic disease (e.g., apolipoprotein E4, amyloid precursor protein).<sup>14,38,39</sup>
- increasing coagulation and altering vasomotor tone in cerebral vasculature.<sup>29</sup>
- increasing the risk of ischemic brain damage.<sup>29,31</sup>
- compromising blood brain barrier integrity.<sup>40</sup>
- releasing pro-inflammatory mediators (e.g., cytokines, prostaglandins, interleukins) that promote neurotoxicity, thereby exacerbating neuronal damage.<sup>26,40,41</sup>
- generating RNS and ROS that damage neuronal receptors (e.g., acetylcholine), proteins, lipids, membrane thiols (e.g., glutathione), and DNA.<sup>16,42,43</sup>
- stimulating PARP.<sup>35,43,44</sup>

### II. MITOCHONDRIAL DYSFUNCTION

Tissues that have a high energy (ATP) requirement, such as the brain and heart, have a higher density of mitochondria—the cell's energy-producing powerhouse. Since the brain depends so highly on mitochondrial energy supply, dysfunction of mitochondria may affect the central nervous system (CNS) more severely than other tissues, causing or worsening diseases and playing a role in or speeding the biological deterioration of aging.<sup>45-49</sup>

The probability that age-associated diseases, including neurologic disease, may be precipitated, propagated, or caused by impaired mitochondrial function is a prevailing theory. Changes in mitochondria that occur with age and cause dysfunction include loss of membrane potential and function, reduced enzyme activity, increased mutations in mitochondrial DNA (mtDNA), and reduced ATP synthesis.<sup>50</sup> In addition, oxidant production and leakage goes up, while antioxidant defenses go down. Mitochondrial respiratory chain dysfunction and free radical generation independently adversely affect mitochondrial membrane potential—an early event (preceding nuclear fragmentation) in the apoptotic pathway. Therefore, mitochondrial dysfunction in neurodegenerative disorders may result in a fall in the apoptotic threshold of neurons.<sup>51</sup>

As a result of the high metabolic demands on mitochondria, mtDNA experiences about 10 times as much oxidative damage and has about 17 times the mutation rate of nuclear DNA.<sup>52</sup> mtDNA codes proteins

essential for mitochondrial ATP synthesis. Acquired mutations, such as deletions in mtDNA, are caused mainly by damage from ROS. Accumulation of these mutations over time causes bioenergetic deficits leading to neurodegeneration, and can be accelerated by individual genotype.<sup>53-56</sup>

The research suggests two methods of supporting mitochondrial health and function: supporting healthy mitochondrial energy production and combating ROS/RNS production and damage by increasing mitochondrial antioxidants.<sup>45-57</sup>

### III. ENDOCRINE IMBALANCE

Endocrine function directly and indirectly influences neurologic aging through its complex effects on inflammatory balance, cerebral and overall glucose metabolism, neurotransmitter and neurotrophic factor production, circulatory function, and the stress response.<sup>58</sup>

#### Hypothalamic-Pituitary-Adrenal Influences in Neurologic Aging

The hypothalamic-pituitary-adrenal (HPA) axis is an endocrine closed-loop system that controls the secretion of stress hormones (glucocorticoids). Aging is associated with a reduced ability to adapt to stress, increased HPA activation, and chronic elevations of glucocorticoids (e.g., cortisol).<sup>7,8</sup> Animal and human data suggest that cumulative exposure to high levels of glucocorticoids can be particularly detrimental to the aged hippocampus (the brain structure involved in learning and memory).<sup>59</sup>

Under sustained immune, traumatic, metabolic, or emotional stress, chronically elevated glucocorticoid levels can propagate neurologic decline in many ways. They can contribute to inflammatory 5-lipoxygenase (5-LOX) gene expression; increase neuronal sensitivity to toxins and ischemia; inhibit sex steroid and growth hormone secretion; affect mood and behavior; permanently downregulate hippocampal cell receptors; alter neurotransmitter function; disrupt memory, recall, and cognition; and can eventually result in neuronal atrophy and death.<sup>60-65</sup> Glucocorticoids may also exacerbate neuronal injury by compromising the function of the neuronal glucose transporter and increasing insulin resistance. Reduced glucose availability results in ATP depletion and sets in motion a failure of mitochondrial mechanistic systems, contributing to neurotoxicity.<sup>66</sup>

Lifestyle changes and nutritional interventions that help reduce glucocorticoid levels and the body's ability to cope with stress are two ways to intervene in the neurologic decline associated with hyperglucocorticoidemia.

