

# Energy, Mood & Neurotransmitters

## Nutrients that Naturally Build Energy, Enhance Mood and Promote a Sense of Well-Being

### Introduction

Webster defines energy as: "Vigor in performance of an action; Vitality; The capacity for action or accomplishment." Whether at work or play, we need energy to sustain endurance and derive pleasure. Moreover, an enhanced quality of life depends not only on physical energy, but emotional health and mental well-being.

The standard American diet is deficient in many of the nutrients we need to stay healthy, both physically and mentally. What causes these deficiencies? We need only consider the high-sugar, low-fiber, additive-preserved foods that many people consume on a regular basis, combined with the impaired absorption of nutrients that accompanies such poor nutrition. They are at once overfed and under nourished, and a poorly nourished body contains a malnourished brain. Deficiencies in almost any of the vitamins and minerals we need can show up first as emotional or mental symptoms, such as lack of energy, depression, anxiety, or impaired memory and concentration.

Lack of energy and depression can result if brain messengers called neurotransmitters are in short supply. Amino acids, the building blocks of protein, are the precursors, or raw materials, for neurotransmitters and other mood-regulating compounds. There are three amino acids that are most directly related to mood and depression: phenylalanine, tyrosine and tryptophan. Phenylalanine and tyrosine produce the neurotransmitter norepinephrine, and tryptophan is eventually converted to serotonin. Both phenylalanine and tyrosine – which is created in the body from phenylalanine – have been found to be as effective as the anti-depressant drug, imipramine in studies. Phenylalanine has also been shown to reduce pain by preserving brain levels of endorphins, the body's natural painkiller. It is important to take sufficient amounts of amino acid cofactors,

such as the vitamin B complex, which your body needs to properly process amino acids. Our bodies cannot create vitamins, so a well-balanced, supplemented diet is necessary to obtain adequate amounts of these essential nutrients. Vitamins act as catalytic agents in the body, helping to speed up the chemical processes that are vital for both survival and brain function. The Recommended Daily Allowance (RDA) is inadequate. These figures are based on the minimal requirements for prevention of severe deficiency disease, rather than on the requirements for optimum health or deficiency correction. The brain uses vitamin B1 (thiamine) to help convert glucose, or blood sugar, into fuel, and without it the brain rapidly runs out of energy. Subclinical deficiencies of vitamin B3 (niacin) can produce agitation and anxiety, as well as mental and physical slowness. Vitamin B6 (pyridoxine) is essential for the creation of neurotransmitters. Studies have found a strong correlation between vitamin B6 deficiency and depression. Shortages can also produce anemia. Because vitamin B12 (cyanocobalamin) is important to red blood cell formation, deficiency leads to an oxygen-transport problem known as pernicious anemia. This disorder can cause mood swings, paranoia, irritability, or mania, eventually followed by appetite loss, dizziness, and weakness. Folic acid, another B vitamin, helps assist in the creation of many neurotransmitters. It is also essential to the production of hemoglobin, the oxygen-bearing substance in red blood cells, so deficiencies often lead to anemia. Studies have shown abnormally low levels of this vitamin in a quarter to a third of all depressed persons. Another symptom is fatigue.

Panax ginseng has a long history of use and a wide range of possible therapeutic applications. Thus the term "Panax," which is derived from the Latin word panacea meaning "cure all." Panax ginseng helps the body to cope with stress through its effects

upon the functioning of the adrenal gland. Research has suggested that ginseng reduces fatigue, increases stamina and produces positive results in mood enhancement. Ginseng is considered to be an adaptogen. An adaptogen is a substance that has the ability to bring the body back into a healthy, balanced state.

DMAE is a chemical compound that is one of the raw materials for the production of the B complex vitamin, choline. DMAE is considered to be a non-essential nutrient since small amounts are produced in the human brain, however, supplementation can increase natural levels of choline. Choline is an important physiological agent that the body is unable to produce on its own. DMAE is believed to work primarily by speeding the production of acetylcholine, a crucial neurotransmitter responsible for carrying messages between brain cells and from the brain to the muscles that control body movements. Inositol is another nutrient closely related to the B complex vitamins. Small amounts are manufactured in the human body and the rest we get from our diet. Because of its roles in cellular communication, inositol is used in several different neurological related conditions. It has been the subject of numerous studies that have shown its positive effects on mood, depression and panic disorder. Some of the research points to the ability of inositol to act similarly to the selective serotonin reuptake inhibitor (SSRI) drugs in certain neurological conditions, such as depression.

Supplementation of nutrients, such as those mentioned above, can have profound effects on individuals who are deficient. Their properties are proven to relieve stress, restore energy, and elevate mood, all of which promotes an enhanced quality of life. This review presents clinical evidence and general information on these nutrients.

## **Nutrients That Have a Positive Effect On Energy, Mood and Neurotransmitters**

### **GINSENG**

#### **What is Ginseng?**

The herbal remedies referred to as 'ginseng' are derived from the roots of several plants. For thousands of years, the roots of this slow-growing plant have been valued in Chinese medicine as a tonic indicated for its beneficial effects on the central nervous system, protection from stress ulcers, increase of gastrointestinal motility, anti-fatigue action, enhancement of

sexual function and acceleration of metabolism. The two most commonly used species are Asian or Korean ginseng (*Panax ginseng* C.A. Meyer) and American ginseng (*Panax quinquefolius* L.). [1,2]

Written records of the medical use of ginseng first appeared about 2,000 years ago. The word 'panax' comes from the Latin 'panacea,' meaning 'all healing' or 'universal remedy,' indicating the wide belief that ginseng is effective in combating ailments of all kinds. [3]

The main active components of *Panax ginseng* are ginsenosides, which are triterpene saponins. The majority of published research on the medicinal activity of *Panax ginseng* has focused on ginsenosides. These are the compounds to which some ginseng products are now standardized. [4]

Ginseng contains a complex mixture of carbohydrate compounds, nitrogenous compounds, fat soluble compounds, vitamins and minerals. It is the complex carbohydrate compounds called ginsenosides that are the significant active ingredients. These compounds have chemical structures similar to human hormones and it is believed that they may work similarly. [5]

#### **General Functions**

Quality research teams in China, Japan, Korea and the US suggest that ginseng helps the formation of red blood cells and helps to eliminate anemia. [6,7] Their research has also found positive results in mood enhancement and the ability to perform mental tasks, reduce fatigue after mental exertion, and reduce blood sugar levels (used to prevent and/or treat diabetes). [1,8]

Ginseng has been found to enhance sexual functions. Animal studies have shown that ginseng can increase sperm production, sexual activity, and sexual performance. A study of 46 men has also shown an increase in sperm count as well as motility. [9,10] Ginseng properties were studied to conclude that the root helps facilitate liver regeneration and enhances blood alcohol clearance, thus reducing the effects of alcohol consumption. [11,12]

Ginseng is considered to be an adaptogen. An adaptogen is a substance that has the ability to bring the body back into a healthy, balanced state. Ginseng is seen as having both soothing and revitalizing adaptogenic properties. Ginseng seems to be able to increase the body's ability to adapt and adjust. It is believed that the active ingredients in ginseng can

harmonize body functions and are only used as needed, even if taken regularly. [5]

## Ginseng and Energy

Having enough energy to get through each stress-filled day has become a challenge. A healthy 'tonic' is much preferred to the strong stimulants that take you to the heights, only to crash and burn a short time later. Ginseng is considered 'energizing,' but has not been shown to stimulate the central nervous system the way coffee and other stimulants do. As stated above, ginseng contains natural compounds plus vitamins and minerals.

- > In a double-blind study, 50 healthy male sports teachers between 21 and 47 years of age were given, every day for 6 weeks, 2 capsules of a preparation containing ginseng extract, DMAE, vitamins, minerals and trace elements or 2 placebos. They were assessed for physical performance by a treadmill with increasing work loads. The total work load and maximal oxygen consumption were significantly greater during exercise after this preparation was administered, versus placebo. At the same work load, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production and heart rate during exercise were significantly lower after the ginseng and DMAE preparation, versus placebo. These results indicate that the combination of ginseng, DMAE, etc. can increase the subjects' work capacity by improving muscular oxygenation. [13]

## Ginseng and Sexual Function

Few people would disagree with the idea that sex is basic to human existence. It is not only a tremendous source of pleasure, but also a key element of both male and female identity. Panax ginseng has long been reputed to increase sexual energy and endurance. It promotes overall good health, which in turn promotes optimal sexual health. Ginseng revitalizes the adrenal glands, boosts the immune system, and works to reduce the effects of stress. It has also been shown to stimulate the central nervous system in a natural way. Experts agree that the most potent sensory organ in the body is the brain, and numerous studies have concluded that ginseng enhances mental activities and mood. [14]

- > A study published in the Journal of Urology notes that Korean ginseng, when ingested at a dose of 900 mg, three times per day, significantly increased sexual

desire and satisfaction with sexual performance, compared to placebo. Sixty percent of men taking the 2,700 mg daily dose of the Korean ginseng reported better erections and in general, better maintenance of the erection. [15]

- > The efficacy of Korean ginseng (*Panax ginseng*) in treating erectile dysfunction was demonstrated in a random-controlled clinical trial involving a total of 90 patients studied over 3 months, 30 each receiving placebo, trazadone, or ginsenosides. Ginseng was the most efficacious treatment with improvements measured in erectile parameters such as girth, libido, and patient satisfaction. [16]

## Ginseng and Blood Sugar

Diabetes is a major health problem in North America reaching epidemic proportions. In the past decade, the United States has seen a dramatic 33% rise in diabetes coupled to increases in obesity and unhealthy lifestyle. [17,18] This increase in diabetes has occurred in spite of major inroads in understanding the pathophysiology and treatment of this insidious disease. Current therapies seem to be insufficient to prevent diabetic complications in type 2 diabetes with two- to four- fold likelihood for developing cardiovascular events. [19] Because of these limitations, there is a continuous need for the development of novel health promotion strategies and therapeutic modalities.

- > Ginseng non-nutritive polysaccharides (GP) known as panaxans have anti-diabetic, blood sugar lowering effects. GP reduces blood sugar and liver glycogen formation through enhanced metabolism (oxidative phosphorylation) of carbohydrates and decreased liver glycogenesis (this result shows that reduction in blood sugar may be partially mediated through non-insulin mechanisms) and increased insulin release. [20]
- > The effects of Panax ginseng, given in a dosage of 100-200 mg per day for eight weeks, were studied in 36 patients with newly diagnosed non-insulin-dependent diabetes. The study showed improved fasting blood glucose levels, elevated mood, and improved psychophysical performance on a numbered diagram test. The 200 mg dose also resulted in improved hemoglobin A1C values. [21]
- > In a study in the U.K., people with type 2 diabetes who consumed ginseng and a highly viscous fiber similar to

pectin had a notable reduction in blood sugar levels. The study enrolled 30 people with diabetes in whom medication helped to control, but did not normalize, blood sugar levels. The participants received either capsules containing ground, North American grown ginseng and a highly viscous fiber, or dummy capsules, three times a day for 12 weeks. After a 4-week break, the participants switched to the alternate regimen. Blood samples taken before and after each 12-week period showed that hemoglobin A1C, a standard measure of blood sugar levels, dropped into the normal range when participants were taking the ginseng/fiber capsules, but not when they were taking placebo. The herbal preparation appeared to be safe, with no adverse effects. [22]

ments induced a significant increase in a quality of life index in comparison to placebo, but the increase was significantly higher for the ginseng/vitamins group. [29]

- > A study by Sorensen and Sonne on cognitive effects of ginseng involved 112 healthy participants over 40 years old (40-70) who received either 400 mg of standardized ginseng extract or placebo daily for 8-9 weeks. Tests included the finger tapping test, both auditory and visual simple reaction time tests, a verbal fluency test and a Logical Memory and Reproduction Test. Results showed statistically significant performance improvements for the ginseng group, in comparison to placebo. [30]

## **Ginseng – Mood Enhancement, Cognitive Performance and Neurotransmitters**

Ginseng has been attributed with a plethora of physiological effects that could potentially benefit cognitive performance and mood. Studies involving animals show that ginseng and its constituent ginsenosides can modulate indices of stress, fatigue, and learning. Recent research has demonstrated that single doses of ginseng most notably engender cognitive benefits in terms of improved memory, and has also been shown to modulate cerebroelectrical (EEG) activity. [23] According to the Natural Standard Patient Monograph, mental performance benefits from ginseng have been seen both in healthy young people and in older ill patients. [24] People taking ginseng often report feelings of improved overall well-being. [25]

- > A double-blind study by Wiklund et al using the same primary endpoint as their previous (1994) study, demonstrated significant improvements in comparison to placebo on several subscales of the Psychological General Well Being Index to 394 symptomatic postmenopausal women. This finding has offered some qualified support to the results of a controlled trial by Tode et al, which showed that 12 postmenopausal women with climacteric syndrome showed improvements both in an imbalance of hormones and on measures of mood following 30 days administration of 6 g of ginseng. [26-28]
- > A study by Marasco et al attempted to isolate the effect of ginseng on the well-being of subjectively stressed and fatigued participants (625), in a double blind study administering either multivitamin capsules or multivitamin/ginseng capsules taken for 12 weeks. Both treat-

## **SAFETY**

It is important that consumers ensure that they are purchasing authentic ginseng extract that has been standardized, and comes from a reputable company. There are wide variations in quality among different brands. That being noted, standardized ginseng extract has been well tolerated by most people in scientific studies when used at recommended doses, and serious side effects appear to be rare. [24]

Based on human research, ginseng may lower blood sugar levels. This effect may be greater in patients with diabetes than in non-diabetic individuals. Caution is advised in patients with diabetes or hypoglycemia and in those taking drugs, herbs, or supplements that affect blood sugar. Avoid use of ginseng in patients with hormone sensitive conditions, such as breast cancer, uterine cancer, or endometriosis. [24]

Ginseng should be discontinued at least 7 days prior to surgery for two reasons. First, ginseng can lower blood glucose levels and, therefore, create problems for patients fasting prior to surgery. Second, ginseng may act as a blood thinner, thereby increasing the risk of bleeding during or after the procedure. [9]

## **GUIDELINES FOR USE**

Adults (18 years and older): 100-200 mg of a standardized ginseng extract taken by mouth once or twice daily has been used in studies for up to 12 weeks. [24]

## DMAE / DEANOL

### What is DMAE / Deanol?

DMAE and deanol are the abbreviated names for 2-dimethylaminoethanol, a chemical compound that is one of the raw materials for the production of the B complex vitamin, choline, and is produced in small amounts within the human brain. In the brain, choline is a precursor to the neurotransmitter acetylcholine, which is associated with a wide variety of processes throughout the body, including cognitive functions such as memory and attention. DMAE is found in foods such as anchovies, sardines, and other fish. In supplement form, DMAE is available in many salt or ester forms under a number of different name endings; all of these chemical versions are given the first name of 'deanol', thereby assisting in its identification. DMAE is considered to be a non-essential nutrient, however supplementation can increase natural levels of choline, which is an important physiological agent that the body is unable to produce on its own. Therefore, DMAE should be replenished everyday through the diet or through dietary supplementation. [31]

### General Functions

DMAE is a memory enhancing substance common to a number of European drugs and has shown positive results for a variety of cognitive and disruptive disorders, including attention deficit hyperactivity disorder (ADHD). [32] It has been shown to stabilize cell membranes. Cell membrane degradation has been proposed as one of the prime mechanisms of aging. [33] DMAE has been known as a "smart drug" as far back as 1959 when treatment with DMAE was demonstrated to result in significantly improved test scores. [34] Given the ever-increasing pressures to achieve in modern society, it was only natural that a compound long used to treat brain dysfunction and memory disorders would be explored for its potential use as a memory enhancer and brain "booster." [35]

Research has shown that DMAE's cholinergic effects help produce brain chemicals such as acetylcholine that are necessary for mental sharpness. [36] Some individuals accordingly report that DMAE supplementation causes a noticeable boost in their ability to concentrate. DMAE users also routinely report better memory (especially short-term memory), as well as improved focus and mental clarity, which may be particularly valuable for those who work in high-pressure or deadline-oriented environments. [37]

DMAE is a precursor to choline and acetylcholine. It is the choline inside cells that is converted to phosphatidylcholine, used in the building and repair of cell membranes, especially in the brain. DMAE is believed to work primarily by speeding the production of acetylcholine, a crucial neurotransmitter responsible for carrying messages between brain cells and from the brain to the muscles that control body movements. Acetylcholine, a synthesized product of choline, is also involved in higher brain functions such as learning, recall, and memory. [38] Animal studies show that taking DMAE can boost levels of choline in the brain, [39] which in turn increases the body's ability to produce acetylcholine, resulting in a corresponding increase in memory ability and potency. Studies suggest that DMAE crosses the blood-brain barrier more effectively than choline itself enabling it to reach the brain and increase the brain's choline levels more efficiently. [40]

### DMAE/Deanol Affects Choline Metabolism

- > In an animal study by Haubrich et al, administration of deanol caused an increase in the concentration of both choline and acetylcholine in the corpus striatum, indicating that synthesis of brain acetylcholine can be stimulated *in vivo* by elevating the tissue concentration of its precursor. This finding suggests that the concentration of free choline in the brain is below that necessary for a maximal rate of synthesis of acetylcholine, and raises the possibility that the availability of choline in the brain may regulate the rate of synthesis of acetylcholine. These results also provide biochemical evidence for the view that the clinical effects of deanol result from its conversion to acetylcholine. [41]

### DMAE/Deanol Effects on Cerebral Cortical Neurons

- > In another animal study by Kostopoulos and Phillis, sixty-seven spontaneously firing neurons in the sensorimotor area of rat's cortex were tested, including 19 identified corticospinal cells. Deanol excited all 19 corticospinal cells and of the 48 unidentified neurons, 71% were excited and 8% inhibited. [42] Their results showed that injection of labeled DMAE into animals is rapidly taken up by brain tissue and incorporated into lipids. [43] Deanol has been shown in this study to activate muscarinic receptors on neurons of the rat cerebral cortex, including corticospinal cells. [42]

## **DMAE Influence on the Mental and Physical Efficiency in Man**

- > This study involved 120 healthy soldiers, volunteers 20 years old, receiving DMAE in the dose 100-200 mg or 150-300 mg daily during 2 weeks. It was found that DMAE increases the ability to remember in evaluation of Wechsler, Kirschner and Babcock test. It also significantly increased the concentration of attention, logical understanding, and improved the ability of association mathematical calculation and reasoning, with the greater dose having a better effect. There was increased muscle strength, an increase of the index of physical efficiency, an increase in speed, a greater ability to learn and a good general feeling. [36]

## **The Effect of DMAE on Life Span**

- > Cellular membrane degradation has been proposed as a prime mechanism of aging. DMAE is common to a number of drugs known to stabilize cellular membranes. Of additional significance with respect to tests of the membrane hypothesis is the fact that DMAE is the immediate precursor of choline in the biosynthesis and repair of cellular membranes. Of particular interest to the present investigation is the fact that dietary choline is inferior to dietary DMAE as a source of choline for membrane biosynthesis. DMAE has a remarkable ability to cross the blood-brain barrier; choline does not. Aging is associated with an increasing biochemical imbalance and age changes may be partly the result of cells not having optimum or correct amounts of vital substances needed for their function. Because of its essential role in membrane biosynthesis, DMAE is one such vital substance. In this study done by Hochschild, senile mice from a long-lived strain were used and divided into a control group and a drug-treated group. The DMAE group outlived the control group by 36%. The author considered this a sizeable life span extension even though drug administration was started late in the animals' life. It was concluded that life span may be influenced pharmacologically well into old age. [33]

## **SAFETY**

DMAE is safe to use for adults. With proper dosage, no adverse effects have been reported as a result of DMAE supplement intake. Consult your physician prior to taking DMAE,

or any other supplement for the first time or with an existing treatment.

## **GUIDELINES FOR USE**

Normal daily doses of DMAE in single-ingredient form range from 100 mg to 500 mg.

## **PHENYLALANINE**

### **What is Phenylalanine?**

Phenylalanine is an essential amino acid – meaning that the body cannot synthesize it on its own and we must get it from the diet. The primary dietary sources of phenylalanine are high protein foods such as meat, fish, eggs and dairy products. Amino acids come in two forms, designated as “L” and “D” forms. The L-form is the naturally occurring form in foods, whereas the D-form is the synthetic variety. Sometimes the D-form is removed, but in the case of phenylalanine, the combination of the two forms is used to take advantage of the unique characteristics of both forms. The combined form of the supplement is known as DL-phenylalanine or DLPA. [44]

### **General Functions**

DLPA has two distinct fates in the body. The L-form of phenylalanine can be converted in the body to another amino acid – tyrosine. Tyrosine, in turn, can be converted into one of several neurotransmitter molecules (L-dopa, norepinephrine, and epinephrine), each of which have important functions in brain metabolism. The D-form of phenylalanine cannot be converted to tyrosine, but it can be converted to another compound called phenylethylamine (as can the L-form), which may have effects in elevating mood, treating depression and altering pain sensation. [44]

In addition, phenylalanine teams up with tryptophan, another amino acid, to control the release of cholecystokinin, an intestinal hormone commonly called CCK. It plays an instrumental role in controlling appetite by signaling the brain when the stomach is full, thereby turning off the hunger signals that can lead to overeating. Phenylalanine is capable of passing through the brain's protective blood-brain barrier and acting directly on brain chemistry. It is thought to play roles in memory and alertness. Phenylalanine is also thought to prevent the breakdown of the brain's natural painkillers. [45]

## Phenylalanine and Pain Management

Research suggests that DL-phenylalanine has an analgesic (pain relief) effect by way of blocking the degradation of enkephalin by the enzyme carboxypeptidase A. Enkephalins are endorphins in the brain that bind to specific receptor sites, including pain-related opiate receptors. Unlike other substances that target opiate receptors, there has been no data to indicate addiction or withdrawal symptoms associated with phenylalanine. The slow-acting, but long-lasting compound is recommended for chronic pain rather than acute pain.