#### Dysglycemia

During aging, changes in glucose and insulin metabolism may result in dysglycemia which can lead to neuronal degeneration. Peripheral neuropathic changes can be seen early in dysglycemic states, even before the formal diagnosis of diabetes. Though the mechanism is unclear, reduced glucose metabolism and transport have been observed in AD. In addition, hypoglycemia is known to contribute to neuronal damage in stroke. Glucocorticoids may play a significant role due to their negative affect on glucose transporters and insulin resistance.<sup>66</sup> On the other hand, hyperglycemia upregulates glycation (the reaction of blood glucose with proteins) of structural and functional proteins in the nervous system resulting in the formation of damaging advanced glycation endproducts (AGEs).<sup>14,67</sup>

Protein glycation is associated with the induction of oxidant stress, increased NF- $\kappa$ B activity, inflammation, mitochondrial dysfunction, nerve degeneration, AGE accumulation on blood vessel walls, and accumulation of amyloid.<sup>14,67-70</sup> Furthermore, AGE accumulation is associated with increased cross-linking and reduced elasticity of structural support proteins.<sup>14,67</sup> Such structural and functional damage to proteins in membranes and inner structures of neurons may be associated with declining cognitive function in aging.

In individuals with dysglycemia, proper diet, exercise, and modula-

tion of their condition with nutritional factors such as fiber, chromium, vanadium, magnesium, antioxidants, and conjugated linoleic acid (CLA) may help reduce the associated neurologic decline.

### IV. HYPOMETHYLATION

Methylation, the transfer of a methyl group (CH<sub>3</sub>) from one molecule to another, is required for numerous biochemical reactions vital to good health. In fact, methylation of DNA influences binding of transcription factors and is an integral means by which gene expression is regulated. Hypomethylation is considered by some researchers to be a biological marker of aging and others theorize that age-associated changes in methylation lead to the selective activation of pro-senescent and pro-apoptotic genes.<sup>71-77</sup> In addition, many important second messenger and information-carrying molecules, such as catechol neurotransmitters, require methylation and use the homocysteine pathway for provision of a methyl group.<sup>78</sup> An increase in blood homocysteine levels is strongly linked to cognitive decline.<sup>79</sup>

#### Homocysteine (Hcy)

Hcy is an amino acid product of protein digestion that can accumulate in the blood if there is an insufficiency of one or more of the vitamin cofactors of methylation, which include folate and vitamins B<sub>6</sub> and B<sub>12</sub>.<sup>80</sup> In addition, genetic polymorphisms that lead to less efficient Hcy methylation are not uncommon.<sup>81</sup>

Hyperhomocysteinemia is a very strong and graded independent risk factor for cerebrovascular disease (CD), which is the second most common cause of irreversible dementia.<sup>79,82</sup> In one study, 42% of CD patients had hyperhomocysteinemia.<sup>83</sup> In addition, those with AD have significantly higher blood Hcy levels and lower folate and vitamin B<sub>12</sub> levels compared to controls.<sup>84,85</sup> In another study, up to 27% of psychogeriatric patients had hyperhomocysteinemia despite normal levels of blood folate and vitamin B<sub>12</sub>.<sup>86</sup>

At least four hypotheses explain why the accumulation of Hcy may lead to cognitive impairment: 1.) endothelial dysfunction, with decreased perfusion of the brain and consequent decreases in cognitive function, 2.) decreases in the relative availability of either folate or vitamin B<sub>12</sub>, and/or a genetic defect that decreases their function, may lead to a functional deficiency of one or both vitamins, causing cognitive impairment, 3.) higher blood levels of excitotoxic metabolites of Hcy that can alter brain function, and 4.) diversion of serine from supporting neuronal membrane and BBB integrity and neurotransmitter production to Hcy metabolism.<sup>58,80,87,89</sup>

### NUTRITIONAL MODULATION OF THE FOUR PATHWAYS OF NEUROLOGIC DECLINE

Multimodal nutritional intervention creates the opportunity for healthcare professionals to simultaneously intervene in the multiple and overlapping pathways leading to neurologic decline. By combining nutrients that have high CNS activity and address chronic inflammation, mitochondrial dysfunction, endocrine imbalance, and hypomethylation, as well as the free radical load that propagates these pathways, there is a better chance of interrupting the damaging cascade (Table 2).

#### Niacinamide

Niacinamide is a potent inhibitor of PARP and nitric oxide synthase (which can increase peroxynitrite formation and PARP activation), thereby reducing the cyclic inflammatory cascade.<sup>90-92</sup> In animal models of ischemia, administration of niacinamide inhibited PARP, resulting in reduced brain damage and neurologic functional losses.<sup>33,35,93</sup> As a co-factor for the production of mitochondrial NAD, niacinamide dose-dependently reduces ischemic neuronal infarction, presumably through preserving neuronal NAD and ATP.<sup>93</sup> Because niacinamide may help preserve levels of NAD and modulate the expression of pro-inflammatory molecules, it may have

**Table 2. Nutritional Modulation of the Pathways of Neurologic Health**

Pathway	Nutrient	Mechanism
Chronic Inflammation	Niacinamide EPA/DHA Ginkgo Resveratrol CoQ10, alpha-lipoic acid, vitamin E, mixed carotenoids	PARP inhibitor Replaces AA in brain cells, downregulates inflammatory COX activity Antioxidant, vasodilator, inhibits platelet-activating factor (PAF) Antioxidant, inhibits inflammatory COX and LOX activity and products, reduces platelet aggregation Antioxidant
Mitochondrial Dysfunction	Niacinamide Magnesium Thiamin CoQ10 Ginkgo, mixed carotenoids Acetyl-L-carnitine N-acetylcysteine Alpha-lipoic acid	Cofactor for NAD production Membrane integrity, ATP transfer Enzyme activity Antioxidant, respiratory chain activity, enzyme activity Antioxidant Transport and clearance of fatty acids, increases cardiolipin Antioxidant, increases GSH, improves mitochondrial electron transport chain Cofactor in ATP synthesis, antioxidant
Endocrine Imbalance	Ginkgo Adaptogenic herbs Magnesium Dysglycemia program (including alpha-lipoic acid)	Adaptogenic properties, decreases glucocorticoids Improves body's ability to cope with stress Deficiency can increase physiologic susceptibility to stress Nutrients that improve glycemic control help prevent neuronal damage mediated by hypoglycemia and nerve protein glycation mediated by hyperglycemia
Hypomethylation	Folate, B <sub>6</sub> , B <sub>12</sub>	Methylation of DNA, DNA stability, reduce homocysteine levels, neurotransmitter synthesis

antioxidant potential as well. In rats, administration of niacinamide inhibits oxidant-induced activation of NF- $\kappa$ B and of glial inducible nitric oxide synthetase (iNOS), both of which are potentially neurotoxic.<sup>94,95</sup>

Niacinamide, unlike niacin, does not cause flushing and pruritis. Mild side effects, mostly limited to GI disturbances, can be managed by taking niacinamide with food or fluids.

#### Essential Fatty Acids: EPA and DHA

The brain is particularly rich in polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Changes in the tissue membrane composition of these essential fatty acids are reflective of intake.<sup>96</sup> Fish oils, which contain EPA and DHA, are precursors of anti-inflammatory eicosanoids and are well known for their anti-inflammatory activity. Research indicates that substitution of EPA/DHA for AA in brain phospholipids may result in less cyclooxygenase (COX)-dependent cerebrovascular reactivity.<sup>97</sup> Furthermore, DHA is required for normal brain function in adults and is taken up in preference to other fatty acids. Decreases in brain DHA content are associated with age-related cognitive decline, dementias, and AD.<sup>98</sup> The amount of EPA/DHA estimated to prevent deficiency in the elderly is 300 to 400 mg per day combined.<sup>99</sup> Anti-inflammatory activity in conditions of chronic inflammation is observed at doses of 6 g per day.