- > In a human trial, patients suffering from chronic pain were given 250 mg phenylalanine orally 3 or 4 times a day for 5 weeks. Significant relief occurred after 4 weeks for the total population (n=43) and after 2 weeks for the subset of arthritic patients (n=30). [46]
- > In animal studies, D-phenylalanine decreased chronic pain within 15 minutes of administration and the effects lasted up to six days. [47] It also decreased responses to acute pain. These findings have been independently verified in at least five other studies. [48,49]
- > Twenty adult patients with longstanding intractable pain of various conditions, resistant to previous therapy, were admitted to a double-blind, crossover study in which orally administered D-phenylalanine, 250 mg, three times daily was compared with placebo. Assessments were made at two weeks, the crossover time and at four weeks when patients reported whether they had less or more pain or that there was no change. Of the twenty patients, seven showed an improvement of 50% or more while receiving D-phenylalanine, one patient improved on placebo, two patients withdrew because of lack of analgesia and four patients on D-phenylalanine reported the occurrence of side-effects. It was concluded that D-phenylalanine produced significant analgesia in the patients studied and further investigation of this class of agent was warranted. [50]

## Phenylalanine and Mood Enhancement

Mild depression, “the blues” and lack of energy can, often times, be non-specific responses to a wide variety of stressors, hormone imbalances or biochemical abnormalities. There are millions of tired and stressed-out people who can relate to promises of natural products that will enhance their

brain function; and the number is continually growing as the worldwide population ages. An important part of maintaining optimal brain function is ensuring that the brain receives an adequate supply of nutrients that promote improvements in mood, emotions, confidence and self-efficacy. Along with the proper nutrients, regular exercise and adequate diet can result in profound changes in the body’s own production of mood elevating chemicals such as the endorphins that cause “runner’s high” and neurotransmitters such as serotonin that contribute to emotional well-being. Phenylalanine has been associated with improved mental function – particularly under conditions of chronic stress. Phenylalanine is converted to the amino acid, tyrosine, and then in turn converted to the neurotransmitter norepinephrine, which may help elevate mood. [51]

- > In a double-blind controlled study, DL-phenylalanine (150-200 mg/24 h) or imipramine, an antidepressant drug, (150-200 mg/24 h) was administered to 40 depressed patients (20 patients in each group) for 30 days. Diagnoses were established according to the International Classification of Diseases. The AMP system, the Hamilton Depression Scale and the Bf-S self-rating questionnaire were used to document psychopathological, neurologic, and somatic changes. Twenty-seven patients (14 on imipramine, 13 on phenylalanine) completed the 30 day trial. No statistical difference could be found between these two drug treatments. It was concluded that DL-phenylalanine might have substantial antidepressant properties. [52]
- > Another human study compared the effectiveness of D-phenylalanine to imipramine, an antidepressant drug. Sixty people with depression were randomly assigned 100 mg daily doses of either DPA or imipramine for 30 days. The results in both groups were statistically significant, with the DPA showing positive effects more quickly than the antidepressant drug. [53]

## SAFETY

The amount of phenylalanine needed to produce toxicity in humans remains unknown. Transient headaches and nausea has, however, been reported when persons supplemented with amounts reaching nearly 1500 mg per day. [54]

Phenylalanine should be avoided by persons with phenylketonuria (PKU) and tardive dyskinesia. Tardive dyskinesia (TD) is characterized by a condition of abnormal, repetitive and uncontrollable movements, resulting from the long-term use

of antipsychotic medications (e.g. schizophrenia). These individuals may suffer from an abnormality, which sharply inhibits the processing of phenylalanine. [54]

## GUIDELINES FOR USE

The National Research Council has established recommended dietary allowances (RDAs) for phenylalanine. Individuals over 13 years of age should get 14 mg/kg of bodyweight per day.

Some adults may need to tailor intake to an allowance approaching 39 mg/kg of bodyweight to obtain physiological improvement. The median intake of phenylalanine ranges from 750 to 3,000 mg per day for adults. [54]

In addition, the U.S. National Academy of Sciences recommends that healthy people achieve 0.36 grams of highly bioavailable protein for each pound of bodyweight – equaling 0.8 grams of protein, per kilogram of bodyweight per day. [54]

## INOSITOL

### What is Inositol?

Inositol is a nutrient that is often referred to as a B vitamin compound, but is not a true vitamin in that small amounts are manufactured in the human body and biosynthesized primarily from glucose. Inositol works within cells, assisting in the processes of cellular communication, regulation of metabolism, and growth. It is known to exist in several different forms called stereoisomers, or chemicals with similar structural makeup yet different biologic function. [55] Myo-inositol is the most widely available stereoisomer of the brain. Inositol is found widely in foods derived from both plants and animals. A standard American diet will provide roughly one gram of the nutrient per day. More specifically, inositol is found in the largest amounts in cereals, legumes, and other rich sources of dietary fiber. [56]

### General Functions

Inositol in the body exists as part of the cell membrane, phospholipid arrangement. It can work as a weak lipotropic agent, meaning it has the ability to move fat from the liver and intestinal cells. [57] Because of its roles in cellular communication, inositol is used in several different neurological related conditions. Inositol plays a key role in cellular signals,

which involve serotonin, norepinephrine, and cholinergic receptors in the brain. [58] In fact, some research points to the ability of inositol to act similarly to the selective serotonin reuptake inhibitor (SSRI) drugs in certain neurological conditions such as depression. For persons with obsessive-compulsive disorder (OCD), inositol supplementation may improve their symptoms after a minimal duration; usually several weeks of treatment. [59] Similarly, in people with panic disorder, inositol supplementation can decrease the number and intensity of panic attacks after only 4 weeks of treatment. [60] Studies have also compared inositol to a commonly used drug for panic attacks (fluvoxamine), deeming it equally effective. [61]

### Inositol and Depression, Mood

The prevalence of depression in the United States is not definitively known. Depressive symptoms occur in 13-20 percent of the U.S. population. Depression is twice as likely to occur in females, average age of onset being 35-45; whereas it is 55 years of age for men. The biological origin of depression is believed to be linked to a deficiency of neurotransmitters at post-synaptic receptor sites. In the catecholamine theory the deficiency is norepinephrine; in the indolamine theory the deficiency is serotonin. Receptors linked to the inositol signaling system include serotonin and norepinephrine. Therefore, inositol may be an important participant in this neurological arena. Presently, SSRIs are the primary class of drugs used for depressed patients. [55] However, orgasm dysfunction, nausea, vomiting, somnolence, and sweating are frequently reported side-effects. [62] In 1978, researchers demonstrated that depressed patients had significantly decreased cerebral spinal fluid (CSF) levels of inositol as compared to healthy patients. [63] In 1993 this theory was expanded to conclude that administration of high-dose inositol could increase CSF levels by as much as 70%. [64] This led to the study of inositol for treatment of depression. [57,65]

> In 1995, Levine et al completed a double-blind study for treatment of depression using inositol at a dose of 12 grams daily compared to placebo. Patients receiving inositol showed significant improvement in depression as ranked by the Hamilton Depression Rating Scale. Side-effects experienced by the inositol group were nausea and flatus. There were no hematological abnormalities in laboratory parameters. A few patients experienced mild elevations in fasting serum glucose concentrations. The researchers concluded that 12 grams daily was well-tolerated. Another important observation was

the absence of manic episodes in the bipolar patients treated with inositol. This lack of manic episodes may suggest that when the signaling system is not overactive, addition of inositol will not increase the signaling system's activity. [66]

- > Another study reported in 1995 by Levine et al evaluated the potential for relapse of depression once inositol therapy was discontinued. In this study, patients treated with 12 grams inositol daily experienced significant antidepressant effects. Half of the patients who responded to therapy relapsed rapidly on discontinuation of inositol. [67]

## Inositol and Panic Disorder

Panic disorder is a common condition in which a person has episodes of intense fear or anxiety that occur suddenly, often without warning. These episodes – called panic attacks – can last from minutes to hours. They may occur only once in a while, or they may occur quite frequently. The cause, or “trigger,” for these attacks may not be obvious. [68] The disorder is usually progressive and patients may develop anticipatory anxiety as a result. Most patients will eventually develop symptoms of avoidance behavior or agoraphobia. Several drugs for the treatment of panic disorders are available, although response is often unpredictable. These include SSRIs, antidepressants, or monoamine oxidase inhibitors (MAOIs). [55] The drug paroxetine (brand name Paxil) was evaluated for panic disorder by Ballenger et al who reported adverse drug reactions consistent with those most commonly reported for the class as a whole. [69] Rosenbaum et al concluded clonazepam (anti-anxiety medication) in higher doses was more likely to cause somnolence (sleepiness) and ataxia (lack of coordination), while normal maintenance doses were more likely to be associated with depression, dizziness, fatigue, and irritability. [70]

Propelled by incredible advances in the understanding of the pathological causes and characteristics of psychiatric disorders, prospects for treatment have brightened considerably in the last 18 years. It is known that a change in the central nervous system concentration of inositol may lead to modified brain cell signaling pathways, and possibly to the development of a psychiatric disorder. The evidence indicates inositol has psychoactive effects by interacting with the second messenger system and ultimately regulating the cytosolic concentration of calcium. The signaling by calcium is known to mediate an array of cellular functions involving a number of active and passive transport systems. Inositol is now

established as a significant mediator of calcium mobilization in the endoplasmic reticulum. Modifying this mobilization of calcium may be effective in treating some central nervous system disorders like depression, panic disorder, and as an analgesic for pain control. [55]

- > Benjamin et al expanded the clinical use of inositol by evaluating its effectiveness in panic disorder. This was an eight week double-blind, crossover study whereby patients were treated with 12 grams inositol daily for four weeks and then crossed over to the other study arm. Improvement was assessed using patient diaries, the Marks-Matthews Phobia Scale, the Hamilton Anxiety Rating Scale, and the Hamilton Depression Scale. The frequency and severity of panic attacks and the severity of agoraphobia declined significantly more after inositol than after placebo (a decrease from 10 attacks per week to 3 per week in the treated group compared to a decrease from 10 to 6 in the placebo group). The authors conclude inositol's efficacy and safety, and the fact that inositol is a natural component of the human diet make it potentially attractive therapeutic agent for panic disorder. [60]
- > A double-blind, controlled, random-order crossover study was undertaken to compare the effect of inositol with that of fluvoxamine in panic disorder. Twenty patients completed one month of treatment with inositol up to 18 g/day and one month of fluvoxamine up to 150 mg/day. Improvements on Hamilton Rating Scale for Anxiety scores, agoraphobia scores, and Clinical Global Impressions Scale scores were similar for both treatments. In the first month, inositol reduced the number of panic attacks per week by 4.0 compared with a reduction of 2.4 with fluvoxamine ( $p = 0.049$ ). Nausea and tiredness were more common with fluvoxamine ( $p=0.02$  and  $p=0.01$ , respectively). Because inositol is a natural compound with few known side effects, it is attractive to patients who are ambivalent about taking psychiatric medication. Continuing reports of inositol's efficacy in the treatment of depression, panic disorder, and OCD should stimulate replication studies. [61]

## SAFETY

Inositol supplementation is generally well tolerated. Gastrointestinal effects are occasionally reported. Because of a lack of long-term safety data, inositol should be avoided by pregnant women and nursing mothers. Also, high-dose inosi-

tol may induce uterine contractions. Theoretically, high-dose inositol may have additive effects with SSRIs. [71]

## **GUIDELINES FOR USE**

For the management of depression and panic attacks, 12 grams of inositol daily, in divided doses, were used in clinical studies. In the clinical studies performed with inositol, effects were seen in about one month. [71]

## **VITAMIN B COMPLEX**

### **Vitamin B1 (thiamine)**

There is substantial research that suggests that inadequate intakes of B vitamins can result in low mood or other depressive conditions. For example, studies suggest that about a third of depressed persons are at least mildly deficient in thiamine (vitamin B1). [72] Thiamine is a water-soluble B complex vitamin and is involved in numerous body functions, including: nervous system and muscle functioning; flow of electrolytes in and out of nerve and muscle cells; carbohydrate metabolism; and production of hydrochloric acid (which is necessary for proper digestion). Humans are dependent on dietary intake to fulfill their thiamine requirements. Because there is very little thiamine stored in the body, depletion can occur within 14 days. Thiamine deficiency can result from inadequate thiamine intake (for example: increased body requirements for thiamine such as with strenuous exercise), or excessive loss of thiamine from the body, (such as those taking diuretics), or consumption of large amounts of anti-thiamine factors in foods (such as coffee, tea, or vitamin C). [73]

In a particularly well-known study, researchers studied 120 female college students given 50 mg per day of thiamine or a placebo. After just two months the students who took thiamine more than doubled their previous psychological test scores on clear-headedness and mood while students taking the placebo showed no change. Those taking thiamine also increased their quickness on a reaction time test, while the placebo group was unchanged. [72]

### **Vitamin B2 (riboflavin)**

Vitamin B2, commonly called riboflavin, is one of eight water-soluble vitamins. Like its close relative, vitamin B1, riboflavin plays a crucial role in certain metabolic reactions, particularly the conversion of carbohydrates into sugar, which is “burned” to produce energy. Together, the eight B vitamins, often referred to as B complex vitamins, are also essential in the breakdown of fats and protein. The reason B vitamins are generally combined in B complex products is that deficiency in one has a direct or indirect impact on the others. Riboflavin is an example of this. A deficiency in riboflavin affects the metabolism of vitamin B6, niacin (vitamin B3), and folate (a B vitamin) as well as the metabolism of iron. Unlike other B vitamins, riboflavin is not found in many foods, so the most common cause of deficiency is lack of dietary intake. In addition, long-term use of antibiotics, along with some other medications can deplete vitamin B levels in the body. Poor dietary habits in combination with birth control medications can interfere with the body’s ability to use riboflavin. One of the symptoms of deficiency is fatigue. Adequate nutrient supplementation with riboflavin may be required for the maintenance of adequate cognitive function. Treatment with B vitamins, including riboflavin has been reported to improve scores of depression and cognitive function in patients taking tricyclic antidepressants. [74]

### **Vitamin B3 (niacin, nicotinic acid, niacinamide)**

Niacin, or vitamin B3, is one of eight water-soluble B vitamins. It helps the body to convert carbohydrates into glucose (sugar), which is “burned” to produce energy. Niacin plays an important role in ridding the body of toxic and harmful chemicals. It also helps the body make various sex and stress-related hormones in the adrenal glands and other parts of the body. Niacin is effective in improving circulation and reducing cholesterol levels in the blood. [75] Traditional uses include anxiety and depression. [76]

### **Vitamin B5 (pantothenic acid, calcium D-pantothenate)**

Pantothenic acid (vitamin B5) is essential to all life, and is a component of coenzyme A (CoA), a molecule which is necessary for numerous vital chemical reactions to occur in cells. Pantothenic acid is essential to the metabolism of carbohydrates, proteins, and fats, as well as for the synthesis of hormones and cholesterol. The average adult daily intake of pantothenic acid is between 5-6 mg. Rich food sources include meats, vegetables, legumes, yeast, eggs and milk. However,

freezing and canning may lead to a loss of much of the pantothenic acid content and refining of whole grains may degrade much of the pantothenic acid content. Traditional uses for vitamin B5 include anxiety prevention, chronic fatigue syndrome, and depression. [77]

## **Vitamin B6 (pyridoxine)**

Vitamin B6 is a water-soluble vitamin that is required for the synthesis of the neurotransmitters serotonin and norepinephrine. Mild deficiency of vitamin B6 is common. A prescription antibiotic (Cycloserine) may cause anemia, peripheral neuritis or seizures by acting as a pyridoxine antagonist or increasing excretion of pyridoxine and may be supplemented by pyridoxine to prevent these adverse effects. Some studies show decreased pyridoxine levels in women who take birth control pills. Preliminary evidence suggests that because pyridoxine increases serotonin and gamma aminobutyric acid (GABA) levels in the blood, it may benefit people in dysphoric mental states. One randomized, placebo-controlled double-blind trial suggests that vitamins B1, B2, and B6 may add to the effects of tricyclic antidepressants in the treatment of affective and/or cognitive disturbances in geriatric depression. [78]

## **Folate (folic acid)**

Folate and folic acid are forms of a water-soluble B vitamin. Folate occurs naturally in food and folic acid is the synthetic form of this vitamin. Folic acid is well-tolerated in amounts found in fortified foods and supplements, doses less than 1000 micrograms per day. Folate deficiency will occur if the body does not get the adequate amount of folic acid from dietary intake. [79] Nutrition Reviews published a 1997 study suggesting that folate deficiency most likely manifests in the form of depressive symptoms. [80] Folic acid deficiency has been found among people with depression and has been linked to poor response to antidepressant treatment. Folate supplements have been used for enhancing treatment response to antidepressants. [79]

## **Vitamin B12 (cyanocobalamin)**

Vitamin B12 is an essential water soluble vitamin that is commonly found in a variety of foods such as meats, fish and dairy products. It helps maintain healthy nerve cells and red blood cells and is also needed to make DNA, the genetic material in all cells. While a nutritional deficiency of this vitamin is rare, it can result from being unable to use and absorb vitamin B12. Studies have shown that a deficiency of vitamin

B12 can lead to abnormal neurologic and psychiatric symptoms, including muscle weakness, mood disturbances, and dementia. Researchers report that these symptoms may occur when vitamin B12 levels are just slightly lower than normal and are considerably above the levels normally associated with anemia. [81] Low mood and PMS (premenstrual syndrome) are commonly linked. A connection between PMS and pyridoxine deficiency was demonstrated in a study published in the Journal of Reproductive Medicine.

Supplementation of the vitamin was shown to help correct the deficiency, and at the appropriate dosage, to improve the symptoms of PMS tension. [82] Some patients diagnosed with Alzheimer's disease have been found to have abnormally low vitamin B12 levels in their blood. There is some evidence that intramuscular injections of 5 mg of vitamin B12 given twice per week might improve the general well being and happiness of patients complaining of tiredness and fatigue. [81]

## **Biotin**

Biotin is a water-soluble vitamin, generally classified as a B complex vitamin. Biotin is required by all organisms but can only be synthesized by bacteria, yeasts, molds, algae, and some plant species. [83] While biotin deficiency is rare, it can happen in certain cases. Neurologic symptoms of deficiency in adults have included depression and lethargy. [84] Recent research suggests that a substantial number of women develop marginal or subclinical biotin deficiency during normal pregnancy. [85,86] Certain medications increase the risk of biotin depletion, such as anticonvulsant medications, sulfa drugs and other antibiotics. [87-90]

## **COLA NUT (Kola nut, *Cola acuminata*)**

The cola nut tree is native to West Africa. It has been traded to other countries since at least the fourteenth century, and today cola nut is exported worldwide. [91] For thousands of years people in Africa have chewed the seeds to enhance mental alertness and fight fatigue. Centuries ago, Arabs traded gold dust for cola nuts before starting out on long treks across the Sahara. [92]

Related to cocoa, cola nut is the source of a stimulant, and contains the methylxanthine alkaloids that occur also in coffee, cocoa, tea, mate, and guarana. Of the 40 known species, *Cola acuminata* and *Cola nitida* bear the nuts most readily

available in the United States and Europe. Its stimulant effects are its predominant application in the US and Europe. Commission E approves cola nut for conditions of mental and physical fatigue and also as a supportive treatment for depressive states. [93] Cola nut is used in the manufacture of methylxanthine-based pharmaceuticals to treat conditions such as asthma. Caffeine is sometimes given in conjunction with other analgesics to produce stronger and quicker pain-killing actions. [94] Cola nut is also used in non-pharmaceutical preparations, including cola soft drinks [95] and “high-energy” products such as food bars. The Council of Europe and the U.S. Food and Drug Administration have approved it as a food additive. [92]

## Discussion

Physical and mental energy, stamina, and a bright outlook are generally the result of optimal nutritional status. There is much evidence supporting the idea that a healthy, balanced diet, exercise, and the proper nutrients promote good health. It is, however, nearly impossible to get all the nutrients you need from whole foods each day. Due to the busy, stressful lifestyle that most Americans live, their meals are not balanced – quite the contrary. Most eat fast food, processed convenience foods and high-fat, high-calorie snacks, all of which are nutrient-depleted. Without the proper maintenance (nutrients), the body cannot function at optimal levels and that leaves us tired, moody, depressed and hungry. We are at the same time a nation of overfed and undernourished people.

Fatigue and exhaustion are the body's way of telling you that enough is enough. It means that the already limited amount of energy stores in your body have been depleted – often by stress. During times of increased stress and greater demands, your body consumes nutrients even more rapidly to meet the biochemical needs of your metabolism. To combat this drain on your systems, specific nutrients and vitamins should be supplied. Deficiencies in any or all essential nutrients can affect all systems of the body, causing myriad health problems, minor and major.

Amino acids are the raw materials for neurotransmitters and other mood-regulating compounds. Evidence supporting supplementation of these nutrients, particularly phenylalanine and tyrosine, have been shown to be as effective as the antidepressant drug, imipramine, in studies. Phenylalanine has also been shown to reduce pain by preserving brain levels of endorphins, the body's natural painkiller. There is substantial research that suggests that inadequate intakes of B vitamins

can result in low mood or other depressive conditions. Also, vitamin B12 has long been used in patients to restore energy.

Panax ginseng has been valued in Chinese medicine for thousands of years. Ginseng research teams in the US, China, Japan, and Korea have found positive results in mood enhancement, the ability to perform mental tasks, sexual function and reduce fatigue. Ginseng is considered an adaptogen. It seems to be able to increase the body's ability to adapt and adjust, bringing the body back into a healthy, balanced state.

DMAE and inositol are nutrients closely related to B complex vitamins. Both play important roles in cellular communication, particularly within brain cells. Research points to the ability of inositol to act similarly to the SSRIs (antidepressants) in certain neurological conditions, such as depression. Mild stimulants, such as cola nut, are used in medications and are approved as food additives. Moderate amounts have been found to be useful for conditions of mental and physical fatigue.

We have become a society of drugs. Drugs are foreign chemicals not essential to human health and most have adverse side-effects. Patients have come to expect and, at times, even demand drugs for a “quick fix.” Natural medicine works in a gradual manner and is consistent with the rhythms of nature. The goal should be balance, in body as well as in mind and spirit. Imbalance in one area is reflected in problems in other areas. Each imbalance should be treated accordingly to alleviate symptoms, and also to treat the underlying problem. Although the response may not be as quick, proper and adequate nutrition, diet, and supplementation of specific nutrients can have meaningful health benefits for many individuals.