#### Resveratrol

Resveratrol is a polyphenol found in the skins of red grapes and various other plants. In vitro, animal, and epidemiologic research suggests that resveratrol may be protective against central nervous system disorders.<sup>100</sup> In one study, chronic administration of resveratrol in young-adult rats protected the olfactory cortex and hippocampus from an injected toxin.<sup>101</sup> It has been shown to inhibit the COX-1, COX-2, and 5-LOX inflammatory pathways and prevent

the activation of NF- $\kappa$ B.<sup>102-104</sup> Resveratrol has potent antioxidant activity, inhibits the oxidation of lipids, inhibits platelet aggregation, and induces hepatic phase II detoxification activity.<sup>100,105</sup>

#### N-Acetylcysteine (NAC)

The protective effect of NAC is believed to be related to its restoration of brain glutathione (GSH) levels.<sup>106</sup> However, GSH does not cross the BBB, so oral supplementation with precursors such as NAC and alpha-lipoic acid are the best way to increase brain levels. GSH is central to antioxidant defenses in the brain, is an important component of the cellular detoxification of ROS, and is involved in the disposal of exogenous peroxides by astrocytes and neurons.<sup>107</sup> In preclinical stages of PD, a decrease in total GSH concentrations in the substantia nigra has been observed.<sup>108</sup>

NAC has been shown to increase complex I activity (a mitochondrial enzyme that is part of the machinery by which mitochondria generate the energy required by cells) and markedly improve mitochondrial electron transport chain complex (ETC) activity. NAC may also interfere with apoptosis.<sup>106,109</sup> In animal models of traumatic brain injury, NAC significantly restored mitochondrial energy producing mechanisms (electron transfer, energy coupling capacity, calcium uptake activity).<sup>106</sup>

#### Alpha-Lipoic Acid (ALA)

ALA is a cofactor in the synthesis of ATP and improves overall mitochondrial function.<sup>110</sup> It may also enhance mitochondrial function by protecting mtDNA and preventing oxidative changes in the mitochondrial membrane, which would impact its functional, energy-producing capacity.<sup>110,111</sup>

ALA is an excellent antioxidant agent in neurodegenerative diseases due to the fact that it can interrupt the free radical cascade at several points. It is a metal chelator, it supplies both intra-

cellular and extracellular antioxidant protection in brain tissue, it scavenges potent ROS (hydroxyl, superoxide, peroxy radicals) that initiate and propagate damage in neural tissue, it is protective against the formation of AGEs, and it promotes accelerated GSH synthesis.<sup>110-112</sup>

ALA also extends the functional capacities of other critical antioxidants in neurologic health, namely vitamins C and E and coenzyme Q10. Animal research has shown that ALA supplementation reduces lipid peroxidation, elevates antioxidants in various brain regions, and improves memory in aged mice.<sup>112,113</sup> In addition, ALA supports the removal of glucose from the bloodstream via the insulin signaling pathway. Mechanisms include the activation of kinases in target cells, which enhances the metabolic effects of insulin; increasing cell membrane glucose transporter (GLUT 1 and GLUT 4) content; and mimicking insulin action at the receptor. The vast majority of human research in ALA has been done in patients with diabetic neuropathy, showing clinical benefit at doses of 800 to 1200 mg/day.