## References

1. Kiefer, D. and Pantuso, T. (2003) Panax Ginseng. *Am Fam Physician*, 68, 1539-42.
2. (2003) *Ginseng*. Supplement Watch. Available Online [<http://www.supplementwatch.com/supatoz/supplement.asp?supplementId=143>] 3/3/2003.
3. Chan, C. (2002) *Ginseng, the Miracle Healer*. Association for Asia Research. Available Online [<http://www.asianresearch.org/articles/2849.html>] 5/19/2006.

4. (1999) World Health Organization Monographs on Selected Medicinal Plants. World Health Organization, Geneva.
5. (2006) *Cornermark Ginseng Studies and Research - Health Benefits Revealed*. Available Online [http://www.cornermark.com/ginseng/ginseng\_research\_benefits.html] 5/19/2006.
6. Gai, Y., et al. (2003) [Effect of Panax Notoginsenosides on the Proliferation of Hematopoietic Progenitor Cells in Mice with Immune-Mediated Aplastic Anemia]. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 23, 680-3.
7. Kim Yu, A., et al. (2000) Hyperosmotic Hemolysis and Antihemolytic Activity of the Saponin Fraction and Triterpene Glycosides from Panax Ginseng C. A. Meyer. *Membr Cell Biol*, 14, 237-51.
8. Reay, J.L., et al. (2006) Effects of Panax Ginseng, Consumed with and without Glucose, on Blood Glucose Levels and Cognitive Performance During Sustained 'Mentally Demanding' Tasks. *J Psychopharmacol*.
9. (2002) *American Ginseng*. University of Maryland Medical Center. Available Online [http://www.umm.edu/altmed/ConsHerbs/Print/GinsengAmericanch.html] 5/19/2006.
10. Murphy, L.L., et al. (1998) Effect of American Ginseng (Panax Quinquefolium) on Male Copulatory Behavior in the Rat. *Physiol Behav*, 64, 445-50.
11. Kwon, Y.S. and Jang, K.H. (2004) The Effect of Korean Red Ginseng on Liver Regeneration after 70% Hepatectomy in Rats. *J Vet Med Sci*, 66, 193-5.
12. Lee, F.C., et al. (1987) Effects of Panax Ginseng on Blood Alcohol Clearance in Man. *Clin Exp Pharmacol Physiol*, 14, 543-6.
13. Pieralisi, G., et al. (1991) Effects of a Standardized Ginseng Extract Combined with Dimethylaminoethanol Bitartrate, Vitamins, Minerals, and Trace Elements on Physical Performance During Exercise. *Clin Ther*, 13, 373-82.
14. Watson, C. (1997) Love Potion: The Daminana Formula. *Journal of Longevity Research*, 3, 42-43.
15. Hong, B., et al. (2002) A Double-Blind Crossover Study Evaluating the Efficacy of Korean Red Ginseng in Patients with Erectile Dysfunction: A Preliminary Report. *J Urol*, 168, 2070-3.
16. Choi, H.K., et al. (1995) Clinical Efficacy of Korean Red Ginseng for Erectile Dysfunction. *Int J Impot Res*, 7, 181-6.
17. Morkdad, A., et al. (2000) Diabetes Trends in the U.S.: 1990 - 1998. *Diabetes Care*, 23, 1278-1283.
18. Sorensen, T.I. (2000) The Changing Lifestyle in the World. Body Weight and What Else? *Diabetes Care*, 23 Suppl 2, B1-4.
19. Haffner, S.M., et al. (1998) Mortality from Coronary Heart Disease in Subjects with Type 2 Diabetes and in Nondiabetic Subjects with and without Prior Myocardial Infarction. *N Engl J Med*, 339, 229-34.
20. Wang, B.X., et al. (2003) Hypoglycemic Mechanism of Ginseng Glycopeptide. *Acta Pharmacol Sin*, 24, 61-6.
21. Sotaniemi, E.A., et al. (1995) Ginseng Therapy in Non-Insulin-Dependent Diabetic Patients. *Diabetes Care*, 18, 1373-5.
22. Jenkins, A.L., et al. (2003) Reduction of Hba1c after Long Term Administration of American Ginseng and Konjac Mannan Fiber in Type 2 Diabetes. Abstract #1676-P., *American Diabetes Association 63rd Scientific Sessions*, New Orleans, LA.
23. Kennedy, D.O. and Scholey, A.B. (2003) Ginseng: Potential for the Enhancement of Cognitive Performance and Mood. *Pharmacol Biochem Behav*, 75, 687-700.
24. (2004) *Ginseng*. Natural Standard Patient Monograph. Available Online [http://www.naturalstandard.com/natural-standard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-ginseng.asp] 7/12/2004.
25. Leigh, E. (1997 - 2001) *Ginseng*. The Herb Research Foundation: Herb Information Greenpaper. Available Online [http://www.herbs.org/greenpapers/ginseng.html] 5/19/2006.
26. Wiklund, I.K., et al. (1999) Effects of a Standardized Ginseng Extract on Quality of Life and Physiological Parameters in Symptomatic Postmenopausal Women: A Double-Blind, Placebo-Controlled Trial. Swedish Alternative Medicine Group. *Int J Clin Pharmacol Res*, 19, 89-99.
27. Wiklund, I.K., et al. (1994) A Double Blind Comparison of

the Effects of Quality of Life of a Combination of Vital Substances Including Standardised Ginseng G115 and Placebo. *Curr Ther Res* 55, 32-42.

28. Tode, T., et al. (1999) Effect of Korean Red Ginseng on Psychological Functions in Patients with Severe Climacteric Syndromes. *Int J Gynaecol Obstet*, 67, 169-74.

29. Marasco, A., et al. (1996) Double-Blind Study of a Multivitamin Complex Supplemented with Ginseng Extract. *Drugs Exp Clin Res*, 22, 323-329.

30. Sorensen, H. and Sonne, J. (1996) A Double Masked Study of the Effects of Ginseng on Cognitive Functions. *Curr Ther Res*, 57, 959-968.

31. (2006) *Dmae*. Supplement News. Available Online [<http://www.supplementnews.org/dmae/index.html>] 5/26/2006.

32. Lewis, J.A. and Lewis, B.S. (1977) Deanol in Minimal Brain Dysfunction. *Dis Nerv Syst*, 38, 21-4.

33. Hochschild, R. (1973) Effect of Dimethylaminoethanol on the Life Span of Senile Male a-J Mice. *Exp Gerontol*, 8, 185-91.

34. Re, O. (1974) 2-Dimethylaminoethanol (Deanol): A Brief Review of Its Clinical Efficacy and Postulated Mechanism of Action. *Curr Ther Res Clin Exp*, 16, 1238-42.

35. Ward, D. (1992) Smart Drugs and Nutrients: How to Improve Your Memory and Increase Your Intelligence Using the Latest Discoveries in Neuroscience. *Smart Publications*.

36. Danysz, A., et al. (1967) The Influence of 2-Dimethylaminethanol (Dmae) on the Mental and Physical Efficiency in Man. *Act Nerv Super (Praha)*, 9, 417.

37. Levin, E.D., et al. (1995) Effects of Nicotinic Dimethylaminoethyl Esters on Working Memory Performance of Rats in the Radial-Arm Maze. *Pharmacol Biochem Behav*, 51, 369-73.

38. Perry, E., et al. (1999) Acetylcholine in Mind: A Neurotransmitter Correlate of Consciousness? *Trends Neurosci*, 22, 273-80.

39. Jope, R.S. and Jenden, D.J. (1979) Dimethylaminoethanol (Deanol) Metabolism in Rat Brain and

Its Effect on Acetylcholine Synthesis. *J Pharmacol Exp Ther*, 211, 472-9.

40. Millington, W.R., et al. (1978) Deanol Acetamidobenzoate Inhibits the Blood-Brain Barrier Transport of Choline. *Ann Neurol*, 4, 302-6.

41. Haubrich, D.R., et al. (1981) Deanol Affects Choline Metabolism in Peripheral Tissues of Mice. *J Neurochem*, 37, 476-82.

42. Kostopoulos, G.K. and Phillis, J.W. (1975) The Effects of Dimethylaminoethanol (Deanol) on Cerebral Cortical Neurons. *Psychopharmacol Commun*, 1, 339-47.

43. Ansell, G. and Spanner, S. (1970) Drugs and Cholinergic Mechanisms in the Cns. In Heilbronn, E. and Winter, A. (eds.).

44. (2003) *Phenylalanine*. Supplement Watch. Available Online [<http://www.supplementwatch.com/supatoz/supplement.asp?supplementID=214>] 3/3/2003.

45. Roberts, A.J. and O'Brien, M.E. (2001) *Nutraceuticals the Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods*. Perigee Books, New York.

46. Ehrenpreis, S. (1985) Analgesic Properties of Enkephalinase Inhibitors: Animal and Human Studies. *Prog Clin Biol Res*, 192, 363-70.

47. Ehrenpreis, S., et al. (1979) Naloxonr Reversible Analgesia in Mice Produced by D-Phenylalanine and Hydrocinnamic Acid, Inhibitors of Carboxypeptidase A. In Bonica, J.J. (ed.), *Advances in Pain Research and Therapy, Vol. 3*. Raven Press, New York.

48. Ehrenpreis, S. (1985) Pharmacology of Enkephalinase Inhibitors: Animal and Human Studies. *Acupunct Electrother Res*, 10, 203-8.

49. Balagot, R., et al. (1983) Analgesia in Mice and Humans by D-Phenylalanine: Relation to Inhibition of Enkephalin Degradation and Enkephalin Levels. In Bonica, J.J. (ed.), *Advances in Pain Research and Therapy, Vol. 5*. Raven Press, New York.

50. Budd, K. (1981) The Use of D-Phenylalanine, an Enkephalinase Inhibitor, in the Treatment of Intractable Pain. *Pain*, S95 (S1).

51. (2003) *Brain/Mood Support*. Supplement Watch. Available Online [http://www.supplementwatch.com/supcat/category.asp?categoryid=12] 3/3/2003.
52. Beckmann, H., et al. (1979) DI-Phenylalanine Versus Imipramine: A Double-Blind Controlled Study. *Arch Psychiatr Nervenkr*, 227, 49-58.
53. Heller, B. (1978) Pharmacological and Clinical Effects of D-Phenylalanine in Depression and Parkinsons Disease. In Mosnaim, A. and Wolf, M. (eds.), *Noncatecholic Phenylethylamines*. Part 1. Marcel Dekker, New York, pp. 397-417
54. (2006) *Phenylalanine*. Supplement News. Available Online [http://www.supplementnews.org/phenylalanine/index.html] 6/1/2006.
55. Colodny, L. and Hoffman, R.L. (1998) Inositol-Clinical Applications for Exogenous Use. *Altern Med Rev*, 3, 432-47.
56. (2006) *Inositol*. Supplement News. Available Online [http://www.supplementnews.org/inositol/index.html] 6/5/2006.
57. Levine, J. (1997) Controlled Trials of Inositol in Psychiatry. *Eur Neuropsychopharmacol*, 7, 147-55.
58. Benjamin, J., et al. (1995) Inositol Treatment in Psychiatry. *Psychopharmacol Bull*, 31, 167-75.
59. Fux, M., et al. (1996) Inositol Treatment of Obsessive-Compulsive Disorder. *Am J Psychiatry*, 153, 1219-21.
60. Benjamin, J., et al. (1995) Double-Blind, Placebo-Controlled, Crossover Trial of Inositol Treatment for Panic Disorder. *Am J Psychiatry*, 152, 1084-6.
61. Palatnik, A., et al. (2001) Double-Blind, Controlled, Crossover Trial of Inositol Versus Fluvoxamine for the Treatment of Panic Disorder. *J Clin Psychopharmacol*, 21, 335-9.
62. Kavoussi, R.J., et al. (1997) Double-Blind Comparison of Bupropion Sustained Release and Sertraline in Depressed Outpatients. *J Clin Psychiatry*, 58, 532-7.
63. Barkai, A.I., et al. (1978) Reduced Myo-Inositol Levels in Cerebrospinal Fluid from Patients with Affective Disorder. *Biol Psychiatry*, 13, 65-72.
64. Levine, J., et al. (1993) Inositol Treatment Raises Csf Inositol Levels. *Brain Res*, 627, 168-70.
65. Cohen, H., et al. (1997) Inositol Has Behavioral Effects with Adaptation after Chronic Administration. *J Neural Transm*, 104, 299-305.
66. Levine, J., et al. (1995) Double-Blind, Controlled Trial of Inositol Treatment of Depression. *Am J Psychiatry*, 152, 792-4.
67. Levine, J., et al. (1995) Follow-up and Relapse Analysis of an Inositol Study of Depression. *Isr J Psychiatry Relat Sci*, 32, 14-21.
68. (1995) *Panic Disorder: Panic Attacks and Agoraphobia*. familydoctor.org. Available Online [http://familydoctor.org/137.xml?printxml] 6/8/2006.
69. Ballenger, J.C., et al. (1998) Double-Blind, Fixed-Dose, Placebo-Controlled Study of Paroxetine in the Treatment of Panic Disorder. *Am J Psychiatry*, 155, 36-42.
70. Rosenbaum, J.F., et al. (1997) Clonazepam in the Treatment of Panic Disorder with or without Agoraphobia: A Dose-Response Study of Efficacy, Safety, and Discontinuance. Clonazepam Panic Disorder Dose-Response Study Group. *J Clin Psychopharmacol*, 17, 390-400.
71. (2006) *Myo-Inositol*. PDR Health. Available Online [http://www.pdrhealth.com/drug\_info/nmdrugprofiles/nutsupdrugs/myo\_0145.shtml] 5/18/2006.
72. Benton, D., et al. (1997) Thiamine Supplementation Mood and Cognitive Functioning. *Psychopharmacology (Berl)*, 129, 66-71.
73. (2006) *Thiamin (Thiamine), Vitamin B1*. Natural Standard Available Online [http://www.naturalstandard.com/natural-standard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-thiamin.asp] 6/8/2006.
74. (2006) *Riboflavin (Vitamin B2)*. Natural Standard. Available Online [http://www.naturalstandard.com/natural-standard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-riboflavin.asp] 6/8/2006.
75. (2004) *Vitamin B3 (Niacin)*. University of Maryland Medical Center. Available Online

- [<http://www.umm.edu/altmed/ConsSupplements/Print/VitaminB3Niacins.html>] 6/13/2006.
76. (2006) *Niacin (Vitamin B3, Nicotinic Acid), Niacinamide*. Natural Standard. Available Online [<http://www.naturalstandard.com/naturalstandard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-niacin.asp>] 6/8/2006.
77. (2006) *Pantothenic Acid (Vitamin B5), Dexpanthenol*. Natural Standard. Available Online [<http://www.naturalstandard.com/naturalstandard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-niacin.asp>] 6/8/2006.
78. (2006) *Vitamin B6*. Natural Standard. Available Online [<http://www.naturalstandard.com/naturalstandard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-b6.asp>] 6/8/2006.
79. (2006) *Folate (Folic Acid)*. Natural Standard. Available Online [<http://www.naturalstandard.com/naturalstandard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-folate.asp>] 6/8/2006.
80. Alpert, J.E. and Fava, M. (1997) Nutrition and Depression: The Role of Folate. *Nutr Rev*, 55, 145-9.
81. (2006) *Vitamin B12*. Natural Standard. Available Online [<http://www.naturalstandard.com/naturalstandard/monographs/monoframeset.asp?monograph=/monographs/herbssupplements/patient-vitaminb12.asp>] 6/8/2006.
82. Stewart, A. (1987) Clinical and Biochemical Effects of Nutritional Supplementation on the Premenstrual Syndrome. *J Reprod Med*, 32, 435-41.
83. Mock, D.M. (1996) Biotin. In Ziegler, E.E. and Filer, L.J. (eds.), *Present Knowledge in Nutrition 7th Edition*. ILSI Press, Washington D.C., pp. 220-236.
84. Mock, D.M. (1999) Biotin. In Shils, M., Olson, J.A., Shike, M. and Ross, A.C. (eds.), *Nutrition in Health and Disease 9th Edition*. Williams & Wilkins, Baltimore, pp. 459-466.
85. Zemleni, J. and Mock, D.M. (2000) Marginal Biotin Deficiency Is Teratogenic. *Proc Soc Exp Biol Med*, 223, 14-21.
86. Pabuccuoglu, A., et al. (2002) Serum Biotinidase Activity in Children with Chronic Liver Disease and Its Clinical Significance. *J Pediatr Gastroenterol Nutr*, 34, 59-62.
87. Mock, D.M. (1999) Biotin Status: Which Are Valid Indicators and How Do We Know? *J Nutr*, 129, 498S-503S.
88. Schulpis, K.H., et al. (2001) Low Serum Biotinidase Activity in Children with Valproic Acid Monotherapy. *Epilepsia*, 42, 1359-62.
89. Flodin, N. (1988) *Pharmacology of Micronutrients*. Alan R. Liss, Inc., New York
90. Zemleni, J. and Mock, D.M. (1999) Biotin Biochemistry and Human Requirements. *J Nutr Biochem*, 10, 128-138.
91. Trindall, R. (1997) *Ethnobotanical Leaflets: The Culture of Cola: Social and Economic Aspects of a West African Domesticated*. Southern Illinois University Herbarium, Carbondale.
92. (2004) *Cola Nut*. Caremark. Available Online [<http://healthresources.caremark.com/GetHerbContent.do?primerid=103411036&name=Cola+Nut>] 6/14/2006.
93. Bradley, P.R. (ed.) (1992) *British Herbal Compendium*. British Herbal Medicine Association, Bournemouth.
94. Goodman, L.S., et al. (1990) *The Pharmacological Basis of Therapeutics, 8th Edition*. Pergamon Press, New York.
95. Leung, A.Y. and Foster, S. (1996) *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics 2nd Edition*. John Wiley & Sons, Inc., New York.

# L-Arginine

*Anti-Atherogenic*  
*Lipid (Cholesterol) Lowering*  
*Vascular Dilating*  
*Cardio-Tonifying*  
*Inhibition of Oxidative Stress/Damage*  
*Immune System Enhancement*  
*Wound Healing*  
*Sexual Function*  
*Anabolic*

## Introduction

Arginine is an amino acid present in the proteins of all life forms. L-arginine is a semi-essential amino acid involved in numerous areas of human physiology, including production of nitric oxide (NO) – a key messenger molecule involved in vascular regulation, immune activity, and endocrine function. Arginine is also involved in protein production, wound healing, erectile function, and fertility. Arginine is not considered essential because humans can synthesize it *de novo* from glutamine, glutamate, and proline. However, dietary intake remains the primary determinant of plasma arginine levels, since the rate of arginine biosynthesis does not compensate for depletion or inadequate supply. [1,2] Supplemental arginine is readily absorbed. [3] About 50-percent of ingested arginine is rapidly converted in the body to ornithine, primarily by the enzyme arginase. [4]

Arginine is the biological precursor of nitric oxide (NO), an endogenous gaseous messenger molecule involved in a variety of endothelium-dependent physiological effects in the cardiovascular system. [5] Much of arginine's influence on the cardiovascular system is due to endothelial NO synthesis, which results in vascular smooth muscle relaxation and subsequent vasodilation, as well as inhibition of monocyte adhesiveness, platelet aggregation, and smooth muscle proliferation. A great deal of research has explored the biological roles and properties of nitric oxide [6,7], which is also of critical importance in maintenance of normal blood pressure [8], myocardial function [9], inflammatory response [10], apoptosis [11], and protection against oxidative damage. [12]

L-arginine was first isolated in 1886. In 1932, L-arginine was found to be required for the generation of urea, which is necessary for the removal of toxic ammonia from the body. In 1939, L-arginine was also shown to be required for the synthesis of creatine. Preliminary evidence suggests that arginine may be useful in the treatment of medical conditions that are improved by vasodilation, such as angina, atherosclerosis, coronary artery disease, erectile dysfunction, heart failure, intermittent claudication/peripheral vascular disease, and vascular headache. Arginine also stimulates protein synthesis and has been studied for wound healing, bodybuilding, enhancement of sperm production (spermatogenesis), and prevention of wasting in people with critical illness. [13]

## L-Arginine and Cardiovascular Conditions

Arginine is a key component of the nitric oxide pathway – an important cascade of reactions involved in vasodilation and related to cardiovascular function. Arginine supplements have been linked with reductions in symptoms associated with coronary artery disease and may be capable of slowing the progression of atherosclerosis. In the body, arginine serves as the substrate for the nitric oxide synthase enzyme, which catalyzes the oxidation of arginine to produce citrulline and nitric oxide (NO). In the cells that line the blood vessels (endothelium cells), nitric oxide production causes vasodilation (opening of the vessels). NO is involved in the overall regulation of systemic vascular resistance, where it inhibits the adherence of cells and foreign substances to the blood vessel walls and helps suppress the overgrowth of smooth muscle cells in the

lining of the vessels. Because humans can synthesize arginine, it has been classified as a non-essential amino acid. Recent evidence suggests that the rate of synthesis of arginine in the body is insufficient for optimal health. [14]

## Angina Pectoris

- > Six months of oral treatment with L-arginine (3 doses of 3 g/day) resulted in a significantly improved angina symptom score and improved coronary blood flow response to acetylcholine in a placebo-controlled study that included 26 patients with small-vessel coronary artery disease. [15] In another study, 36 patients with chronic, stable angina given 6 g/day arginine for two weeks showed significant improvement in flow-mediated vasodilation, exercise time, and quality of life, compared to placebo. [16]
- > Ceremuzynski et al showed that exercise capacity was improved as compared to placebo in patients with stable angina pectoris after 3 days of 6 g/day L-arginine. [17]

## Congestive Heart Failure

- > In a randomized, double-blind trial, six weeks of oral arginine supplementation (5.6-12.6 g/day) significantly improved blood flow, arterial compliance, and functional status in patients with congestive heart failure (CHF), compared to placebo. [18] Another double-blind trial found arginine supplementation (5 g three times daily) improved renal function in people with CHF. [19]
- > Yousufuddin et al conducted a prospective, randomized, double-blind trial with 30 males with stable CHF. After a one-week oral dosing with 6 g arginine daily, significant improvements were seen in exercise duration, anaerobic threshold, and maximal oxygen uptake (VO<sub>2</sub>). [20]