### Acetyl-L-Carnitine (ALC)

Carnitine is a vitamin-like substance that is responsible for the transport of fatty acids into the mitochondria. It also supports the clearance of toxic accumulations of fatty acids and increases cardiolipin—an important phospholipid that serves as a cofactor for a number of critical mitochondrial transport proteins.<sup>114-117</sup> A deficiency in carnitine causes a decrease in mitochondrial fatty acid content, which can result in reduced energy production, and supplementation may improve energy production within brain cells. Carnitine in the form of ALC is thought to be substantially more active in the CNS and is the form found naturally in the brain.<sup>116</sup>

An analysis of controlled studies reports that persons with subclinical or clinical dementia given ALC supplementation (1.5 to 3 g daily) have shown improvement on numerous clinical measures of cognitive function.<sup>114</sup> Two large multicenter, crossover trials of geriatric patients given 1500 mg ALC daily for 90 days found improvements in clinical tests of cognition, memory, and depression in supplemented patients over controls.<sup>118,119</sup> In other double-blind, placebo-controlled trials, ALC-treated subjects showed less mental deterioration as rated by cognitive and AD assessment test scores.<sup>120,121</sup>

In addition to its beneficial impact on mitochondrial function, ALC supports the synthesis of the neurotransmitter acetylcholine, which is responsible for memory and brain function. Research suggests that ALC may be very beneficial in the early stages of neurodegeneration.<sup>116,117</sup>

### Magnesium

Magnesium plays an important role in maintaining the integrity and permeability of the mitochondrial membrane. Also, magnesium binds phosphate groups in ATP, forming a complex that assists in the transfer of ATP, which is critical for energy production. It is believed that magnesium deficiency creates a “sluggish” respiratory chain.<sup>80,122</sup>

Magnesium deficiency also increases susceptibility to physiologic damage produced by stress and hyperglucocorticoidemia, while elevated glucocorticoids negatively affect magnesium homeostasis.<sup>123</sup> Furthermore, magnesium deficiency, or dietary imbalances such as high intakes of fat and/or calcium that can intensify magnesium inadequacy, may increase risk of cerebrovascular constriction and occlusion.<sup>123</sup>

### Thiamin

Thiamin is a cofactor in mitochondrial metabolism. Deficiency results in depressed activity of enzyme complexes, resulting in a decrease in citric acid cycle activity and activities of the respiratory chain. Thiamin deficiency also decreases erythrocyte transketolase activity—an enzyme that catalyzes phosphate reactions.<sup>80,124</sup> Abnormal transketolase is associated with several metabolic distur-

bances including impairment of ATP synthesis, acetylcholine disturbances, and abnormalities in the serotonergic system.<sup>80,124</sup>

### Coenzyme Q10 (CoQ10)

CoQ10 is a lipid soluble mitochondrial antioxidant cofactor that has been shown to be neuroprotective.<sup>13</sup> In addition to being a potent free radical scavenger in lipid and mitochondrial membranes, CoQ10 is critical for the function of the mitochondrial respiratory chain. Physiological levels are known to decrease with age and supplementation has proven efficacious in a variety of age-related illnesses.<sup>125</sup>

Low levels of CoQ10 are associated with reduced mitochondrial enzyme activity (complexes I and II/III). In Parkinsonian patients, administration of CoQ10 showed a trend toward an increase in complex I activity.<sup>126</sup> Treatment of patients having various mitochondrial cytopathies with 150 mg per day CoQ10 improved all brain variables. These findings are consistent with the view that increased CoQ10 concentration in mitochondrial membrane improves the efficiency of oxidative phosphorylation.<sup>128</sup> A dose of 200 mg/kg in 12- and 24-month-old rats produced significant increases in CoQ10 levels of the cerebral cortex mitochondria.<sup>125</sup> CoQ10 administration was also shown to protect against striatal lesions and dopamine depletion produced by toxins.<sup>125</sup> Vitamin E and CoQ10 taken together are believed to have an interactive effect; CoQ10 has a sparing effect on vitamin E and vitamin E plays a key role in determining tissue retention of exogenous CoQ10.<sup>128</sup>

### Vitamin E

Vitamin E is the primary lipid soluble antioxidant found in all tissues. Low vitamin E levels are consistently associated with an increased risk and occurrence of neurologic disease, including AD and PD.<sup>129,130</sup> Patients with prolonged deficiency may develop decreased reflexes, failure of muscular coordination (ataxia), dementia, and blindness.<sup>131</sup> In a double-blind, placebo-controlled, randomized, multicenter trial in patients with AD, treatment with 2000 IU of vitamin E per day for 2 years was beneficial in delaying the primary outcome (time to the occurrence of death, institutionalization, loss of ability to perform activities of daily living, severe dementia) of disease progression.<sup>132</sup> In fact, the estimated increase in median survival with vitamin E supplementation was 7.5 months. The results of other studies of neurodegeneration have been mixed and further clinical trials in the early stages of neurodegeneration are needed.