## L-Arginine and Hypercholesterolemia

In people with elevated cholesterol levels, it is common to see a reduced ability of the endothelium to produce NO and, therefore, to dilate effectively. In addition, because NO production may be limited, blood cells such as monocytes and platelets are more likely to attach themselves to the inner vessel wall and lead to blockages. Arginine supplements (8-21 grams per day) have been shown to restore endothelial vasodilation in the coronary arteries of people with high cho-

lesterol and reduce the ability of blood cells to adhere to the vessel walls. [14]

- > In a study by Drexler et al, it was shown that local intracoronary infusion of L-arginine normalized coronary vasomotor responses to acetylcholine in hypercholesterolemic humans. [21] A similar observation was also made upon systemic (intravenous) infusion of L-arginine in hypercholesterolemic subjects, in whom endothelium-dependent forearm vasodilation was improved. [22] These were important findings because endothelial dysfunction precedes angiographically visible atherosclerotic lesions in large coronary arteries. [23] Recent evidence from prospective clinical trials suggests that endothelial dysfunction is a predictor of future coronary events. [24,25] Therefore, reversal of endothelial dysfunction by L-arginine *in vivo* may suggest that this amino acid exerts antiatherosclerotic effects in humans. [26]

## L-Arginine and Hypertension

- > Administration of arginine prevented hypertension in salt-sensitive rats. [27] If arginine was provided early, hypertension and renal failure could be prevented. In healthy human subjects, intravenous (IV) administration of arginine had vasodilatory and antihypertensive effects. [28]
- > In a small, controlled trial, hypertensive patients refractory to enalapril, an angiotensin converting enzyme (ACE) inhibitor, and hydrochlorothiazide, a diuretic used to treat hypertension, responded favorably to the addition of oral arginine (2 g three times daily). [29] Small, preliminary trials have found oral and IV arginine significantly lowers blood pressure in healthy volunteers. [30,31]
- > Intravenous infusion of arginine (15 mg/kg body weight/min for 35 min) improved pulmonary vascular resistance index and cardiac output in infants with pulmonary hypertension. [32]

## L-Arginine and Intermittent Claudication

There is abundant evidence that the endothelium plays a crucial role in the maintenance of vascular tone and structure. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO), an endogenous messenger molecule

formed in healthy vascular endothelium from the amino acid precursor L-arginine. Endothelial dysfunction is caused by various cardiovascular risk factors, metabolic diseases, and systemic or local inflammation. One mechanism that explains the occurrence of endothelial dysfunction is the presence of elevated blood levels of asymmetric dimethylarginine (ADMA) – an L-arginine analogue that inhibits NO formation and thereby can impair vascular function. Supplementation with L-arginine has been shown to restore vascular function and to improve the clinical symptoms of various diseases associated with vascular dysfunction. [33]

- > Intravenous arginine injections significantly improved symptoms of intermittent claudication (pain in the legs due to inadequate blood supply to the muscles) in a double-blind trial. Eight grams of arginine infused twice daily for three weeks, significantly improved pain-free walking distance by 230 percent and the absolute walking distance by 155 percent compared to no improvement with placebo. [34]

## L-Arginine and Wound Healing

Studies have indicated that arginine has a positive impact on wound healing including gastric ulcers, bone fractures, diabetic foot ulcers, second-degree burns, radiation enteritis, and ulcerative lesions of the small intestines. [35] Expression of nitric oxide synthase creates a cytotoxic environment that may be important to the early phase of wound healing. As wound healing progresses, increased arginase activity produces an environment favorable for fibroblast replication and collagen production. [36] Burn injuries significantly increase arginine oxidation and can result in depletion of arginine reserves. Total parenteral nutrition (TPN) increases conversion of arginine to ornithine and proportionally increases irreversible arginine oxidation, which, coupled with limited *de novo* synthesis from its immediate precursors, makes arginine conditionally essential in severely burned patients receiving TPN. [37]

- > Arginine is a potent immunomodulator. Evidence is mounting for a beneficial effect of arginine supplementation in catabolic conditions such as sepsis (infection) and postoperative stress. Supplemental arginine appears to up-regulate immune function and reduce the incidence of postoperative infection. [38] Two controlled trials have demonstrated increased lymphocyte mitogenesis and improved wound healing in experimental surgical wounds in volunteers given 17-25 g oral arginine daily. [39,40] Similar results have been

obtained in healthy elderly volunteers. [35]

- > Several trials have demonstrated reduced length of hospital stay, fewer acquired infections, and improved immune function among burn [41] and trauma [42] patients supplemented with various combinations of arginine, fish or canola oil and nucleotides.

## L-Arginine and Growth Hormone Secretion/Athletic Performance

Arginine has been seen, in repeated studies documented as far back as the late 60's and early 70's, as a consistent and potent stimulus for growth hormone (GH) release. [43] In humans, arginine stimulates release of GH from the pituitary gland in some populations, but the mechanism is not well understood. Most studies suggest inhibition of somatostatin secretion is responsible for the effect. [44] An increased release of GH is an effect of interest to body builders wishing to take advantage of the anabolic properties of the hormone. [45]

- > In a human study, the effect of arginine supplementation on the metabolism of healthy, non-smoking, elderly volunteers was examined. A two-week course of supplemental arginine was found to cause significant increase in serum growth hormone and an improved and positive nitrogen balance. No adverse effects were observed. [43,46]
- > In a controlled clinical trial, arginine and ornithine (500 mg of each, twice daily, five times per week) produced a significant decrease in body fat when combined with exercise. [47]
- > Long-term, low-dose supplementation of arginine and ornithine (1 g each, five days per week for five weeks) resulted in higher gains in strength and enhancement of lean body mass, compared with controls receiving vitamin C and calcium. [48]
- > In several studies, low doses (1200-1500 mg of each) of arginine and lysine taken together produced a measurable increase in human GH secretion. [49-51]

## Immune System Enhancement

Arginine has a positive impact on the body's cell-mediated immunity. [52] Earlier studies in animals demonstrated that

arginine supplements enhanced the phagocytic (bacteria or foreign particle digesting) activities of the alveolar (small lung air cell) macrophages (phagocytes that digest dead tissue, degenerated cells, and bacteria cells). Arginine supplementation also led to a net positive nitrogen balance, and suppressed tumor growth due to its ability to activate the immune system. [53]

- > Lymphokines are chemical factors produced and released by T-lymphocytes that attract macrophages to a site of infection or inflammation in preparation for attack. Various researchers have shown that increasing arginine increases neutrophils (white blood cells that remove bacteria, cellular debris, and solid particles), significantly upgrading host defense. [54]
- > The balance of current clinical data suggests that early enteral immunonutrition may influence infectious complications in critically ill patients. Four of these nutrients are arginine, nucleotides, omega-3 fatty acids and glutamine. The target cells for the action of these nutrients appear to be T-lymphocytes and macrophages. [55]

## L-Arginine and Sexual Function

An estimated 30 million men in the U.S. alone experience some erectile dysfunction, of which only 10% seek treatment, urologists say. This piece of information came from an article about prescription impotence drugs (Viagra, Levitra, Cialis) in *The Wall Street Journal*. Moreover, according to data from the National Health and Social Life Survey on a study of adult sexual behavior, sexual dysfunction is more prevalent for women (43%) than men (31%).

Organic erectile dysfunction can be caused by decreased nitric oxide production in the cells that line blood vessels. Nitric oxide directly stimulates the penile tissues to allow the large inflow of blood that causes an erection. Unhealthy cells have trouble making nitric oxide, which can cause problems ranging from chest pain to the inability to get an erection. The popular drug, Viagra, works by stimulating nitric oxide production, but scientists have found that L-arginine performs the same function, and without adverse side-effects. L-arginine is the precursor to nitric oxide, and nitric oxide allows erection of the penis by dilating the blood vessels to penile erectile tissue. One cause of lack of orgasm in women is insufficient blood flow to the genital area. Most often this is a result of constriction of the small blood vessels. Nitric oxide, by relaxation of the blood vessel wall, has been shown to improve blood flow. Also, L-arginine may improve reproduc-

ive health and increase sperm motility in men. [56]

- > In a prospective randomized, double-blind placebo-controlled study, Chen et al determined the effect of 6-weeks of high-dose (5 g/day) orally administered nitric oxide donor L-arginine on 50 men with confirmed organic erectile dysfunction. Thirty-one percent of the patients taking L-arginine reported a significant subjective improvement in sexual function. [57]
- > Because arginine is found in high concentrations in seminal fluid, it may be advantageous in treating sterility in men. [58] As little as four grams of arginine has proven effective in clinical research for this purpose. Some 80% of subjects studied, who received this dosage, reported a dramatic improvement in libido, erection, and in some female cases, pregnancy. [59]
- > A combination of L-arginine (1.7 g per day) and approximately 120 mg per day of Pycnogenol (pine bark extract) was administered to 40 men (aged 25-45 years) with erectile dysfunction in a three month study. After the third month of treatment, 92.5% of the men experienced a normal erection. No adverse side effects were noted. [60]

## Safety

Arginine has been well tolerated by most people in studies lasting for up to six months; however people with serious health conditions should consult a physician before starting a new therapy. Also, some medications and hormone therapy may interact with arginine therefore a healthcare provider should be consulted before use. [13] Individuals with high allergic tendencies should avoid arginine therapy. [61]

It is important to use a safe and reliable source of arginine.

## Guidelines for Use

Doses of arginine used in clinical research have varied considerably, from as little as 500 mg/day to 30 g/day for different conditions. Typical daily doses fall into either the 1-3 g or 7-15 g range, depending on the condition being treated.

## Discussion

After the initial isolation of arginine from lupin seedlings in 1886, intense research has been conducted on the amino

acid and continues to this day. Arginine occupies a significant role in nutrition due to its multiple and sometimes unique physiologic and pharmacologic activities.

Experimental studies strongly support the anabolic or anti-catabolic effects of arginine and its precursors/metabolites through their involvement in protein metabolism, in the immune response and in cell proliferation. There is compelling evidence in favor of the exogenous administration of arginine showing positive effects in reversing endothelial dysfunction associated with major cardiovascular risk factors. Arginine administration is also beneficial for improving reproductive, renal, gastrointestinal, liver and immune functions, and most importantly, wound healing, post-surgery, burns or trauma.

With this information, manipulating arginine metabolism by oral administration of arginine may provide an effective nutritional or pharmacotherapeutic treatment for a wide array of disorders and may hold great promise for improved health and well-being in humans and animals.

## References

1. Castillo, L., et al. (1993) Plasma Arginine and Citrulline Kinetics in Adults Given Adequate and Arginine-Free Diets. *Proc Natl Acad Sci U S A*, 90, 7749-53.
2. Castillo, L., et al. (1994) Plasma Arginine Kinetics in Adult Man: Response to an Arginine-Free Diet. *Metabolism*, 43, 114-22.
3. Preiser, J.C., et al. (2001) Metabolic Effects of Arginine Addition to the Enteral Feeding of Critically Ill Patients. *J Parenter Enteral Nutr*, 25, 182-7.
4. Castillo, L., et al. (1995) Plasma Arginine, Citrulline, and Ornithine Kinetics in Adults, with Observations on Nitric Oxide Synthesis. *Am J Physiol*, 268, E360-7.
5. Wu, G. and Meininger, C.J. (2000) Arginine Nutrition and Cardiovascular Function. *J Nutr*, 130, 2626-9.
6. Gross, S.S. and Wolin, M.S. (1995) Nitric Oxide: Pathophysiological Mechanisms. *Annu Rev Physiol*, 57, 737-69.
7. Wink, D.A., et al. (1996) Chemical Biology of Nitric Oxide: Regulation and Protective and Toxic Mechanisms. *Curr Top Cell Regul*, 34, 159-87.
8. Umans, J.G. and Levi, R. (1995) Nitric Oxide in the Regulation of Blood Flow and Arterial Pressure. *Annu Rev Physiol*, 57, 771-90.
9. Hare, J.M. and Colucci, W.S. (1995) Role of Nitric Oxide in the Regulation of Myocardial Function. *Prog Cardiovasc Dis*, 38, 155-66.
10. Lyons, C.R. (1995) The Role of Nitric Oxide in Inflammation. *Adv Immunol*, 60, 323-71.
11. Brune, B., et al. (1995) The Role of Nitric Oxide in Cell Injury. *Toxicol Lett*, 82-83, 233-7.
12. Wink, D.A., et al. (1995) Nitric Oxide (NO) Protects against Cellular Damage by Reactive Oxygen Species. *Toxicol Lett*, 82-83, 221-6.
13. (2006) *Arginine (L-Arginine)*. Medline Plus. Available Online [http://www.nlm.nih.gov/medlineplus/print/druginfo/natural/patient-arginine.html] 6/19/2006.
14. (2006) *L-Arginine*. SupplementWatch. Available Online [http://www.supplementwatch.com/suplib/supplementPrintFriendly.asp?DocId=1318] 6/19/2006.
15. Lerman, A., et al. (1998) Long-Term L-Arginine Supplementation Improves Small-Vessel Coronary Endothelial Function in Humans. *Circulation*, 97, 2123-8.
16. Maxwell, A.J., et al. (2002) Randomized Trial of a Medical Food for the Dietary Management of Chronic, Stable Angina. *J Am Coll Cardiol*, 39, 37-45.
17. Ceremuzynski, L., et al. (1997) Effect of Supplemental Oral L-Arginine on Exercise Capacity in Patients with Stable Angina Pectoris. *Am J Cardiol*, 80, 331-3.
18. Rector, T.S., et al. (1996) Randomized, Double-Blind, Placebo-Controlled Study of Supplemental Oral L-Arginine in Patients with Heart Failure. *Circulation*, 93, 2135-41.
19. Watanabe, G., et al. (2000) Effects of Oral Administration of L-Arginine on Renal Function in Patients with Heart Failure. *J Hypertens*, 18, 229-34.
20. Yousufuddin, M., et al. (2001) A Short Course of L-Arginine Improves Exercise Capacity and Endothelial Function

in Chronic Heart Failure: A Prospective, Randomised, Double Blind Trial. *J Am Coll Cardiol*, 211A.

21. Drexler, H., et al. (1991) Correction of Endothelial Dysfunction in Coronary Microcirculation of Hypercholesterolaemic Patients by L-Arginine. *Lancet*, 338, 1546-50.

22. Creager, M.A., et al. (1992) L-Arginine Improves Endothelium-Dependent Vasodilation in Hypercholesterolemic Humans. *J Clin Invest*, 90, 1248-53.

23. Zeiher, A.M., et al. (1991) Modulation of Coronary Vasomotor Tone in Humans. Progressive Endothelial Dysfunction with Different Early Stages of Coronary Atherosclerosis. *Circulation*, 83, 391-401.

24. Schachinger, V., et al. (2000) Prognostic Impact of Coronary Vasodilator Dysfunction on Adverse Long-Term Outcome of Coronary Heart Disease. *Circulation*, 101, 1899-906.

25. Suwaidi, J.A., et al. (2000) Long-Term Follow-up of Patients with Mild Coronary Artery Disease and Endothelial Dysfunction. *Circulation*, 101, 948-54.

26. Boger, R.H. and Bode-Boger, S.M. (2001) The Clinical Pharmacology of L-Arginine. *Annu Rev Pharmacol Toxicol*, 41, 79-99.

27. Sanders, P.W. (1996) Salt-Sensitive Hypertension: Lessons from Animal Models. *Am J Kidney Dis*, 28, 775-82.

28. Calver, A., et al. (1991) Dilator Actions of Arginine in Human Peripheral Vasculature. *Clin Sci (Lond)*, 81, 695-700.

29. Pezza, V., et al. (1998) Study of Supplemental Oral L-Arginine in Hypertensives Treated with Enalapril + Hydrochlorothiazide. *Am J Hypertens*, 11, 1267-70.

30. Siani, A., et al. (2000) Blood Pressure and Metabolic Changes During Dietary L-Arginine Supplementation in Humans. *Am J Hypertens*, 13, 547-51.

31. Maccario, M., et al. (1997) Comparison among the Effects of Arginine, a Nitric Oxide Precursor, Isosorbide Dinitrate and Molsidomine, Two Nitric Oxide Donors, on Hormonal Secretions and Blood Pressure in Man. *J Endocrinol Invest*, 20, 488-92.

32. Schulze-Neick, I., et al. (1999) L-Arginine and Substance P Reverse the Pulmonary Endothelial Dysfunction Caused by Congenital Heart Surgery. *Circulation*, 100, 749-55.

33. Boger, R.H. and Ron, E.S. (2005) L-Arginine Improves Vascular Function by Overcoming Deleterious Effects of Adma, a Novel Cardiovascular Risk Factor. *Altern Med Rev*, 10, 14-23.

34. Boger, R.H., et al. (1998) Restoring Vascular Nitric Oxide Formation by L-Arginine Improves the Symptoms of Intermittent Claudication in Patients with Peripheral Arterial Occlusive Disease. *J Am Coll Cardiol*, 32, 1336-44.

35. Kirk, S.J., et al. (1993) Arginine Stimulates Wound Healing and Immune Function in Elderly Human Beings. *Surgery*, 114, 155-9; discussion 160.

36. Bernard, A.C., et al. (2001) Alterations in Arginine Metabolic Enzymes in Trauma. *Shock*, 15, 215-9.

37. Yu, Y.M., et al. (2001) Arginine and Ornithine Kinetics in Severely Burned Patients: Increased Rate of Arginine Disposal. *Am J Physiol Endocrinol Metab*, 280, E509-17.

38. Evoy, D., et al. (1998) Immunonutrition: The Role of Arginine. *Nutrition*, 14, 611-7.

39. Barbul, A., et al. (1983) Wound Healing and Thymotropic Effects of Arginine: A Pituitary Mechanism of Action. *Am J Clin Nutr*, 37, 786-94.

40. Barbul, A., et al. (1990) Arginine Enhances Wound Healing and Lymphocyte Immune Responses in Humans. *Surgery*, 108, 331-6; discussion 336-7.

41. Bower, R.H., et al. (1995) Early Enteral Administration of a Formula (Impact) Supplemented with Arginine, Nucleotides, and Fish Oil in Intensive Care Unit Patients: Results of a Multicenter, Prospective, Randomized, Clinical Trial. *Crit Care Med*, 23, 436-49.

42. Weimann, A., et al. (1998) Influence of Arginine, Omega-3 Fatty Acids and Nucleotide-Supplemented Enteral Support on Systemic Inflammatory Response Syndrome and Multiple Organ Failure in Patients after Severe Trauma. *Nutrition*, 14, 165-72.

43. Bucci, L. (1993) *Nutrients as Ergogenic Aids for Sports and Exercise*. CRC Press, Boca Raton.

44. Besset, A., et al. (1982) Increase in Sleep Related Gh and Prl Secretion after Chronic Arginine Aspartate Administration in Man. *Acta Endocrinol (Copenh)*, 99, 18-23.
45. Macintyre, J.G. (1987) Growth Hormone and Athletes. *Sports Med*, 4, 129-42.
46. Hurson, M., et al. (1995) Metabolic Effects of Arginine in a Healthy Elderly Population. *J Parenter Enteral Nutr*, 19, 227-30.
47. Elam, R.P. (1988) Morphological Changes in Adult Males from Resistance Exercise and Amino Acid Supplementation. *J Sports Med Phys Fitness*, 28, 35-9.
48. Elam, R.P., et al. (1989) Effects of Arginine and Ornithine on Strength, Lean Body Mass and Urinary Hydroxyproline in Adult Males. *J Sports Med Phys Fitness*, 29, 52-6.
49. Isidori, A., et al. (1981) A Study of Growth Hormone Release in Man after Oral Administration of Amino Acids. *Curr Med Res Opin*, 7, 475-81.
50. Wolinsky, I. and Hickson, J.F. (1998) Nutrition in Exercise and Sport, Second Edition. In Wolinsky, I. and Hickson, J.F. (eds.), *Nutrition and the Strength Athlete*. CRC Press, Boca Raton.
51. Suminski, R.R., et al. (1997) Acute Effect of Amino Acid Ingestion and Resistance Exercise on Plasma Growth Hormone Concentration in Young Men. *Int J Sport Nutr*, 7, 48-60.
52. Brittenden, J., et al. (1994) L-Arginine Stimulates Host Defenses in Patients with Breast Cancer. *Surgery*, 115, 205-12.
53. Tachibana, K., et al. (1985) Evaluation of the Effect of Arginine-Enriched Amino Acid Solution on Tumor Growth. *J Parenter Enteral Nutr*, 9, 428-34.
54. Muhling, J., et al. (2002) Effects of Arginine, L-Alanyl-L-Glutamine or Taurine on Neutrophil (Pmn) Free Amino Acid Profiles and Immune Functions in Vitro. *Amino Acids*, 22, 39-53.
55. Keith, M.E. and Jeejeebhoy, K.N. (1997) Immunonutrition. *Baillieres Clin Endocrinol Metab*, 11, 709-38.
56. Allen, A.d.W. (2006) *Clinical Benefits of L-Arginine in Achieving Maximum Sexual Performance*. Arginine Research. Available Online [<http://www.arginineresearch.com/L-arginine.html>] 7/14/2006.
57. Chen, J., et al. (1999) Effect of Oral Administration of High-Dose Nitric Oxide Donor L-Arginine in Men with Organic Erectile Dysfunction: Results of a Double-Blind, Randomized, Placebo-Controlled Study. *BJU Int*, 83, 269-73.
58. Quillin, P. (1997) *Healing Nutrients*. Avon Books, New York.
59. Lamm, S. and Couzens, G.S. (1997) *Younger at Last: The New World of Vitality Medicine*. Simon & Schuster, New York.
60. Stanislavov, R. and Nikolova, V. (2003) Treatment of Erectile Dysfunction with Pycnogenol and L-Arginine. *J Sex Marital Ther*, 29, 207-13.
61. Tiwary, C.M., et al. (1973) Anaphylactic Reaction to Arginine Infusion. *N Engl J Med*, 288, 218.

**FOR MORE INFORMATION, OR TO RECEIVE ADDITIONAL COPIES  
OF THIS BOOK FOR YOUR PATIENTS, PLEASE CONTACT:**

**INFOMEDICA  
TOLL FREE (877) 664-6684**