Peroxynitrite is a potent RNS formed by the reaction of nitric oxide and superoxide. It is implicated in multiple phases of neurologic damage, including producing a pro-inflammatory environment, inducing DNA strand breaks that activate PARP, depleting GSH, damaging multiple cellular and mitochondrial components, and inducing the formation of beta-amyloid. The gamma-tocopherol form of vitamin E is a potent trapper of peroxynitrite and is more effective than alpha-tocopherol in protecting lipids against peroxynitrite.<sup>133</sup>

### Ginkgo (*Ginkgo biloba*)

The leaves of the ginkgo tree have been used medicinally for thousands of years for ailments ranging from asthma and bronchitis to impaired cerebral blood flow. *Ginkgo biloba* extract (GBE) is an approved treatment for dementia in Germany, and it is the only nonprescription substance considered a treatment for dementia in Canada.<sup>134</sup> Many European clinical studies have demonstrated the effectiveness of GBE in the treatment of patients with age-associated memory and cognitive impairment as well as dementia and AD.<sup>135-138</sup> The first clinical trial conducted in the U.S. to assess the efficacy and safety of GBE was published in the *Journal of the American Medical Association*.<sup>139</sup> In this randomized, double-blind, placebo-controlled study, patients with dementia and AD received 120 mg/day GBE or placebo for 1 year. The results of the study indi-

cated that GBE was safe and improved the cognitive performance and social functioning of the patients in a substantial number of cases, in contrast to worsening of these functions in controls.

GBE has been shown to have several mechanisms of action: it scavenges oxidative radicals, inhibits platelet aggregation, improves circulation to the brain, and may help normalize cerebral metabolism under hypoxic conditions.<sup>138,140,141</sup> The therapeutic actions of GBE are thought to be due to synergy among its flavonoid, terpenoid, and organic acid constituents. High quality GBE is typically standardized to 24% ginkgo flavone glycosides (quercetin, kaempferol, and isorhamnetin) and 6% terpene lactones (primarily ginkgolides and bilobalide), and most clinical trials have used a dose of 120 mg/day. The primary neuroprotective actions of GBE have been attributed to the terpene lactones, particularly the ability of the ginkgolides to block the action of platelet activating factor (PAF).<sup>140</sup> PAF produces pro-inflammatory effects and has a direct effect on neuronal function and long-term potentiation. The flavonoids are responsible for GBE's antioxidant properties: it dose-dependently inhibits induced in vitro lipid peroxidation, prevents hydroxyl radical damage to neurons and their DNA, scavenges superoxide radicals, and protects against the age-associated oxidative damage to mtDNA and oxidative losses of mitochondrial glutathione.<sup>141-146</sup> In addition, GBE may also prevent changes in mitochondrial morphology and function associated with aging of the brain.<sup>146</sup>

GBE also shows anti-stress and adaptogenic properties in animals: it decreases blood glucocorticoid levels and increases adrenocorticotrophic hormone levels, showing positive potential for stress-related cognitive impairment; prevents stress-induced learning impairment and elevations in stress hormones in young and old rats; and increases acetylcholine synthesis and the turnover of norepinephrine.<sup>147-149</sup> The safety of GBE is well established and side effects occur very seldom (gastrointestinal upset, headache, and allergic skin reactions).<sup>134</sup> Concern over interactions between GBE and blood-thinning drugs seems reasonable, though few clinical examples have been reported.

Due to the decreased ability to handle stress and increased activation of the HPA axis associated with aging and neurodegeneration, additional herbs with adaptogenic properties may be beneficial. Ayurvedic herbs such as ashwagandha (*Withania somnifera*), gotu kola (*Centella asiatica*), and Brahmi (*Bacopa monniera*) have a positive influence on stress response, mental function, and cognition. Furthermore, they have been used historically in the traditional model of Ayurveda to nourish the brain and support mental function, alertness, and memory. (Please refer to "Ayurvedic Herbs for Mental Function" for a thorough discussion of these herbs.)

### Mixed Carotenoids with Lutein

Carotenoids are a class of naturally occurring plant pigments that provide the bright red, orange, and yellow colors of fruits and vegetables. The data support a balanced intake of mixed carotenoids, as found in a healthy diet, to provide the best protection against oxidative damage and to maintain their spectrum of activities. A variety of biological activities may account for the association of carotenoids with lower risk of chronic diseases, which often manifest with increasing age. For example, beta-carotene is more effective at protecting membranes from damage by free radicals than other carotenoids and lutein is more efficient in scavenging ROS.<sup>150</sup> As potent quenchers of singlet oxygen—a highly reactive and destructive free radical that also forms peroxyxynitrite—carotenoids may support neurologic tissue health. Peroxyxynitrite may propagate multiple phases of neurodegeneration in the mitochondrial and chronic inflammation pathways.

In addition, the carotenoid lutein, along with zeaxanthin, is found concentrated in the retina of the eye where it offers protection from structural damage via antioxidant mechanisms. Research suggests

lutein as a preventative strategy for reducing the risk of conditions associated with oxidative damage to eye structures, including age-related macular degeneration (ARMD).<sup>150,151</sup> Reduced risk of chronic disease has been observed at doses of 1 to 2 mg of lutein per day and therapeutic levels can reach 10 to 12 mg per day.<sup>151</sup>

### Folate, Vitamin B<sub>6</sub>, and Vitamin B<sub>12</sub>

Folate and vitamins B<sub>6</sub> and B<sub>12</sub> are needed for proper methylation, genome stability, and Hcy metabolism. Rosenberg and Miller of the USDA Human Nutrition Research Center on Aging state that age-related impairment of cognitive function is likely related to mild or subclinical vitamin deficiencies, and is "preventable or reversible with improved vitamin nutrition, especially vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, and folate."<sup>152</sup> Cognitive health conditions associated with insufficiencies of these nutrients include forgetfulness, memory loss, confusion, depression, dementia, and mood and sensory changes.<sup>80,152-154</sup>

Methods of reducing Hcy have been a target of investigation due to its extremely harmful effects on body systems—including the nervous system.<sup>155</sup> Methylation and transsulfuration are the main pathways by which Hcy is metabolized or removed. Low levels or poor absorption and utilization of folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> have been associated with an increased risk of hyperhomocysteinemia.<sup>154-156</sup>

Studies have repeatedly shown that supplementation with the B vitamins required for Hcy metabolism are effective in lowering blood Hcy levels. In a placebo-controlled study, 100 men with hyperhomocysteinemia were randomly assigned to 5 groups and treated with a daily dose of either a placebo, 650 mcg of folic acid, 400 mcg of vitamin B<sub>12</sub>, 10 mg of vitamin B<sub>6</sub>, or a combination of the three vitamins for 6 weeks.<sup>157</sup> Compared to the control group, plasma Hcy concentrations were reduced by 41.7% in the folic acid group, 14.8% in the vitamin B<sub>12</sub> group, and 49.8% in the group supplemented with all three vitamins. Vitamin B<sub>6</sub> alone did not significantly reduce plasma Hcy concentrations. It should be noted that it is important to balance intake of these nutrients; for instance, vitamin B<sub>6</sub> in isolation in amounts above 150-200 mg per day can cause neuropathics due to accumulation of metabolic products toxic to the nerves.

## CONCLUSION

Healthcare professionals and their patients must take a preventative stance against neurologic decline. Because of the great deal of interest and research in this area, information about appropriate nutritional supplementation is constantly evolving. By looking for early warning signs and providing nutritional guidance that simultaneously addresses chronic inflammation, mitochondrial dysfunction, endocrine imbalance, and hypomethylation, perhaps more patients can live out their most rewarding years with mind and body intact.

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